

ADMINISTRATIVE REVIEW OF NDA (review pkg)
OFFICE OF DRUG EVALUATION III

NDA: 21-400
 Drug: Levitra (vardenafil HCl) Tablets
 Classification: '1 S
 Sponsor: Bayer Corporation
 Project Manager/CSO: Freshnie DeGuia

Reviewer: Bronwyn Collier, ADRA ODE III
 Review Date: August 18, 2003

Review Cycle 1

Date Submitted: September 24, 2001
 Date Received: September 24, 2001
 Action: approvable July 23, 2002

Review Cycle 2

Date Submitted: February 17, 2003
 Date Received: February 19, 2003
 Goal Date: August 19, 2003
 Proposed Action: approval

	CONFORMS TO REGS & CDER POLICY	COMMENTS
ACTION LETTER	X	
EXCLUSIVITY CHECKLIST	X	completed, needs to be checked into DFS and signed
DEBARMENT STATEMENT	X	
PEDIATRIC PAGE	X	completed, needs to be checked into DFS and signed
TRADE NAME REVIEW	X	
DSI AUDITS	X	
FACILITY INSPECTIONS	X	

REVIEWS	COMPLETED	COMMENTS
DIV. SUMMARY REVIEW		pending
CLINICAL	X	in draft
SAFETY UPDATE	X	included in clinical review
FINANCIAL DISCLOSURE	X	

STATISTICAL	X	
BIOPHARM	X	in draft
CMC	X	
EA	X	see CMC review #1 for acceptance of categorical exclusion
MICRO (validation of sterilization)		not applicable
STABILITY (stats)		included in CMC review
PHARM/TOX	X	completed 1 st review cycle
CAC (stats)	X	completed 1 st review cycle
CAC/ECAC REPORT	X	completed 1 st review cycle

Labeling: negotiations ongoing
 Postmarketing Commitments: none
 Advisory Committee Meeting: none

Comments:

- Division summary review and draft documents must be completed and finalized prior to taking an action.

APPROVED
 ON ORIGINAL

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/s/

Bronwyn Collier
8/18/03 01:25:41 PM
CSO

Division of Reproductive and Urologic Drug Products (HFD-580)

ADMINISTRATIVE REVIEW OF APPLICATION

Application Number: **NDA 21-400**

Name of Drug: **varденаfil hydrochloride**

Sponsor: **Bayer Corporation**

Material Reviewed:

Submission Date: **September 24, 2001**

Receipt Date: **September 24, 2001**

Filing Date: **November 23, 2001**

User-Fee Goal Date(s): **July 24, 2002 (primary); September 24, 2002 (secondary)**

Proposed Indication: **erectile dysfunction**

Other Background Information: **This NDA is a full electronic submission.**

Regulatory Project Manager Review

PART I: OVERALL FORMATTING^a and REGULATORY REQUIREMENTS

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Cover Letter (original signature)	x		
2. Form FDA 356h (original signature)	x		
a. Reference to DMF(s) & Other Applications			See Chemistry Reviewer's Filing Memo.
3. Patent information & certification	x		
4. Debarment certification (note: must have a definitive statement)	x		
5. Financial Disclosure	x x		

6. Comprehensive Index	x		Electronic submission
7. Pagination	x		Electronic submission
8. Has the applicant submitted a complete Environmental Assessment, that addresses 21 CFR 25.31 or provided a request for categorical exclusion under 21 CFR 25.24?		x	
9. On its face, is the NDA legible?	x		
10. Has the sponsor submitted all special Studies/ data requested during Presubmission discussions?	x		
11. Does the application contain a statement that all nonclinical laboratory studies were conducted in compliance with Part 58 or a statement why it has not complied?	x		
12. If required, has the applicant submitted carcinogenicity studies?	x		
13. On its face, does the application contain at least two adequate and well-controlled clinical trials?	x		
14. Does the application contain a statement that all clinical trials were conducted in accord with the IRB/Declaration of Helsinki provisions of the CFR?	x		
15. Have all articles/ study reports been submitted either in English or translated into English?	x		
16. Summary Volume	x		Section 3
17. Review Volumes			
18. Labeling (PI, container, & carton labels)	x		
a. unannotated PI	x		
b. annotated PI			
c. immediate container	x		
d. carton	x		
e. foreign labeling (English translation)		x	

19. Foreign Marketing History	x	
20. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	x	Section 11
21. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	x	Section 12

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY^b

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	x		
2. Summary of Each Technical Section	x		
a. Chemistry, Manufacturing, & Controls (CMC)	x		Section 4
b. Nonclinical Pharmacology/Toxicology	x		Section 5
c. Human Pharmacokinetic & Bioavailability	x		Section 6
d. Microbiology		x	N/A
e. Clinical Data & Results of Statistical Analysis	x		
3. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	x		
4. Summary of Safety	x		
5. Summary of Efficacy	x		

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS^c

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. List of Investigators	x		
2. Controlled Clinical Studies	x		
a. Table of all studies	x		
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	x		
c. Optional overall summary & evaluation of data from controlled clinical studies	x		
3. Integrated Summary of Efficacy (ISE)	x		
4. Integrated Summary of Safety (ISS)	x		
5. Drug Abuse & Overdosage Information	x		
6. Integrated Summary of Benefits & Risks of the Drug	x		
7. Gender/Race/Age Safety & Efficacy Analysis Studies	x		

