CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	1/21/2010
From	Ellis F. Unger, M.D., Deputy Director, ODE-I
Subject	Deputy Office Director Decisional Memo
NDA#	22-567
Applicant Name	PGx Health, LLC
Date of Submission	March 22, 2010
PDUFA Goal Date	January 22, 2011
Proprietary Name / Established (USAN) Name	Viibryd Vilazodone Hydrochloride
Dosage Forms / Strength	Oral tablets: 10 mg, 20 mg, and 40 mg
Indication	… for the treatment of major depressive disorder (MDD)
Action:	*Approval*

Material Reviewed/Consulted Action Package, including:	
Project Manager	William Bender
Medical Officer Clinical Review	Cheri Lindberg/Robert Levin (team leader)
Clinical Pharmacology Review	Bei Yu/Huixia Zhang/Jee Eun Lee/Jogarao Gobburu/Venkatesh Bhattaram/Yaning Wang/Issam Zineh
Statistical Review	Phillip Dinh/Peiling Yang (team leader)
Pharmacology Toxicology	Violetta Klimek/ Linda Fossom (team leader)
Chemistry Manufacturing and Controls	Pei-I Chu/ Chhagan Tele (team leader)
Statistical Review and Evaluation of Carcinogenicity Study	Mohamed Nagem/Karl Lin (team leader)
Environmental Assessment	Pei-I Chu/ Chhagan Tele (team leader)
Division of Scientific Investigations	Anthony Orencia/Purohit-Sheth, Tejashri
Division of Medication Error Prevention and Analysis, Office of Surveillance and Epidemiology	Loretta Holmes/Kristina Tolliver (team leader)
Division of Risk Management, Office of Surveillance and Epidemiology	Shawna Hutchinson – REMS Robin Duer - Med Guide
Division of Drug Marketing, Advertising and Communications (DDMAC)	Jessica Cleck Derenick
Cross-Discipline Team Leader	Robert Levin/Mitchell Mathis
Proprietary Name Review	Loretta Holmes
Director, Division of Psychiatry Products	Thomas Laughren

Action:

The Division of Psychiatry Products is recommending approval of vilazodone hydrochloride, 10-, 20-, and 40-mg Tablets for oral administration for the treatment of major depressive disorder (MDD). I concur with their recommendation for approval.

Introduction:

Vilazodone is a small molecule, both a selective serotonin reuptake inhibitor (SSRI) and a partial 5-HT_{1A} receptor agonist, although the clinical significance of the latter is unknown. Vilazodone is not marketed anywhere.

Regulatory Background:

The IND for vilazodone for this indication was submitted on 11/21/1997 by Lipha Pharmaceuticals. Sponsorship of the IND was transferred numerous times, as summarized in Dr. Levin's CDTL review. The applicant had originally hoped to use genetic markers to direct clinical decision-making; however, those plans were ultimately abandoned. A pre-NDA meeting was scheduled for June, 2009; however, the applicant found the Division's preliminary comments sufficient to address their questions and the meeting was cancelled.

Chemistry Manufacturing and Controls (CMC):

Pursuant to their initial review, the CMC team sent an information request (IR) letter to the applicant on 10/15/2010, and the applicant's responses were deemed adequate. The ONDQA Biopharmaceutics review the found the proposed dissolution methodology and specifications to be acceptable. The Environmental Assessment review found no pending issues. Accordingly, the NDA was recommended for approval from a CMC perspective.

Pharmacology/Toxicology:

The review found the application approvable. Vilazodone binds with high affinity to the serotonin reuptake site (Ki = 0.1 nM), but not to the dopamine or norepinephrine reuptake sites. Vilazodone inhibits reuptake of serotonin (IC_{50} = 1.6 nM) and binds to 5-HT_{1A} receptors with an IC_{50} of 2.1 nM, where it functions as a partial agonist.

(b) (4)

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Serotonergic mechanisms in the central nervous system (CNS) are complex. Experimentally, vilazodone has been observed to exhibit both agonism and antagonism, depending on the experimental model and region of the brain studied. Moreover, 5-HT_{1A} receptors are present at both presynaptic and postsynaptic nerve terminals, and their various interactions are not fully understood. In short, the net effect of 5-HT_{1A} partial agonism on serotonergic transmission in the CNS has not been well-characterized, and the clinical significance of those effects, if any, is certainly unknown.

(b) (4)

Moreover, their proposed

proprietary name, "Viibryd," (b) (4) Through much discussion and negotiation, the review team was able to reach agreement with the applicant on a description of vilazodone's mechanism of action (section 12.1 of the label):

> "The mechanism of the antidepressant effect of vilazodone is not fully understood but is thought to be related to its enhancement of serotonergic activity in the CNS through selective inhibition of serotonin reuptake. Vilazodone is also a partial agonist at serotonergic 5-HT_{1A} receptors; however, the net result of this action on serotonergic transmission and its role in vilazodone's antidepressant effect are unknown."

