

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022567Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: December 03, 2010

To: Thomas Laughren, MD, Director  
**Division of Psychiatry Products (DPP)**

Through: Claudia Karwoski PharmD, Director  
**Division of Risk Management (DRISK)**

From: Shawna Hutchins, MPH, BSN RN  
Patient Labeling Reviewer  
**Division of Risk Management (DRISK)**

Subject: DRISK Review of Proposed Risk Evaluation and Mitigation  
Strategy (REMS)

Drug Name(s): vilazodone HCL tablets

Application Type/Number: NDA 22-567

Applicant/sponsor: PGxHealth, LLC

OSE RCM #: 2010-784

## **1. INTRODUCTION**

This review is written in response to a request by the Division of Psychiatry Products (DPP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document for vilazodone hydrochloride (HCL) tablets. The trade name for this NDA is currently under review.

Please send these comments to the Applicant and request a response within two weeks of receipt. Let us know if you would like a meeting to discuss these comments before sending to the Applicant.

The DRISK review of the Medication Guide will be provided under a separate cover. The DRISK review of the methodology and survey instruments to be submitted by the Applicant to evaluate the REMS will be provided under separate cover.

## **2. BACKGROUND**

On March 22, 2010 PGxHealth, LLC, submitted a New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for vilazodone (HCL) 10 mg, 20 mg, and 40 mg tablets for the treatment of major depressive disorder (MDD).

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. In accordance with section 505-1 of FDCA, the FDA determined that a REMS is necessary for vilazodone HCL tablets to ensure the benefits of the drug outweigh the increased risk of suicidality in children, adolescents, and young adults as observed in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. The components of the REMS include a Medication Guide (MG) and a timetable for submission of assessments.

## **3. MATERIAL REVIEWED**

- vilazodone HCL tablets Risk Evaluation and Mitigation Strategy (REMS) Notification Letter dated November 01, 2010.
- Proposed vilazodone HCL tablets Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document, submitted on March 22, 2010, and received by DRISK on November 23, 2010.

## **4. RESULTS OF REVIEW**

In our review of the proposed REMS, we have:

- Ensured it includes the elements outlined in the REMS Notification Letter.
- Ensured it meets the statutory requirements under the Food and Drug Administration Amendments Act (FDAAA) of 2007.

## 5. CONCLUSIONS AND RECOMMENDATIONS

DRISK concurs with the elements of the proposed REMS.

Please note, the timetable for submission of the assessment is required to be approved as part of the REMS, but not the Applicant's proposed information about the details of the REMS evaluation (methodology/instruments). The methodology and instruments do not need to be reviewed or approved prior to approval of the REMS.

We have the following comments and recommendations for the Applicant with regard to the proposed REMS.

### Comments to PGxHealth, LLC:

See the appended vilazodone HCL tablets REMS proposal (Appendix A of this memo) for track changes corresponding to comments in this review.

#### a. GOAL

Revise your goal as follows:

The goal of this REMS is to inform patients about the serious risk associated with the use of vilazodone HCL tablets.

#### b. Your Medication Guide distribution plan appears to be acceptable. Your detailed plan for how you plan to distribute the Medication Guide in accordance with 21 CFR 208.24 is more appropriate for the REMS Supporting Document.

- We remind you that under 21 CFR 208.24, you are responsible for ensuring that sufficient numbers of Medication Guides are provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription.
- We remind you that under 21 CFR 208.24, you are responsible for ensuring that the vilazodone HCL tablets carton or container label contains a prominent statement that the Medication Guide should be dispensed to each patient. We recommend one of the following statements, depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):
  - “Dispense the enclosed Medication Guide to each patient.” Or
  - “Dispense the accompanying Medication Guide to each patient.”
- See our editorial comments on this section of the proposed REMS (see Appendix A).

#### c. Your proposed timetable for submission of assessments (18 months, 3 years and 7 years) is acceptable.

We have some editorial comments in this section of the REMS.

#### d. Regarding your REMS Assessment Plan

We acknowledge that you provided a brief description of the REMS Assessment Plan. We recommend that you submit for review the detailed plan you propose to use to evaluate patients' understanding about the safe use of vilazodone HCL tablets. You may submit the proposed plan after approval of the REMS, however submit it at least 90 days before you conduct the evaluation. Code the submission "REMS Correspondence." Make sure the submission includes all methodology and instruments used to evaluate the knowledge about the risks associated with and safe use of vilazodone HCL tablets.