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population			Pediatric Study Waiver Request
2. Diskettes			NDA is full electronic submission.
a. Proposed unannotated labeling in MS WORD 8.0	x		
b. Stability data in SAS data set format	x		
c. Efficacy data in SAS data set format	x		
d. Biopharmacological information & study summaries in MS WORD 8.0		x	
e. Animal tumorigenicity study data in SAS data set format	x		
3. User-fee payment receipt	x		User Fee # 4168

Y=Yes (Present), N=No (Absent)

^a"GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987) and 21 CFR 314.100(d)

^b"GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

^c"GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

Additional Comments:**Conclusions: This NDA is fileable.**

Eufrecina DeGuia

November 23, 2001

Regulatory Health Project Manager

cc:

Original NDA

HFD-580/Div. Files

ADMINISTRATIVE REVIEW

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/s/

Eufrecina deGuia
7/17/02 09:36:44 AM
CSO

Eufrecina deGuia
7/17/02 09:39:21 AM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 4, 2003

TO: Daniel Shames, M.D., Director
Division of Reproductive and Urologic Drug Products, HFD-580

FROM: Office of Drug Safety
Division of Drug Risk Evaluation, HFD-430
Division of Surveillance, Research and Communication Support, HFD-410
Division of Medication Errors and Technical Support, HFD-420

SUBJECT: PID# D030396
Drug: vardenafil (Levitra), Bayer
NDA - 21400
Topic: Risk Management Plan

EXECUTIVE SUMMARY: The first phosphodiesterase type 5 (PDE5) inhibitor on the market (sildenafil – Viagra, Pfizer) was approved by the FDA in March of 1998. Vardenafil (Levitra) manufactured by Bayer (the Sponsor) is a new member of the class of PDE5 inhibitors for the treatment of male erectile dysfunction and has not yet been approved in the United States. In February 2003 the sponsor for vardenafil submitted a patient package insert (PPI) and a risk management plan (RMP) to provide an overview of their strategies to assess known safety issues associated with PDE5 inhibitors and to identify any new safety issues arising following the launch of vardenafil.^{1,2} The Division of Surveillance, Research, and Communication Support (DSRCS) completed the review of the proposed PPI in June 2003.³ Subsequently, the Division of Reproductive and Urologic Drug Products (DRUDP) requested a review of the risk management plan for vardenafil in July 2003. For the purpose of this review we compared the overall structure of the RMP with the essential elements contained in the FDA's draft concept paper *Risk Management Programs*.⁴ In addition, we compared concerns associated with vardenafil and class effects of PDE5 inhibitors to the risks highlighted by the Sponsor in the RMP.^{5,6,7}

¹ Bayer Corporation, Package insert (PI) and Patient package insert (PPI) for Levitra, submitted to FDA, February 17, 2003.

² Bayer Corporation, "Vardenafil Risk Management Plan", *Risk/Benefit Consideration*, submitted to FDA, February 17, 2003; Sec. 6.1-6.5, pp. 35-40.

³ Jeanine Best, ODS/DSRCS Review of Patient Labeling for Levitra (vardenafil HCL) tablets, June 19, 2003.

⁴ *Concept Paper: Risk Management Programs* published in the Federal Register and available on CDER intranet: <<http://www.fda.gov/cder/meeting/riskManagemII.htm>>, March 3, 2003.

⁵ Bayer Corporation, "Risks of Vardenafil", *Risk/Benefit Consideration*, submitted to FDA, February 17, 2003; Sec. 4.0-4.9, pp. 7-31.

⁶ Wysowski DK, Sexually-transmitted diseases and use of sildenafil (Viagra), February 19, 2002.

⁷ Kahan SE, Seftel AD, Resnick MI. Sildenafil and the Internet. *J Urol.* 2000;163(3):919-23.

DRUDP and the Office of Drug Safety (ODS) expressed particular concern about the following:

- hypotensive effects of vardenafil (particularly if co-administered with nitrates or alpha-blockers).
- use of vardenafil in patients with underlying cardiovascular conditions, which may increase the risk of cardiovascular events (such as myocardial infarction, arrhythmias, or stroke).
- effects on cardiac repolarization leading to QTc prolongation (particularly if co-administered with cytochrome P450 3A4 hepatic enzyme inhibitors that can increase vardenafil plasma levels).
- use in patients who obtain vardenafil from a friend or directly from Internet websites and bypass the "safety screen" of physician-patient discussion of risks.

Other concerns include: drug interactions with cytochrome P450 hepatic enzyme inhibitors that can increase vardenafil plasma levels and increase adverse events, lack of protection against sexually transmitted diseases, risk of priapism, and the use of vardenafil in patients with retinitis pigmentosa, a rare genetic eye disease.⁸

The Sponsor has proposed additional postmarketing surveillance for PDE5 inhibitor class effects and a multifaceted approach to communicate the nitrate contraindication to both patients and health care providers, primarily by including the contraindication in vardenafil promotional vehicles. As part of postmarketing surveillance, the Sponsor will be using two databases to identify cohorts of vardenafil users and to calculate the incidence of selected cardiovascular and ocular adverse events among these men, compared to cohorts of men using sildenafil. The RMP also describes, in brief, another proposed large observational study of 30,000 adult male patients with erectile dysfunction to collect data on safety, efficacy, and patient acceptance of vardenafil treatment under daily life conditions.