(b) (4) It is notable that the applicant has made no effort to show a benefit in comparison to other antidepressants; no comparators were included in the phase 3 program. Vilazodone has two major human metabolites, M10 and M17, each circulating at greater than 10% of total drug-related exposure. Neither is thought to have important serotonergic activity. Both have been assessed for toxicity; however, it is unclear if M17 has been adequately assessed for embryo-fetal toxicity because it was not found to be present in the plasma of either rats or rabbits. The applicant has agreed to explore this issue in a reproductive toxicity study, post-approval, in which M17 is administered by a route that will produce systemic exposure greater than or equal to the exposure in humans at the maximum recommended human dose (MRHD). Alternatively, they could show that the original rabbit study was adequate to assess the embryo-fetal toxicity of M17 by demonstrating that the rabbit's systemic exposure to M17 in that study was greater than or equal to that in humans at the MRHD.

Two-year carcinogenicity studies were conducted in B6C3F1 mice and Wistar rats, given oral vilazodone at approximately 16.5 and 36 times the MRHD, respectively. The studies were deemed to be acceptable. In mice, the incidence of hepatocellular carcinomas was increased in males at 16.5 times, but not 5.5 times, the MRHD. Mammary gland adenocarcinomas were increased in females at 5.5 and 16.5 times the MRHD (associated with increased prolactin levels – known to cause mammary tumors in rodents), but not at 1.8 times the MRHD. In rats, there were no biologically relevant drug-related increases in incidences of neoplasms at doses up to 36 times the MRHD.

Results of mutagenicity assays were mixed: vilazodone was clastogenic *in vitro* in assays for chromosomal aberrations using V79 CHO cells in the presence and in absence of S9 metabolic activation, and using human lymphocytes in the presence of S9 activation. Vilazodone was negative for mutagenicity in the Ames test and in the hypoxanthine-guanine phosphoribosyl transferase (HPRT) assay. It was also negative in several *in vivo* studies that included: 1) a chromosomal aberration assay in the rat bone marrow cells; 2) a micronucleus test in rats; and 3) an unscheduled DNA synthesis (UDS) assay in rat hepatocytes.

Treatment of rats with vilazodone at 30 times, but not 6 times, the MRHD caused impairment of male fertility; there was no effect on female fertility.

Vilazodone caused developmental toxicity in rats (reduced fetal weight and delayed bone ossification) but was not teratogenic in either rats or rabbits.

Relevant to gastrointestinal adverse reactions observed in the phase 2 and 3 clinical trials, there were no notable effects on gastrointestinal transport or gastric emptying in rodents in the safety pharmacology studies.

Site Inspections:

Four U.S. investigators (2 in each of the phase 3 trials) were inspected in support of this NDA; the applicant was inspected as well. Because larger sites were selected for inspection, the Division of Scientific Investigations had access to records of 311 subjects at 6 centers during their inspections, or approximately 35% of subjects in the phase 3 trials.

Minor regulatory deficiencies were found in one of the studies, but they were isolated and thought to have minimal impact on either data integrity or protection of human subjects. Overall, the data were deemed reliable for the proposed indication, with general adherence to Good Clinical Practices (GCP) regulations governing the conduct of clinical investigations.

Pharmacokinetics:

Vilazodone exhibits dose-proportional pharmacokinetics over a dose range from 5 to 80 mg. Administration with a high-fat or light meal increases oral bioavailability, and when administered with food, vilazodone's absolute bioavailability is ~72%. The applicant proposes that vilazodone be taken with food, as it was in the phase 3 program, and the Division agrees with this recommendation. The median T_{max} is 4-5 hours, and terminal half-life is ~25 hours.

Vilazodone is widely distributed, with a volume of distribution of 600 L after a 5 mg infusion, and the drug is highly protein-bound (96-99%).

Vilazodone's accumulation is predictable from single-dose data (accumulation factor of about 1.8, and consistent across different doses), and steady state is achieved in ~3 days. The mean steady state C_{max} after daily 40 mg dosing under fed conditions is ~160 ng/mL.

Vilazodone is extensively metabolized through CYP and non-CYP pathways, with 1% and 2% of the unchanged drug recovered in urine and feces, respectively. Among the CYP pathways, CYP3A4/5 is principally responsible for vilazodone's metabolism, with only minor contributions from CYP2C19 and CYP2D6. *In vitro* studies show that vilazodone is unlikely to inhibit or induce the metabolism of other CYPs (except for CYP2C8). Strong CYP3A4 inhibitors can reduce vilazodone's metabolism and increase exposure modestly (coadministration with ketoconazole increases the AUC and C_{max} by 50%). The label includes a recommendation to reduce the vilazodone dose from 40 to 20 mg daily when administered with strong CYP3A4 inhibitors. Theoretically, CYP3A4 inducers (e.g., carbamazepine) might decrease vilazodone exposure, although this was not studied. The applicant has agreed to conduct a drug-drug interaction trial of vilazodone using carbamazepine in healthy subjects as a postmarketing commitment.

Vilazodone had minimal effects on other drugs, except that coadministration of vilazodone with a CYP2C8 substrate can lead to an increase in the concentration of the other drug.

Thorough QT Study:

As described by others, vilazodone was tested in a thorough QT study at doses up to 80 mg. The study demonstrated appropriate assay sensitivity, and the baseline-corrected QTc interval was <10 msec for vilazodone, below the threshold of clinical concern.

Phase 2 Dose-Finding Trials:

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