If you plan to use a survey to conduct the assessment, we offer the following guidance as you develop your proposal.

1. Recruit respondents using a multi-modal approach. For example, you might recruit respondents through physicians' offices, pharmacies, managed care providers, consumer panels, or on-line.

Explain how often you perform non-respondent follow-up or reminders.

If you use an incentive or honorarium, provide details on what is offered and the estimated dollar value.

Explain how you select recruitment sites.

Submit for review any recruitment advertisements.

2. Describe the rationale for your sample size. Report the 95% confidence interval around the expected level(s) of patient knowledge for each key risk(s).
3. Define the expected number of people to be contacted to obtain the proposed sample size, and how the sample is determined (selection criteria).
4. Ensure the sample is demographically representative of the population who use the drug (patients).
5. When possible and appropriate, ensure the sample is diverse in terms of age, race, ethnicity, sex, socio-economic status, education level, and geographically.
6. List the inclusion criteria. For example, eligible patient respondents must be:
  - Age 18 or older
  - Currently taking vilazodone HCL tablets or have taken the drug in the past 3 months
  - Not currently participating in a clinical trial involving vilazodone HCL tablets
  - Not a healthcare providerSubmit any screener instruments, and describe any quotas of sub-populations used.
7. Explain how you administer surveys and the intended frequency.

Offer respondents multiple options for completing the survey. Be sure to include an option for the lower literacy population. For example, respondents might complete surveys online or through email, in writing or by mail, over the phone, and in person.

Explain how you train surveyors.

8. Explain how you control for limitations or bias associated with the methodology and survey instrument(s).
9. Submit for review the introductory text used to inform respondents about the purpose of the survey.

Tell potential respondents that their answers will not affect their ability to receive or take (patients) the drug, and that their answers and personal information will be kept confidential and anonymous.

10. Clarify in your methodology that respondents are eligible for one wave of the survey only.
11. The assessment evaluates the effectiveness of the REMS in achieving the goal by evaluating patients' knowledge of the serious risks associated with use of the drug. The assessment does not evaluate consumer comprehension of the Medication Guide.

According to regulation (21 CFR 208.24), patients receive the Medication Guide at the time the prescription is filled/dispensed. Do not offer respondents an opportunity to read or see the Medication Guide, Package Insert, or any other related educational materials again prior to taking the survey.

12. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in the Medication Guide.
13. Ensure the patient knowledge survey includes questions that ask about the specific risks or safety information conveyed in the Medication Guide to determine if the patient understands the information and knows what to do if they experience an adverse event.

Derive the risk-specific questions from information located in the "What is the Most Important Information I should know about vilazodone HCL?" section of the Medication Guide.

Ensure the risk-specific questions are not biased or leading, and that multiple choice questions include an instruction to "select all that apply." Ensure that each question has an "I don't know" answer option.

Randomize the order of the multiple choice responses on each survey.

14. Order questions so the risk-specific questions are asked first, followed by questions about receipt of the Medication Guide. Collect demographic questions last or as part of any screener questions.

Do not allow respondents the opportunity or ability to go back to previous questions in the survey.

Explain if and when any education will be offered for incorrect responses.

15. Include questions about receipt of the Medication Guide in the patient survey as a way to fulfill the obligation to report on the distribution of the Medication Guide.

16. Prior to the questions about receipt of the Medication Guide, include text that describes a Medication Guide. For example,

Now we are going to ask you some questions about the Medication Guide you may have received with vilazodone HCL tablets. The Medication Guide is a paper handout that contains important information about the risks associated with use of vilazodone HCL tablets and how to use vilazodone HCL tablets safely. Medication Guides always include the title “Medication Guide” followed by the word vilazodone HCL and its pronunciation. The Medication Guide usually has sections titled “What is the most important information I should know about vilazodone HCL,” “What is vilazodone HCL,” and “Who should not take vilazodone HCL.”

17. Use the following (or similar) questions to assess receipt and use of the Medication Guide.

- Who gave you the Medication Guide for vilazodone HCL tablets? (Select all that apply)
  - a) My doctor or someone in my doctor’s office
  - b) My pharmacist or someone at the pharmacy
  - c) Someone else - please explain: \_\_\_\_\_
  - d) I did not get a Medication Guide for vilazodone HCL tablets
- Did you read the Medication Guide?
  - a) All,
  - b) Most,
  - c) Some,
  - d) None
- Did you understand what you read in the Medication Guide?
  - a) All,
  - b) Most,
  - c) Some,
  - d) None
- Did someone offer to explain to you the information in the Medication Guide?