In contrast to concerns associated with vardenafil and class effects of PDE5 inhibitors, the Sponsor has only focused on the reduction of risk associated with co-administration of vardenafil with nitrates. The Sponsor has not specified whether emergency room health care providers or cardiologists will be targeted with information about the nitrate contraindication. In addition, the plan put forth by the Sponsor does not mention QTc prolongation as a risk. The risk of patients obtaining vardenafil via the Internet or by other illicit means and bypassing the "safety net" of physician-patient discussion is also not addressed in the RMP. Furthermore, the risks of vardenafil administered with alpha-blockers or to patients with certain underlying cardiovascular conditions are not communicated beyond the PI and PPI. Conditions or outcomes that would lead to revising the proposed plan are not included. There is no clear plan to evaluate the effects of the RMP.

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⁸ Vardenafil can inhibit both PDE5 and PDE6. PDE6 is found in high concentrations in the retina and may adversely affect patients with retinitis pigmentosa.

Recommendations:

- A. Health care providers: The multifaceted educational plan should include more than just information on the nitrate contraindication and should target all potential prescribers of vardenafil, alpha-blockers and nitrates (i.e. urologists, general/family practitioners, internists, osteopaths, physician's assistants, nurse practitioners, cardiologists). Nurses, emergency room medical staff, and paramedics also need to be aware of risks associated with vardenafil. The multifaceted educational plan should include information on the following:
- ◆ Drug interactions with nitrates, alpha-blockers, and cytochrome P450 hepatic enzyme inhibitors.
 - ◆ Recommendations for patients with underlying cardiovascular conditions, patients at increased risk for QTc prolongation, and patients with retinitis pigmentosa.
 - ◆ Hypotensive effects of vardenafil.
 - ◆ How to manage patients treated with vardenafil that may need nitrates to be administered in a cardiac emergency. (A Dear Health Care Provider letter at launch time containing this information to emergency room health care providers is suggested.)
- B. Patients: The multifaceted educational plan should include more than just information on the nitrate contraindication. The educational plan should use tools that will communicate risks to patients who may obtain vardenafil directly from the Internet or by other illicit means. The plan should include information on the following:
- ◆ Drug interactions with nitrates, alpha-blockers, and cytochrome P450 hepatic enzyme inhibitors.
 - ◆ Recommendations for patients with underlying cardiovascular conditions, congenital QTc prolongation, retinitis pigmentosa.
 - ◆ Cardiac risk associated with sexual activity.
 - ◆ Risk of hypotension.
 - ◆ Signs and symptoms of QTc prolongation such as fainting or palpitations.
 - ◆ Risk of priapism, including the signs and symptoms of priapism.
 - ◆ Lack of protection against sexually transmitted diseases.
 - ◆ Risk of taking vardenafil with other medicines or treatments for erectile dysfunction.
 - ◆ Risk of giving vardenafil to friends/other people.
- C. It is recommended that the Sponsor submit promotional and educational materials to the FDA for review to assure that risks have been adequately addressed. The Sponsor submitted a Patient Package Insert (PPI) separately from the RMP in February, 2003 however it is not clear if the Sponsor intends to use a PPI as a patient educational tool, since the RMP does not specifically mention it.

D. Postmarketing surveillance:

- ◆ Issues of insurance coverage and payment for erectile dysfunction drugs and their anticipated impact on study validity should be clearly addressed by the Sponsor in relation to all databases (U.S. and U.K.) used to study adverse outcomes associated with these therapies.
- ◆ For the other proposed large observational study of 30,000 patients with erectile dysfunction it is imperative that follow-up be ascertained on all enrolled patients issued vardenafil, since death / myocardial infarction is a potential side effect of therapy. Clinician review of the patient questionnaire with the patient is recommended for critical subject areas, such as typical and atypical symptoms of angina.
- ◆ In addition, changes to the questionnaire to allow greater readability and better phrasing of questions and possible answers are recommended. The questionnaire should be pre-tested.
- ◆ An explanation of how the additional postmarketing surveillance and studies will translate to evaluation of the RMP's effectiveness, and timeline for communication of the results to the FDA is recommended.

INTRODUCTION/BACKGROUND: The first phosphodiesterase type 5 (PDE5) inhibitor on the market (sildenafil – Viagra by Pfizer) was approved by the FDA in March of 1998. Vardenafil (Levitra by Bayer) is a new member of the class of PDE5 inhibitors for the treatment of male erectile dysfunction and has not yet been approved in the United States. Vardenafil has a similar side effect profile to sildenafil, and has a similar half-life (5 hours). The NDA received an approvable action on July 23, 2002.⁹

In February 2003 the sponsor for vardenafil submitted a patient package insert (PPI) and a risk management plan (RMP) to provide an overview of their strategies to assess known safety issues associated with PDE5 inhibitors and to identify any new safety issues arising following the launch of vardenafil.^{1,2} DSRCS completed the review of the proposed Patient Package Insert (PPI) on June 19, 2003.³ The Division of Reproductive and Urologic Drug Products (DRUDP) requested a review of the RMP for vardenafil on July 2, 2003. This review contains input from three divisions in the Office of Drug Safety: Division of Drug Risk Evaluation (DDRE), Division of Surveillance, Research, and Communication Support (DSRCS), and Division of Medication Errors and Technical Support (DMETS).

