CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review Memo

Date of review	January 5, 2011
From	Robert L. Levin, M.D.
Subject	Cross-Discipline Team Leader Review
NDA	22-567
Sponsor	PGx Health, LLC
Submission Date	March 22, 2010
Related IND	54-613
Proprietary / Established name	VIIBRYD Vilazodone Hydrochloride
Dosage forms / strength	10, 20, and 40 mg oral tablets
Proposed Indication	Major Depressive Disorder in Adults
Recommended:	Approval

1. Introduction to the Review

The sponsor has submitted NDA 22-567 for vilazodone hydrochloride oral tablets in the treatment of adults with major depressive disorder. Vilazodone is a new molecular entity that has selective serotonin reuptake inhibitor (SSRI) properties as well as 5-HT_{1A} partial agonist properties. The sponsor has evaluated vilazodone in 24 phase 1 studies, five phase 2 studies, and three phase 3 studies. The five phase 2 controlled studies were either negative (2) or failed (3). In these studies, the sponsor explored a dose range of 5-100 mg per day. There was no clear trend toward a beneficial treatment effect. Gastrointestinal adverse reactions (nausea, vomiting, and diarrhea) were dose-limiting toxicities associated with a significant proportion of discontinuations, especially at doses above 40 mg/day.

In the two pivotal phase 3 trials, the sponsor studied a single dose (40 mg/day). There were no active comparators in either study. In one study, subjects who did not tolerate 40 mg/day could continue treatment with 20 mg/day. This included a very small number of subjects. In the second study, subjects were discontinued if they could not tolerate 40 mg/day. In all other respects, the studies had the identical design. The review team agrees that, in both studies, the sponsor demonstrated the efficacy of vilazodone 40 mg/day in the treatment of adult subjects with major depressive disorder. The review team also agrees that treatment was reasonably safe and well tolerated in the studies. In general, the safety and tolerability profiles of vilazodone were highly similar to those of other SSRI antidepressants. There were no new or unexpected safety findings with vilazodone, compared to those observed with SSRIs. Currently, it is unclear whether the 5-HT_{1A}

partial agonist properties of vilazodone confer additional benefit or risk compared to SSRI antidepressants.

The review team's main concern about the vilazodone clinical program is whether the sponsor adequately explored a range of doses in the trials, given that the pivotal trials assessed only one dose (40 mg/day). Two of the phase 2 studies (246 and 248) used fixed doses of vilazodone (5, 10, and 20 mg/day). Study 246 included an active control, but Study 248 did not. While these studies were negative or failed on the primary efficacy endpoint (HAMD scores), there appeared to be a trend toward an effect on the secondary endpoint (MADRS scores). However, there are a number of problems in relying on the secondary efficacy analysis. Overall, it is uncertain whether the 20 mg dose might be effective. On the other hand, there are dose-related adverse reactions (nausea and vomiting) that were associated with discontinuation of treatment. Thus, the review team has concluded that the sponsor should be required to conduct a postmarketing placebo-controlled and active-controlled study using fixed doses of vilazodone (20 mg and 40 mg), in order to further explore the effective dose range of vilazodone.

2. Background/Regulatory History

The initial IND (54-613) for vilazodone in the treatment of major depressive disorder was submitted on November 21, 1997 by Lipha Pharmaceuticals, an associate of Merck. A number of sponsors have held the vilazodone IND during the clinical development program. Lipha transferred ownership to Merck on August 26, 1998. On May 1, 2001 Merck transferred ownership to GSK; and on February 11, 2003 GSK transferred ownership to Merck. On November 7, 2003 EMD Pharmaceuticals became the IND holder. On October 25, 2004 EMD transferred ownership to Genaissance Pharmaceuticals. Subsequently, the company name of Genaissance changed to Cogenics on January 8, 2007. The name then changed to PGxHealth on September 28, 2007.

The clinical program was discussed with the sponsor at an end of Phase 2 (EOP2) meeting on December 20, 2005. The Division and the Sponsor reached agreement on the design of the Phase 3 studies (GNSC-04-DP-02 and GNSC-07-02). There was agreement that the Montgomery-Asberg Depression Rating Scale (MADRS) was an acceptable primary endpoint for a study in major depressive disorder. The Division and the Sponsor also agreed that ophthalmologic exams would not be required for these 8-week studies. However, for longer term exposures, the Sponsor would be required to conduct baseline and repeat (every 6 months) slit lamp exams and dilated fundoscopy to assess for lenticular and retinal changes.

During the period, May 8, 2008 and June 10, 2009, the Division provided guidance and feedback to the sponsor during face-face meetings, teleconferences, letters, and email communications. The topics of discussion included pivotal clinical protocols, a thorough QT study protocol, proposed analyses regarding possible genetic markers of response to vilazodone. During a pre-NDA meeting (June 17, 2009), we discussed the content and format of the clinical section for the subsequent NDA submission. We agreed that the efficacy data from the two pivotal trials would be presented separately and would not be

pooled. In addition, we agreed that the 5 phase 2 studies would not be considered supportive of the indication. The sponsor would submit the individual study reports.

