CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-400

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-400

Bayer Corporation
Attention: Mary Taylor, M.P.H.
Vice President, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

Dear Ms. Taylor:

Please refer to your new drug application (NDA) dated September 24, 2001, received September 24, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levitra® (vardenafil hydrochloride) tablets.

We acknowledge receipt of your submissions dated February 17, April 1 and 29, and May 1, 13 and 16, and August 14 and 19, 2003. The February 17, 2003 submission constituted a complete response to our July 23, 2002 action letter.

This new drug application provides for the use of Levitra® (vardenafil hydrochloride) tablets for the treatment of erectile dysfunction in men.

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

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product a misbranded and unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-400.**" Approval of this submission by FDA is not required before the labeling is used.

We remind you of the postmarketing study commitments you made in a teleconference held on August 19, 2003. The commitments are listed below:

1. To conduct a study to evaluate the impact on QT interval prolongation of combining LEVITRA with another drug with a similar QT effect size.

The timeline is as follows:

Protocol Submission	within six months of the date of this letter
Study Initiation	within 12 months of the date of this letter
Final Report Submission	within 20 months of the date of this letter

2. To conduct study(ies) to evaluate the pharmacokinetic/pharmacodynamic drug-drug interaction between LEVITRA 2.5mg and alpha-blockers used for BPH.

The timeline is as follows:

Protocol Submission	within six months of the date of this letter
Study Initiation	within 12 months of the date of this letter
Final Report Submission	within 20 months of the date of this letter

3. To conduct a study to evaluate the pharmacokinetic/pharmacodynamic drug-drug interaction between LEVITRA and the alpha-blocker alfuzosin.

The timeline is as follows:

Protocol Submission	within six months of the date of this letter
Study Initiation	within 12 months of the date of this letter
Final Report Submission	within 20 months of the date of this letter

4. To conduct a study to provide data to support labeling for the quantitative effects of LEVITRA on retinal function following repeat dosing of LEVITRA.

The timeline is as follows:

Protocol Submission	within six months of the date of this letter
Study Initiation	within 12 months of the date of this letter
Final Report Submission	within 20 months of the date of this letter

In addition, we request that you consider sharing the data from your QT studies, including Trial # 10929, with other sponsors who are either marketing or developing drugs in the phosphodiesterase type 5 inhibitor class.

Submit clinical protocols to your IND for this product 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 the 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 number of patients entered into each study. All submissions, including supplements, relating to this postmarketing study commitment must be prominently labeled "**Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you have any questions, please call Eufrecina DeGuia, Regulatory Health Project Manager at (301) 827-4260.

Sincerely,

/S/

{See appended electronic signature page}

Florence Houn, M.D., M.P.H.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Physician Insert
Patient Package Insert

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-400

Approvable Letter (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-400

Bayer Corporation
Attention: Gautam Shah, Ph.D.
Deputy Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

Dear Dr. Shah:

Please refer to your new drug application (NDA) dated September 24, 2001, received September 24, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levitra™ (vardenafil hydrochloride) Tablets.

We acknowledge receipt of your submissions dated September 28 and December 7, 2001, January 17, 25 and 31, February 5, April 15, 18 and 23, May 21, 24, June 3, 6(3), 10, 18(2), 25 and 26, July 8(2) and 10, 2002.

This application proposes the use of Levitra™ for treatment of erectile dysfunction (ED). We have completed our review and find that your application, as amended, for marketing of Levitra™ 2.5 mg, 5 mg, 10 mg, and 20 mg, is approvable.

The Agency believes that use of the lowest effective dose of Levitra™ will support safety. For certain groups of patients, including those taking concomitant medications that inhibit cytochrome P450 3A4, the 2.5 mg dosage strength will be needed.

Before the application may be approved, it will be necessary for you to address the following clinical deficiencies:

1. QT interval prolongation may be a signal for life-threatening cardiac adverse events. Levitra™ has known drug interactions that significantly increase systemic exposure to the parent drug. Therefore, it is important to rule out QT interval prolongation due to Levitra™. Although your application contains results from studies that evaluated the effect of Levitra™ on the QT interval, this information is insufficient to conclude that Levitra™ has no significant effect on the QT interval at the approvable doses for marketing and at systemic vardenafil exposures that result from expected drug interactions. More clinical information is needed to ensure that there is no QT prolonging effect.

   The following information is needed to address this deficiency:

   Conduct clinical studies that characterize the vardenafil plasma concentration-response relationship for QTc interval prolongation and that also evaluate the degree of QTc prolongation at plasma concentrations following maximal potential interaction between Levitra™ and CYP 3A4 inhibitors. These studies must be randomized and double-blinded, and must include a placebo control. An

additional active concurrent control group is desirable. The studies must include a sufficient number of patients to provide reliable results. The doses of Levitra™ to be used must be appropriate to evaluate the degree of QTc interval prolongation at therapeutic concentrations, at supratherapeutic concentrations, and at concentrations that follow maximal potential interaction between Levitra™ and CYP 3A4 inhibitors. We recommend that you submit your proposed plan and protocol(s) for meeting these objectives so that the Divisions of Reproductive and Urologic Drug Products (DRUDP) and Cardio-Renal Drug Products (DCRDP) can assess the acceptability of the protocol to fulfill this requirement.

