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:

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