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APPLICATION NUMBER:

022567Orig1s000

PHARMACOLOGY REVIEW(S)

Tertiary Pharmacology/Toxicology Review

From: Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology, OND IO

NDA: 22-567
Agency receipt date: 3/22/2010
Drug: VIIBRYD (vilazodone hydrochloride)
Applicant: PGxHealth, LLC
Indication: treatment of major depressive disorder

Reviewing Division: Division of Psychiatry Products

Background:
The pharm/tox reviewer and team leader concluded that the nonclinical data support approval of vilazodone hydrochloride for the indication listed above.

Reproductive and Developmental Toxicity:
Reproductive and developmental toxicity studies in rats and rabbits revealed no evidence of teratogenicity although there was some evidence of reduced fetal body weight and delayed ossification in both species. These effects were not seen at doses up to 10 times the MRHD in rats or 4 times the MRHD in rabbits. The reviewer recommended pregnancy category C.

Carcinogenicity:
Vilazodone was tested in 2 year rat and mouse carcinogenicity studies. These studies were reviewed by the division and the executive carcinogenicity assessment committee. The committee concluded that the studies were acceptable. There were no drug-related neoplasms in rat. The Committee concluded that there was an increased incidence of mammary adenocarcinomas and adenoacanthomas (combined) in female mice at the high dose (135 mg/kg) and hepatocellular neoplasms (adenomas, carcinomas, and adenomas or carcinomas, combined), in male mice at the high dose (135 mg/kg). The division has also noted that the mammary adenocarcinomas in female mice appear to be increased at the mid dose of 45 mg/kg even though the incidence did not meet usual CDER standards for statistical significance for pairwise comparison. The reviews also note that vilazodone increased prolactin levels in mice.

Established Pharmacologic Class:
The pharm/tox reviewer, team leader and supervisor have carefully considered the data on the pharmacologic activity of vilazodone. Vilazodone appears to have both SSRI and 5-HT1A partial agonist activity. (b) (4)

[redacted]

(b) (4)

Impurities and metabolites:
Several genotoxic or potentially genotoxic impurities were identified during review of the NDA. This issue is discussed in detail in the team leader memo. Specifications for each of these impurities have been limited so humans will be exposed to not more than (b) (4) µg of each per day at the MRHD of 40 mg.

Two major human metabolites of vilazodone were identified. The nonclinical assessment of these is discussed in detail in the team leader memo. Both metabolites have been adequately assessed for all toxicity endpoints except it is not clear that one metabolite (M17) was adequately assessed for embryofetal toxicity because its presence was not confirmed in rats or rabbits. The division is recommending that M17 be assessed in an embryofetal study or that data be provided demonstrating that M17 was adequately assessed in one of the already conducted embryofetal studies. The division is recommending this as a post marketing requirement.

Pediatric assessment:
The division is recommending that the efficacy and safety of vilazodone be assessed in pediatric patients with major depressive disorder as part of the deferred pediatric requirements. Prior to dosing children less than 13 years of age, the division is recommending that the applicant complete a juvenile animal study in rats and include evaluation of neurological/behavioral development and reproductive development in this study.

Conclusions:
I agree with the division pharm/tox conclusion that this application can be approved from a pharm/tox perspective. The proposed post marketing requirements are acceptable.

I have discussed the proposed carcinogenicity labeling with the team leader. The proposed wording states that mammary adenocarcinomas in female mice were numerically increased at the mid dose in addition to describing the statistically significant increase in tumors. This is a true statement and is acceptable. Proposed labeling includes wording noting the potential role of elevated prolactin in these tumor findings.

(b) (4)

Other labeling as proposed by the reviewer and team leader is acceptable.

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/s/

PAUL C BROWN
01/14/2011

SUPERVISORY PHARMACOLOGY/TOXICOLOGY MEMO TO THE FILE

NDA 22-567.
Submissions: N-000, original submission, letter-dated 3/22/2010, received 3/22/2010.

Drug: vilazodone hydrochloride, as 10-, 20-, and 40-mg oral tablets [VIIBRYD™].
Sponsor: PGxHealth, LLC (original sponsor).
Indication: treatment of major depressive disorder.

Reviewer: Linda H. Fossom, Ph.D., Pharmacologist, Team Leader.
Division of Psychiatry Products, HFD-130.

I. BACKGROUND:

Vilazodone is a new molecular entity submitted under the current NDA for treatment of major depressive disorder. The pharmacology/toxicology studies have been reviewed in detail by Violetta Klimek, Ph.D., Pharmacologist (review finalized 12/22/2010). In her review, Dr. Klimek has thoroughly and critically evaluated the non-clinical information provided in support of this NDA. In general, these studies provided adequate assessment of pharmacology, general toxicity (including chronic studies in rats and dogs), genotoxicity, carcinogenicity (2-year studies in rats and mice), and reproductive toxicity. I agree with Dr. Klimek that vilazodone did not demonstrate any particular concerns based on these studies; the findings for genotoxicity, reproductive toxicity, and carcinogenicity will be included in labeling.

However, late in the review cycle, it became apparent that 2 major human metabolites, one of which had not been identified as circulating in human plasma at the time of NDA submission, might not have been adequately assessed for toxicity in animals. We contacted the Sponsor to obtain their explanation of this issue (on 12/14/10 and again on 12/20/10); however, their full response was not available at the time Dr. Klimek's review was finalized. That information is now available and is discussed below.

This memo contains additional comments on 4 issues:

- (b) (4)
- The carcinogenicity findings presented in labeling;
- The control of genotoxic (and potentially genotoxic) impurities;
- Toxicological assessment of the 2 major circulating human metabolites.

[Of these issues, only the toxicological assessment of one of the major human metabolites (M17) needs further study by the Sponsor and this will be required as a post-marketing commitment.]

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