For the purpose of this review we compared 1) the structure of the RMP to the basic RMP elements outlined in the draft concept paper *Risk Management Programs*⁴ and 2) the risks highlighted in the RMP to concerns associated with vardenafil and PDE5 inhibitors.^{5,6,7}

⁹ Florence Houn, Approvable letter to Bayer Corporation, July 23, 2002.

1) A draft concept paper *Risk Management Programs* as generated for the CDER/CBER Risk Management Public Workshop, April 9-11, 2003 and published in the Federal Register is available from the CDER website.⁴ The concept paper represents FDA's preliminary thoughts on risk management programs and defines a risk management program as "a strategic safety program designed to decrease product risk by using one or more interventions or tools beyond the package insert." The paper further describes desired elements of a risk management program submission, which include:

- I. **Background of the overall risk reduction goals(s) and rationale for the planned approach**
- II. **Targeted goals and objectives**
- III. **One or more proposed tools beyond the package insert with a rationale and implementation plan for each**
- IV. **An evaluation plan detailing the analyses that will be conducted and plan for reporting the evaluation results to FDA**

2) Based on the clinical trials submitted in the NDA for vardenafil and known class effects of PDE5 inhibitors, DRUDP expressed particular concern about the following risks:

- co-administration of vardenafil with nitrates - may lead to a sudden drop in blood pressure. There was a tendency for reports of dizziness and hypotension in clinical trials with 4 or 1 hour dosing separation of vardenafil with nitroglycerin.
- co-administration of vardenafil with alpha-blockers - may lead to a sudden drop in blood pressure. Symptomatic hypotension was observed in clinical trials in some subjects treated with 10mg and 20mg of vardenafil when dosed with an alpha-blocker.
- hypotensive effects - vardenafil alone may cause a drop in blood pressure. In clinical trials, blood pressure was lower on vardenafil than on placebo (in healthy volunteers: mean maximum changes in supine systolic and supine diastolic were -7mmHg and -8mmHg lower than placebo respectively).
- use of vardenafil in pts with cardiovascular history - use of PDE5 inhibitors may increase the risk for cardiovascular adverse events such as myocardial infarction, arrhythmias and stroke.
- effects on cardiac repolarization - in clinical trials vardenafil was found to cause a mean ECG QTc interval prolongation of 10 msec; the concern is QTc prolongation (particularly if co-administered with cytochrome P450 3A4 hepatic enzyme inhibitors that can increase vardenafil plasma levels) may lead to polymorphic ventricular tachycardia (torsade de pointes), a potentially fatal arrhythmia.

In addition, ODS has expressed concerns about patients obtaining vardenafil directly from Internet websites selling erectile dysfunction drugs or by other illicit means (e.g. from a friend/another person). These websites may not convey the risks properly or effectively. This bypasses the "safety screen" of discussion between the patient and his physician to determine if treatment with vardenafil is appropriate.

Other concerns regarding vardenafil include: drug interactions with cytochrome P450 hepatic enzyme inhibitors that can increase vardenafil plasma levels and increase adverse events, lack of protection against sexually transmitted diseases, potential for priapism, and use in patients with retinitis pigmentosa.⁸

PLAN BY SPONSOR TO MANAGE IDENTIFIED RISKS AND ODS

COMMENTS/RECOMMENDATIONS: *ODS recommendations are presented in italics.*

I. Background of the overall risk reduction goals(s) and rationale for the planned approach:

The plan states "proper education in the appropriate use of vardenafil in patients with cardiovascular diseases who frequently have concomitant cardiovascular drug treatments will be implemented to minimize the risk of adverse events." The RMP stated objective is to prevent the co-prescription of vardenafil and nitrates.

The plan will provide additional surveillance measures for general class effects with PDE5 inhibitors. The purpose of the plan is to assess known safety issues with PDE5 inhibitors and to identify any new issues arising following the launch of vardenafil.

In this case the plan to use appropriate education for patients who "frequently have concomitant cardiovascular drug treatments to minimize the risk of adverse events" implies that the Sponsor will caution patients on only one specific issue: the nitrate contraindication. No goals or objectives for other risks were submitted, including co-administration with alpha-blockers. Alpha-blockers are also "concomitant cardiovascular drug treatments" that have been shown to cause symptomatic hypotension when given with vardenafil. Reducing this risk and the other risks associated with vardenafil and PDE5 inhibitors (such as reducing risks for patients buying vardenafil on the Internet) should be part of the goals of the RMP.

II. Targeted goals and objectives:

The RMP only stated objective is to prevent the co-prescription of vardenafil and nitrates.

Conditions or outcomes that would lead to revising the proposed plan for preventing co-administration of vardenafil and nitrates should be included.

