



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022567

NDA APPROVAL

Trovis Pharmaceuticals LLC
Attention: Kimberly Fabrizio
Vice President, Regulatory Affairs
Five Science Park
New Haven, CT 06511

Dear Ms. Fabrizio:

Please refer to your New Drug Application (NDA) dated March 22, 2010, received March 22, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Viibryd (vilazodone hydrochloride) 10 mg, 20 mg, and 40 mg tablets.

We acknowledge receipt of your amendments dated May 4, 2010, May 7, 2010, May 18, 2010, May 19, 2010, May 25, 2010, June 3, 2010, June 8, 2010, June 30, 2010, August 4, 2010, August 19, 2010, August 23, 2010, August 31, 2010, September 27, 2010, November 4, 2010, November 18, 2010, November 30, 2010, December 3, 2010, December 13, 2010, December 15, 2010, December 23, 2010, December 29, 2010, January 4, 2011, January 6, 2011, January 7, 2011, January 11, 2011, and January 13, 2011.

This new drug application provides for the use of Viibryd (vilazodone hydrochloride) for the treatment of Major Depressive Disorder.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels as agreed upon in our January 14, 2011 communication as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 22567.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for vilazodone was not referred to an FDA advisory committee because this drug is not the first in its class, and the safety profile is similar to that of other drugs approved for this indication.

PROPRIETARY NAME

The Division of Medication Error and Prevention and Analysis (DMEPA) and the Division of Psychiatry Products do not object to the use of the proprietary name, Viibryd, for this product.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 6 years old in the treatment of major depressive disorder, because studies are highly impractical due to the low prevalence of this disorder in this age range.

We are deferring submission of your pediatric studies for ages 7 to 17 years old in the treatment of major depressive disorder, because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

- 1723-1 Deferred pediatric study under PREA for the treatment of major depressive disorder in pediatric patients aged 7 to 17. Conduct a study to obtain pharmacokinetic, safety, and tolerability data and provide information pertinent to dosing of vilazodone in the relevant pediatric population.

Final Protocol Submission Date: January 31, 2012
Study Completion Date: February 28, 2013
Final Report Submission: January 31, 2016

- 1723-2 Deferred pediatric study under PREA for the treatment of major depressive disorder in pediatric patients aged 7 to 17. Conduct a study to obtain data on the efficacy and safety of vilazodone in the relevant pediatric population. This must be a placebo-controlled and active-controlled (fluoxetine) study. This study must be a fixed-dose study.

Final Protocol Submission Date: May 31, 2013
Study Completion Date: July 31, 2015
Final Report Submission: January 31, 2016

- 1723-3 Deferred pediatric study under PREA for the treatment of major depressive disorder in pediatric patients aged 7 to 17. Conduct a second study to obtain data on the efficacy and safety of vilazodone in the relevant pediatric population. This must be a placebo-controlled and active-controlled (fluoxetine) study. This study may be a fixed-dose study.

Final Protocol Submission Date: May 31, 2013
Study Completion Date: July 31, 2015
Final Report Submission: January 31, 2016

- 1723-4 To support the use of vilazodone in children less than 13 years of age, you must conduct a study to assess the safety of vilazodone in juvenile rats. This study must include evaluation of neurological/behavioral development and reproductive development. You should submit the protocol for our comments prior to initiating the study.

Final Protocol Submission Date: January 30, 2012

Study Completion Date:	January 30, 2014
Final Report Submission:	January 30, 2015

Submit final reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated “**Required Pediatric Assessment(s).**”

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

The major human metabolite of vilazodone, M17, was not demonstrated to be present in plasma of either rats or rabbits. Therefore the embryo-fetal reproductive toxicity studies with vilazodone did not adequately assess the potential reproductive toxicity of M17.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the reproductive toxicity of the major human metabolite M17.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA is not yet sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 1723-5 Assess the reproductive toxicity of metabolite M17 by conducting an embryo-fetal study in either rats or rabbits in which M17 is administered by a route that will produce systemic exposure equal to or greater than the exposure in humans at the maximum recommended human dose (MRHD).

The timetable, as agreed upon on a January 19, 2011 communication, states that you will conduct this study according to the following schedule:

Final Protocol Submission Date:	Not applicable
Study Completion Date:	November 30, 2012
Final Report Submission:	January 31, 2013

- 1723-6 Assess the reproductive toxicity of metabolite M17 by demonstrating that the original rabbit study was adequate to assess the embryo-fetal toxicity of M17. This will require data demonstrating that the systemic exposure to M17 in rabbits in that study was equal to or greater than that in humans at the MRHD.