3. Chemistry Manufacture and Controls (CMC) Review

Pei-I Chu, Ph.D. from ONDQA DPA1 performed the CMC review for the Division of Psychiatry Products. Dr. Chu has concluded that the sponsor has provided adequate CMC data to support approval of the NDA. There are no outstanding CMC issues. I agree with her conclusions.

3.1 Drug Substance

Dr. Chu has concluded that the drug substance and stability data provided support approval of the NDA.

Vilazodone hydrochloride is a new chemical entity belonging to the structural chemical group of the indolalkylamines. The full chemical designation is 2-benzofuran-carboxamide, 5-[4-[4-(5- cyano- 1H-indol-3-yl)butyl]-1-piperazinyl]-, hydrochloride (1:1) indolalkylamines. The full chemical designation is 2-benzofurancarboxamide, 5-[4-[4-(5- cyano- 1H-indol-3-yl)butyl]-1-piperazinyl]-, hydrochloride (1:1). Vilazodone HCl drug substance is a white to cream-colored solid. It is achiral and slightly hygroscopic. Solid state form analysis demonstrates that it exists in multiple polymorphs (b) (4) (b) (4) form IV was chosen for development. The solubility in water is 0.32mg/mL. The partition coefficient between n-octanol and water is (b) (4) The pKa is 7.1. The melting point and decomposition starts at ~270ºC.

3.2 Drug Product

Dr. Chu has concluded that the drug product and stability data provided support approval of the NDA.

In her review, Dr. Chu notes that Vilazodone HCl Tablets, 10 mg, 20 mg and 40 mg are immediate-release, oval, film-coated, tablets, manufactured from a (b) (4) with total tablet weights of 103 mg, 206 mg and 412 mg, respectively. The 10 mg tablets are pink; the 20 mg, orange; and the 40 mg, blue. The tablets are debossed with the strength on one side and plain on the other. The tablets are packaged in appropriately-sized, 30-count, 90-count and 500-count high-density polyethylene (HDPE) bottles, and in film/aluminum foil blisters.

The drug product will be manufactured by Patheon Puerto Rico, Inc. (Manati, Puerto Rico). Vilazodone HCl Tablets, 10 mg, 20 mg and 40 mg are manufactured from a (b) (4) process using standard techniques, equipment and controls. Manufacturing consists of (b) (4) Excipients used in the formulation include lactose, microcrystalline cellulose, colloidal silicone dioxide, magnesium stearate and (b) (4) film coating. The film coat is comprised of:

(b) (4) The batch formula for a commercial scale batch is (b) (4) for the 10mg, 20mg and 40mg tablets, which would results in (b) (4) 10mg tablets, (b) (4) 20mg tablets or (b) (4) 40mg tablets. Vilazodone HCl tablets may be stored in bulk prior to packaging to accommodate for packaging schedule. The HDPE bottles are sized to accommodate 30, 90, or 500 tablets/bottle. Each bottle also contains a 1-g desiccant canister. The applicant has submitted 18 month stability data for 6 batches using drug substance manufactured by Merck (three each of 10mg and 40mg tablets) and 12 month stability data of drug product manufactured with API from Scino Pharm. Based on real time and accelerated stability data at the ICH conditions, the 10mg and 40mg tablets are considered stable under proposed storage container closure systems. Tablets manufactured with API from SPT have the same stability as those manufactured with API from Merck based on comparison of 12-month stability data for SPT-API tablets and Merck-API tablets. The data support the proposed shelf life of 24 months when stored at room temperature.

3.3 Pre-approval Inspection of Facilities and Quality Issues Observed

The facilities inspection has been completed. The Office of Compliance has determined that the drug substance, drug product, and packaging facilities are adequate. Pre-approval inspections for the drug substance, drug product, and packaging sites are not needed based on the drug profile.

3.4 Unresolved CMC Issues

There are no unresolved CMC approvable issues. The sponsor has committed to meeting the following requests: 1) they will provide a revised (b) (4) validation report to demonstrate the limit of quantitation for Form IV (b) (4), and 2) they will include an updated dissolution method validation report using a stability indicating analytical method. Dr. Chu does not recommend any phase 4 commitments.

4. Nonclinical Pharmacology/Toxicology

Violetta Klimek, Ph.D. performed the pharmacology/toxicology review. Dr. Klimek and the team leader, Linda Fossom, Ph.D. have concluded that the sponsor has provided adequate pharmacology/toxicology data for approval of the NDA. Dr. Klimek and Dr. Fossom have concluded that there are no unresolved pharmacology/toxicology issues. I agree with their conclusions. The pharm/tox team has made a number of recommendations for labeling that we have incorporated.

5. Clinical Pharmacology/Biopharmaceutics

Bei Yu, Ph.D. performed the Clinical Pharmacology/Biopharmaceutics review. Dr. Yu and the OCP team have concluded that the sponsor has provided adequate clinical pharmacology and biopharmaceutics information to support approval of the NDA. There are no outstanding issues. I agree with Dr. Yu's conclusions.

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