III. Proposed tools; Rationale and Implementation plans for each:

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IV. An evaluation plan detailing the analyses that will be conducted and plan for reporting the evaluation results to FDA:

Postmarketing surveillance:

Following its release into the marketplace, the Sponsor will monitor vardenafil's adverse event database biweekly with "special attention" focused on serious and unexpected adverse events, cardiovascular events, cerebrovascular events, ECG abnormalities, arrhythmias, ocular events, myopathy, and events occurring as a consequence of a drug interaction.

Periodic Safety Update Reporting: Updates of the safety profile of vardenafil will periodically be reported to the FDA.

Use of health care databases in U.S. and U.K.: The sponsor states that two studies are already in progress to quantify the frequency of risk factors and adverse events in sildenafil users in the period immediately prior to the launch of vardenafil.

The first of these studies is a U.S.-based, retrospective, matched-cohort study of cardiovascular and ocular outcomes among men with at least one paid prescription claim for sildenafil using administrative claims data from the _____ The objective of the study is to calculate the incidence of myocardial infarction, coronary revascularizations, stroke and ocular events among sildenafil users, and to use multivariate logistic regression modeling to examine risk factors for these events.

The second study is a U.K.-based, cross-sectional cohort study to determine the cumulative incidence of clinical cardiovascular outcomes in a population with erectile dysfunction (ED) treated with sildenafil, yohimbine or alprostadil, or with no pharmacological treatments. This study utilizes the _____ which is an electronic medical record database in the U.K.

Once vardenafil is launched, these same two databases will be used to identify cohorts of vardenafil users and to calculate the incidence of selected cardiovascular and ocular adverse events among these men, compared to cohorts of men using sildenafil.

Prospective Postmarketing Observational Study:

Section 6.4 of the submission describes, in brief, a proposed large observational study. This study is described in further detail in a submission dated July 8, 2003 and outlined as follows. The Sponsor proposes an uncontrolled, prospective, open-label, multi-center study of 30,000 adult male patients with erectile dysfunction who are candidates for vardenafil therapy per U.S. package insert. The study will be conducted in the outpatient setting with participating urologists, internists, and other clinicians. The objective of the study is "to collect data on safety, efficacy, and patient acceptance of vardenafil treatment under daily life conditions." The Sponsor maintains the right to close the study at any time. Patients may receive treatment with 5 mg, 10 mg, or 20 mg of vardenafil per recommendation of the attending physician.

The observation period is defined as the time between initial visit and second follow-up visit, to be within the next 2 months after the first dose of vardenafil. Information to be collected upon enrollment includes demography, erectile dysfunction history, other concomitant medical conditions, and concomitant medical treatments. The patient is then asked to document general and specific questions following each intake of vardenafil following the first 4 weeks of treatment (to conclude in a "First follow-up visit") and a second 4 week interval, to conclude in a "Second follow-up visit." Results are considered to be primarily of explorative and descriptive and will be pooled with a similar 30,000 patient study to be conducted in Europe and other countries.

An explanation of how postmarketing will translate to evaluation of the RMP's effectiveness, and timeline for communication of the results to the FDA was not included in the submission. Additional comments and recommendations are as follows:

Postmarketing surveillance: Spontaneous adverse event data is not an ideal method of evaluating a risk management plan since reporting of adverse events varies due to many factors. In addition, the Sponsor did not specify what it means by monitoring adverse events with "special attention". It is imperative that follow-up be ascertained on all patients with serious, unexpected events, cardiovascular, cerebrovascular, ECG abnormalities, arrhythmias, and events occurring as a consequence of drug interactions. In addition, DMETS suggests monitoring events occurring as a consequence of misuse or incorrect dosing of the product.

Use of health care databases in U.S. and U.K.: The _____ databases are well known and both have been used extensively to conduct pharmacoepidemiologic studies of adverse

events of drug therapy. However, without detailed study protocols, it is not possible to properly evaluate the studies in progress or those planned with regard to their ability to achieve the goals stated. Detailed protocols would minimally include information on the operational definitions of exposure to the drugs and outcomes of interest, an assessment of the ability of each database to capture the outcomes of interest, operational definitions of covariates, estimation of sample size required and feasible to obtain, and the study timeframes. Since myocardial infarction can often result in sudden death, the ability of these databases to detect death as an outcome is of particular interest. Although linkage to _____ for the _____ study is suggested, details regarding past successes or failures with such linkages, details of the approach to be used, as well as a plan for comparable analyses in the U.K. are not presented.

Another issue of great concern when using administrative databases to study outcomes of drug therapy is the coverage of therapies of interest by insurance plans. Coverage determines the capture of drug therapy in the database. Since drugs to treat ED are often not covered by insurance plans, it is not clear that all patients exposed to sildenafil, vardenafil or other ED drugs will be identified through the use of administrative claims. This can affect the validity of the study in several ways:

1. The number of patients available for study may be too few to conduct meaningful studies of rare adverse events;
2. The patients with claims for ED drugs in these systems may be only a select group of users of these products and may differ in substantive ways from those users not included in the system (e.g., they might be sicker or healthier than those without coverage for these products);
3. There may be misclassification of exposure, in that patients who pay cash for their ED drugs or obtain them through other channels (e.g., the Internet) would be classified as not exposed because of the absence of claims for these drugs. Such misclassification would tend to bias any comparative analysis between ED drug users compared to non-users toward seeing no difference. Issues of insurance coverage and payment for erectile dysfunction drugs and their anticipated impact on study validity should be clearly addressed by the Sponsor in relation to all databases (U.S. and U.K.) used to study adverse outcomes associated with these therapies.