The timetable, as agreed upon on a January 19, 2011 communication, states that you will conduct this study according to the following schedule:

Final Protocol Submission Date:	Not applicable
Study Completion Date:	November 30, 2012
Final Report Submission:	January 31, 2013

If you are able to address postmarketing study 1723-6 adequately through analyses of existing data, FDA may release you from postmarketing study 1723-5.

Submit the protocol to your IND 54613, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o),” “Required Postmarketing Final Report Under 505(o),” “Required Postmarketing Correspondence Under 505(o).”**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii), requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments agreed upon in your communications dated January 19, 2011:

1723-7	A controlled trial to evaluate the longer-term (i.e., maintenance) efficacy of vilazodone in the treatment of adults with major depressive disorder. This trial must be placebo-controlled, utilize a randomized withdrawal design, and include an adequate period of stabilization with open-label treatment of vilazodone prior to double-blind randomization.
--------	--

Final Protocol Submission:	September 30, 2011
Trial Completion Date:	January 31, 2015
Final Report Submission:	January 31, 2016

1723-8 It is not apparent from the trials you have conducted in major depressive disorder that the lowest effective dose of vilazodone has been identified, because only one dose (40 mg/day) was studied. However, there are suggestions that 20 mg/day may be effective at least in some subjects. In one of the trials, those who did not tolerate 40 mg/day could continue in the trial on a dose of 20 mg/day, and some may have had a significant treatment effect. In addition, data from the phase 2 fixed-dose trials suggest that there may have been a signal of efficacy with the 20 mg/day dose, as measured by the secondary efficacy measure (MADRS). Moreover, some important adverse reactions are dose-related. Thus, we request that you further characterize the efficacy and safety of vilazodone in the treatment of adults with MDD using fixed doses of vilazodone (20 mg and 40 mg), an active control (for assay sensitivity), and placebo in an adequate and well controlled trial.

Final Protocol Submission: October 31, 2011
Trial Completion: January 31, 2013
Final Report Submission: January 31, 2014

1723-9 Vilazodone is metabolized primarily by CYP3A4. You have not submitted information on the potential effect of CYP3A4 induction on vilazodone exposure. We request that you conduct a drug-drug interaction trial of vilazodone using a CYP3A4 inducer (carbamazepine) in healthy subjects.

Final Protocol Submission: July 31, 2011
Trial Completion: July 31, 2012
Final Report Submission: January 31, 2013

1723-10 Vilazodone is extensively metabolized; however, the pharmacokinetics of vilazodone in patients with severe hepatic impairment has not been assessed. We request that you conduct a Phase 1 trial to evaluate the pharmacokinetics of vilazodone in patients with severe hepatic impairment.

Final Protocol Submission: July 31, 2011
Trial Completion: July 31, 2012
Final Report Submission: February 28, 2013

1723-11 Information on the effect of PgP on the pharmacokinetics of vilazodone and the effect of vilazodone on PgP was not submitted. We request that you conduct an *in vitro* study to evaluate whether vilazodone is a substrate or inhibitor of PgP.

Final Protocol Submission: July 31, 2011
Study Completion: September 30, 2011
Final Report Submission: December 31, 2011

Submit clinical protocols to your IND 54613 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under

21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

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)]. The details of the REMS requirement were outlined in our REMS notification letter dated November 1, 2010.

Your proposed REMS, submitted on December 15, 2010, and appended to this letter, is approved. The REMS consists of a Medication Guide and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include, but is not limited to, the following:

- a. An evaluation of patients’ understanding of the serious risks of Viibryd (vilazodone hydrochloride) Tablets.
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to

the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 22567 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 22567
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 22567
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

Please submit one market package of the drug product when it is available.

DISSOLUTION METHOD AND SPECIFICATIONS

The dissolution method test conditions for all tablet strengths (10 mg, 20 mg, and 40 mg) are as follows:

USP Apparatus: 2 (Paddle) x 60 rpm

Medium: 0.1% Acetic Acid (pH 3.1), 1000 mL at 37°C

Specifications: Q= (b) (4) at 30 min

EXPIRY DATE

A 24 month expiry date is granted based on the available stability data.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at

<http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, email CDR Bill Bender, Senior Regulatory Project Manager, at william.bender@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ellis Unger, M.D.
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:

Content of Labeling
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLIS F UNGER
01/21/2011