2. Patient #10125-110-090 reported fainting on the same day as taking Levitra™ and concomitant terazosin. Patient #10029-044-057 reported syncope one day after his last dose of terazosin and on the same day as taking Levitra™. It is expected that many men who seek treatment with Levitra™ for ED will require concomitant treatment for symptoms of benign prostatic hypertrophy (BPH), and vice versa. Your application contains no information that specifically evaluates the pharmacodynamic interaction between any alpha-blocker used for BPH and Levitra™.

   The following information is needed to address this deficiency:

   Provide data from drug-drug interaction studies to support labeling for the concomitant use of Levitra™ at the maximal to-be-marketed dosage strength and an alpha-blocker used for BPH, such as doxazosin mesylate.

For approval of the 20 mg dosage strength of Levitra™:

3. We agree that the use of Levitra™ should be contraindicated for patients on continuous or intermittent nitrate therapy. However, it is expected that men with cardiovascular disease will use Levitra™. Some of these men will experience cardiovascular events and will be given nitrates in emergency situations. Therefore, you must provide information to label the effects on blood pressure of the combination of nitroglycerin plus Levitra™ for that period of time after Levitra™ dosing until no blood pressure interaction is seen. Your application already contains such information for the 10 mg dosage strength but does not for the maximal dose you propose to market (20 mg).

   The following information is needed to address this deficiency:

   For approval of the 20 mg dose, you must conduct a study in patients treated with doses of Levitra™ of 20 mg or higher with administration of nitrates at various times following the dose of Levitra™ to determine at what point after Levitra™ dosing there is no apparent blood pressure interaction. This study should include elderly subjects (who may have higher exposure than younger patients). The basic trial design of your previous Levitra™ 10 mg – nitrate interaction study is acceptable.

   We remind you that for the approval of Levitra™ at any dosage strength, you must also propose a plan for patient and physician education regarding nitrate contraindication and nitrate interaction.

4. Levitra™ can affect phosphodiesterase Type 5 in platelets. Platelet function is affected by aspirin. There is a potential for pharmacodynamic interaction between aspirin and Levitra™. You have already provided information that indicates no clinically meaningful pharmacodynamic interaction between

aspirin and Levitra™ 10mg. However, you have not done so for the maximal dose you propose to market (20mg).

The following information is needed to address this deficiency:

For approval of the 20 mg dose, you must provide data from a drug-drug interaction study to support labeling regarding interactions of Levitra™ 20 mg and aspirin.

For approval of the 2.5 mg dosage strength of Levitra™:

5. Because the 2.5 mg dosage strength will be needed for safe use in certain groups of patients, you must submit chemistry, manufacturing and controls information to support approval of the 2.5 mg strength. This must include manufacturing information on three (3) batches with accompanying stability data in the proposed market container closure system. This information may be submitted with three months accelerated and room temperature data with a commitment to update the stability data with an additional three (3) months of data when available. However, if the formulation and manufacturing process differ significantly from the 5, 10, and 20 mg strengths, more stability data will be necessary to establish an acceptable shelf life.

For all your new and ongoing clinical studies of Levitra™:

6. Significant back pain was reported by subjects administered Levitra™ 40mg twice daily in one clinical pharmacology trial. The etiology of back pain in this setting is unclear. So far, your evaluation of this adverse event has not revealed significant underlying pathology. Additional information to rule out medically significant underlying pathology in any patient reporting back pain or myalgia in new or ongoing studies is required.

   The following information is needed to address this deficiency:

   You must collect and submit additional information from patients who report "myalgia" and/or "back pain" as adverse events in ongoing and new clinical trials, especially those studies utilizing higher doses or higher systemic exposures of Levitra™. Medical evaluations of these patients should be comprehensive, including assessments meant to rule out vasculitis, rhabdomyalysis, and other inflammatory processes.

We recommend that you contact DRUDP to obtain agreement on how you plan to address the following deficiency:

7. Levitra™ can inhibit phosphodiesterase Type 6 in the retina as evidenced by color visions changes in controlled studies and clinical adverse event reports in Phase 3 trials. Minimal information was submitted in the final study reports for Studies #100196 and 10197.

   The following information is needed to address this deficiency:

   Provide data for labeling the quantitative effects of Levitra™ on retinal function following repeat

dosing with Levitra™. We recommend that you submit your proposed protocol(s) so that DRUDP and the Division of Anti-Inflammatory, Analgesic, and Opthalmological Drug Products (DAAOP) can assess the acceptability of the protocol to fulfill this requirement.

Comments on labeling are deferred until the above deficiencies are addressed.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   - Present tabulations of the new safety data combined with the original NDA data.

   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock

be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with the Division of Reproductive and Urologic Drug Products to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please call Eufrecina DeGuia, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Florence Houn
7/23/02 01:21:51 PM