Prospective Postmarketing Observational Study: The Sponsor proposes a large, observation study based on treatment effects during the first two months of therapy with vardenafil. For the purposes of drug safety, it is imperative that follow-up be ascertained on all enrolled patients issued vardenafil, since death / myocardial infarction is a potential side effect of therapy. Surviving, incident cases could potentially miss follow-up. One hundred percent follow-up should be the goal of this study and exhaustive measures employed to gain information on patients who fail to return for either of the follow-up visits. The standard operating procedures outlining follow-up of "tardy" enrollees is not described in depth nor has the importance of complete follow-up.

It is unknown if the patient questionnaire will serve as the sole source of information on drug efficacy and safety. The protocol does not outline data validation steps or other information gathering activities of participating clinicians, beyond simple enrollment materials. In addition

to active surveillance for "tardy" patients for follow-up, ODS would recommend clinician review of the patient questionnaire with the patient and promoting for some subset of critical subject areas, such as typical and atypical symptoms of angina.

The submission describes prospective collection of information on concomitant medications. It should be noted that Americans apparently use substantial amounts of "herbal" or "alternative" medical preparation.^{11,12} As these agents have pharmacologic activity, we would recommend active prompting by clinic personal to document exposure to all pharmacologically interesting, non-prescription preparations.

The following are DSRCs comments on the one-page Patient Questionnaire. The study objectives suggest that it will be used to study patient acceptance.

- Patients should be instructed by study staff on how to use the form. The protocol states that "The investigator should instruct the patient on how to fill out the Patient Questionnaire....", however, there is no reference to specific written or oral instructions that will be provided to the investigator and/or patient for this purpose. This is a very important step and should be done thoroughly. The investigator should be sure patients understand how to use the questionnaire before they take it home with them. The sponsor should consider giving patients a hypothetical set of facts to use to practice using the form. During training, staff can assist patients in filling out the first line " dealing with erections before the medication is used".
- A larger font size should be used. Many patients will be in the older age range and will have trouble reading the small print.
- The words "Erection before" appears as a subheading for the first column, which is confusing. Staff should instruct patients that the remainder of the column should contain the date of treatments.
- Instructions should tell patients to fill out the lines concerning dosing and the effects of the medication within a few hours of taking Levitra, as opposed to "...encouraged to make entries within 24 hours...". Memories will fade, and if they wait too long, patients will not be able to recall the answers to questions such as how long they had sexual activity after taking the medication, how well they were able to function, and how satisfied they were. The instructions should give a specific time frame that is reasonable, such as 2 hours, within which the form should be filled out.
- The last column, asking for degree of satisfaction, should have more choices. Currently, the choices are "very satisfied," "satisfied," and "unsatisfied." It would be better to have an equal number of choices in the satisfied and unsatisfied ranges, with parallel wording, such as the following: ".very satisfied," "somewhat satisfied," "somewhat unsatisfied," "very unsatisfied."
- The form should have space for comments that might be helpful to the research team.

¹¹ Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone Survey. *JAMA*. 2002;287(3):337-44.

¹² Eisenerg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. *JAMA*.1998;280(18):1569-75.

One way to make room for this is to print the form in a landscape orientation. If there is such space, the instructions should provide guidance as to what types of comments might be helpful.

- The form itself or the instructions should clearly explain what is in the footnote under the chart. That is, the terms "mostly," "sometimes," and "rarely" should be clearly and prominently explained. Be especially clear that the definitions are based on 10 attempts. The way it is now written, that information is at the end of the definitions, where it might be missed, and the footnote itself might be missed.*
- Question 1, about whether treatment has improved the patient's erection, might be better answered on a scale of 1-5 or 1-10, rather than just yes/no. Otherwise, even minute improvement would be scored as a "yes."*
- It may be difficult for some to answer Q.3, asking whether the patient ever had a second successful intercourse within 24 hours of taking the medication. Several issues arise with this question. One is that the patient might have taken a second dose; the current form does not provide a field for this information. The questionnaire also asks how many hours after the medication the second intercourse occurred. If the patient has had more than one occurrence of a second successful intercourse and they were at different times after the medication, how should he answer this question? To guide the patient, the questionnaire should ask for a specific instance, for example, the last time this happened or the incident when it was the longest time after taking the medication.*
- Question 4 asks how satisfied the patient was. Again, at least four parallel choices should be presented, as suggested earlier, or a wider scale anchored at both ends could be used. In this question, the term "earlier" is recommended in place of "prior." Also, this question presumes earlier treatment. If it is not always the case that these patients will have had earlier treatment, this question should be preceded by one asking if they had earlier treatment.*
- There should be a column for adverse events, with appropriate guidance as to how to report them.*
- Additional information that patients will be asked later, but which they may tend to forget if not written down, should be collected on the form. For example, if it is important whether certain OTC medications, vitamins, or herbal supplements were taken around the time of Levitra use, that information should be on the form so it is not forgotten.*
- This form should be pre-tested before use.*