- a) Yes, my doctor or someone in my doctor's office
  - b) Yes, my pharmacist or someone at the pharmacy
  - c) Yes, someone else – please explain: \_\_\_\_\_
  - d) No
- Did you accept the offer? Yes or No
  - Did you understand the explanation that was given to you?
    - a) All,
    - b) Most,
    - c) Some,
    - d) None
  - Did or do you have any questions about the Medication Guide? Yes or No (If Yes, list your question(s) below) Note: Group/code this open text field prior to submitting to FDA

18. Analyze results on an item-by-item or variable-by-variable basis. You may present the data using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).

You may stratify the data by any relevant demographic variable, and presented in aggregate. Submit with your assessments all methodology and instruments utilized.

Please let us know if you have any questions.

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/s/  
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SHAWNA L HUTCHINS  
12/03/2010

CLAUDIA B KARWOSKI  
12/03/2010  
concur

**Risk Evaluation and Mitigation Strategy (REMS) Memorandum**

**U.S. FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
Office of Drug Evaluation I  
Division of Psychiatry Products**

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**NDA/BLA #s:** NDA 22-567  
**Products:** vilazodone HCl 10 mg, 20 mg, and 40 mg tablets  
**SPONSOR:** PGx Health, LLC  
**FROM:** Ellis Unger, M.D., Office of Drug Evaluation I Deputy Director  
**DATE:** October 15, 2010

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Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for vilazodone HCl to ensure that the benefits of the drug outweigh the increased risk of suicidality in children, adolescents, and young adults as observed in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. In reaching this determination, we considered the following:

- A. The estimated size of the population likely to use the drug involved:  
While it is not possible to estimate the size of the population likely to use vilazodone HCl tablets for the indication of major depressive disorder (MDD), the life-time prevalence of MDD was 16.2% (32.6-35.1 million U.S. adults), and the prevalence for a 12-month period was 6.6% (13.1-14.2 million U.S. adults) in a survey of U.S. adults 18 years and older (Kessler et. al. 2003).<sup>1</sup>
- B. The seriousness of the disease or condition that is to be treated with the drug:

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<sup>1</sup> Kessler RC et al: The epidemiology of Major Depressive Disorder. JAMA 2003; 289:3095-3105

Vilazodone HCl will be approved for the indication of treatment of MDD. MDD is a common disorder, widely distributed in the population, and usually associated with substantial symptom severity and role impairment. Patients with MDD have an increased risk of suicidality. MDD is associated with marital, parental, social and vocational difficulties. MDD may also complicate recovery from other medical illnesses.

- C. The expected benefit of the drug with respect to such disease or condition:  
Vilazodone HCl has demonstrated efficacy in the treatment of MDD in clinical studies. Treatment has resulted in significant reduction across the range of depressive symptoms. Presumably, effective treatment can also lead to improvement in various spheres of functioning in patients with MDD.
- D. The expected or actual duration of treatment with the drug:  
The expected duration of therapy with vilazodone HCl in patients who obtain a clinical response will range from 6 months to many years, since MDD is considered a life-long disease, although the severity of symptoms may vary over time.
- E. The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug: Known serious risks associated with use of SSRI and SNRI antidepressants include clinical worsening and suicidality in children, adolescents, and young adults, serotonin syndrome, precipitation of a manic/hypomanic episode, abnormal bleeding, interaction with MAOIs, hyponatremia, potential for cognitive and motor impairment, and discontinuation symptoms. Because vilazodone has SSRI properties, these are potential risks associated with the use of vilazodone HCl.
- F. Vilazodone HCl is a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, the FDA has determined that a Medication Guide is required for Vilazodone HCl tablets. FDA has determined that vilazodone HCl poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of vilazodone. FDA has determined that vilazodone HCL tablets is a product for which patient labeling could help prevent serious adverse effects and that the Medication Guide is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

The elements of the REMS will be a Medication Guide and a timetable for submission of assessments of the REMS.

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WILLIAM H BENDER  
01/04/2011

ELLIS F UNGER  
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