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/s/

Sandra Birdsong
8/4/03 04:15:45 PM
CSO

Toni Piazza Hepp
8/4/03 04:44:37 PM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
8/5/03 08:10:01 AM
DIRECTOR
Satisfactory from DMETS perspective

Min Chen
8/5/03 09:00:29 AM
PHARMACIST
sign-off for Mark Avigan

Confirmation Report - Memory Send

Page : 001
Date & Time: Jul-23-02 01:57pm
Line 1 : 301-827-4267
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Machine ID : FDA/CDER/OND/ODE3/DRUDP

Job number : 461
Date : Jul-23 01:55pm
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End time : Jul-23 01:57pm
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Status : OK

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: July 23, 2002

To: Gautam Shah, Ph.D. Deputy Director, Regulatory Affairs	From: Freshnie De DeGuis Regulatory Project Manager
Company: Bayer Corporation	Division of Reproductive and Urologic Drug Products (HFD-580)
Fax number: (203) 812-5029	Fax number: (301) 827-4267
Phone number: (203) 812-3051	Phone number: (301) 827-4260
Subject: NDA 21-400 Levitra™ vardenafil hydrochloride	

Total no. of pages: 7

Comments: APPROVABLE LETTER

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

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Company: Bayer Corporation	Division of Reproductive and Urologic Drug Products (HFD-580)
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Advertising materials have not been submitted.

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NDA 21-400
Levitra® (vardenafil hydrochloride) Tablets
Bayer Healthcare

Class Labeling

There is no class labeling for this drug group.

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 19, 2003

TO: Dan Shames, M.D. Director
Division of Reproductive and Urologic Drug Products
HFD-580

VIA: Eufrecina DeGuia, Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products
HFD-580

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Toni Piazza-Hepp, Pharm. D., Acting Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of Patient Labeling for Levitra (vardenafil HCL) tablets, NDA 21-400

Summary

The patient labeling which follows represents the revised risk communication materials of the Patient Labeling for Levitra (vardenafil HCL) tablets, NDA 21-400. It has been reviewed by our office and DDMAC. We have simplified the wording, made it consistent with the PI, removed promotional language and other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications, not to provide detailed information about the condition), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

Please let us know if you have any questions. Comments to the review Division are bolded, italicized, and underlined. We can provide marked-up and clean copies of the revised document in Word if requested by the review division.

5 pages redacted from this section of
the approval package consisted of draft labeling

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/s/

Jeanine Best
6/19/03 10:30:39 AM
CSO

Toni Piazza Hepp
6/19/03 10:39:28 AM
DRUG SAFETY OFFICE REVIEWER

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: July 11, 2003

PDUFA DATE: August 19, 2003

ODS CONSULT #: 01-0149-6

DESIRED COMPLETION DATE:
July 30, 2003

TO: Dan Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Eufrecina DeGuia
Project Manager
HFD-580

PRODUCT NAME:
Levitra
(Vardenafil Hydrochloride Tablets)
2.5 mg, 5 mg, 10 mg, and 20 mg

NDA SPONSOR:
Bayer Corporation

NDA: 21-400

SAFETY EVALUATOR: Denise P. Toyer, Pharm.D.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), ODS conducted a re-review of the proposed proprietary name "Levitra" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:

1. DMETS has no objections to the use of the proprietary name, Levitra. If the approval of the NDA is delayed beyond 90 days from the date of this review, the name and its labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.
2. DMETS also recommends implementation of the labeling revisions outlined in Section III of this review.
3. DDMAC finds the proprietary names Levitra acceptable from a promotional perspective.

/s/

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Phone: (301) 827-3242
Fax: (301) 443-9664

/s/

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: August 15, 2003
NDA # 21-400
NAME OF DRUG: Levitra
(Vardenafil Hydrochloride) 2.5 mg, 5 mg, 10 mg, and 20 mg
NDA HOLDER: Bayer Corporation
Pharmaceutical Division

I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580) for a reassessment of the proposed proprietary name Levitra. DMETS conducted a review of the proposed proprietary name, Levitra and found it acceptable on July 2, 2002 (see DMETS consult # 01-0149-3). The unit dose container labels, unit dose carton labeling, container labels (30s), and package insert of Levitra were reviewed for safety issues relating to possible medication errors (see DMETS consult # 01-0149). Revised labels and labeling were submitted with this consult for review and comment.

PRODUCT INFORMATION

Levitra (vardenafil hydrochloride) is a highly selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). Levitra is an oral therapy for the improvement of erectile function in men with erectile dysfunction. The recommended starting dose of Levitra is 10 mg taken 25 to 60 minutes before sexual activity with a maximum of once per day. The dose may be increased to a maximum recommended dose of 20 mg or decreased to 5 mg based on efficacy and tolerability. A maximum dose of 5 mg should not be exceeded when used in combination with potent cytochrome P450 3A4 (e.g., inhibitors ketoconazole, itraconazole, indinavir, and ritonavir). Concomitant use of these products can produce elevated plasma levels of vardenafil. However, a maximum dose of 10 mg should not be exceeded when used in combination with the cytochrome P450 3A4 inhibitor, erythromycin. Consistent with the effects of PDE5 inhibition of the nitric oxide/cyclic guanosine monophosphate pathway, PDE5 inhibitors may potentiate the hypotensive effects of nitrates, and therefore co-administration of vardenafil with nitrates and nitric oxide donors is contraindicated. Levitra will be supplied as 2.5 mg, 5 mg, 10 mg, and 20 mg tablets.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to "Levitra" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted.⁴ The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. Prescription analysis studies were conducted during the first proprietary name review of Levitra and therefore were not repeated.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Levitra." Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. The members of this panel include DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified the proprietary names Brevital, Flextra, Lustrax, and Levora as having the potential for confusion with Levitra. These products are listed in Table 1 (see Page 4), along with the dosage forms available and usual dosage.
2. Through independent review, DMETS also identified Levora, Levoxyl, Levotabs, Levlite, Levlite, Levaquin, Levatol, and Levulan as having the potential for look-alike confusion with "Levitra." These names were identified in a search of the electronic Orange Book, 2000 Drug Topics Red Book, and via a phonetic/orthographic database that is in the final stages of development for DMETS. This latter database was not available at the time of the initial review. The entered search term is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. These products are also listed in Table 1 (see Page 4).
3. DDMAC did not have concerns about the name Levitra with regard to promotional claims.

¹ MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/main/trademarks.htm>

⁵ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Levitra	Vardenafil Tablets 2.5 mg, 5 mg, 10 mg, and 20 mg	10 mg once daily up to a maximum of 20 mg daily.	
Brevital	Methohexital Sodium	Intravenously: 1 mg to 1.5 mg/kg as a 0.2% solution per minute Rectally: 25 mg per kg as a 1% solution	LA
Flextra (650 and DS)	Phenyltoloxamine and Acetaminophen DS Tablets 500 mg/50 mg 650 Tablets 650 mg/60 mg	DS: 1 tablet every 4 hours as needed 650: 1 tablet every 6 hours as needed	LA
Lustra (AF)	Hydroquinone Cream 4%	Apply twice a day, morning and bedtime, to the affected areas	LA
Levora	Ethinyl Estradiol and Levonorgestrel Tablets 30 mcg/0.15 mg	Take one tablet daily	LA
Levlen	Ethinyl Estradiol and Levonorgestrel Tablets 30 mcg/0.15 mg	Take one tablet daily	LA
Levoxyl	Levothyroxine Sodium Tablets 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg	100 mcg to 200 mcg daily	LA
Levotabs	Levothyroxine Sodium Tablets 25 mcg, 50 mcg, 75 mcg, 100 mcg, 125 mcg, 150 mcg, and 200 mcg	100 mcg to 200 mcg daily	LA
Levulan	Aminolevulinic Acid Hydrochloride Topical Solution 20%	Application of the product to the target lesions, followed 14 to 18 hours later by illumination with blue light using Blue Light Photodynamic Therapy Illuminator (BLU-U). The second visit for illumination must take place in the 14- to 18-hour window following application.	LA
Lexapro	Escitalopram Oxalate Tablets and Oral Solution 10 mg, 20 mg, and 5 mg per 5 mL	10 mg to 20 mg daily	LA
Levaquin	Levofloxacin Tablets: 250 mg, 500 mg, 750 mg Injection (concentrate): 500 mg/20 mL and 750 mg/ 30 mL Injection (premix) - 250 mg/50 mL, 500 mg/100 mL, and 750 mg/150 mL	250 mg to 750 mg every 24 hours	LA
* Frequently used, not-all-inclusive. ** LA (look-alike), SA (sound-alike)			

B. AERS SEARCHES

DMETS had concerns with the potential for name confusion among the large number of proprietary names that begin with the letters 'lev.' Thus the Adverse Event Reporting System (AERS) was searched for all post-marketing safety reports of medication errors associated with Levora, Levoxyl, Levotabs, Levlen, Levlite, Levaquin, Levatol, and Levulan. The AERS search identified one new medication error reports. This report is in addition to the two

previously discussed in the initial review of Levitra (see consult # 00-0145-3). The report involved confusion between Levaquin and Levsin. A verbal order for 'Levsin 0.125 mg chewable tab TID before meals' was misinterpreted as 'Levaquin chewable tab TID before meals.' DMETS did not identify any pattern of name confusion between products that begin with the prefix 'Lev.' At this time, we do not feel that there is a concern with the number of proprietary names beginning with the prefix 'Lev;' however, we will continue to monitor these medication error-reports.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Levitra" the primary concerns raised were related to look-alike names that already exist in the U.S. marketplace. The names reviewed during the initial proprietary name review were Levatol, Levlite, Arixtra, Bicitra, Kaletra, Evista, and ——— DMETS identified eleven additional names as having the potential for name confusion with Levitra. These products include ——— Brevital, Flextra, Lustra, Levora, Levlen, Levoxyl, Levotabs, Levulan, Lexapro, and Levaquin. ———

will not be discussed.

1. Brevital and Levitra look similar when scripted. Brevital is a rapid ultrashort-acting anesthetic that is indicated for the intravenous induction of anesthesia prior to, or in conjunction with, other anesthetics. The first letter 'B' in Brevital may look like an 'l' when scripted in lower case (see below), thus increasing the look-alike similarities. Both names share common letters (evit) which also increases the look-alike similarities. However, there are product differences that differentiate the two products. Brevital and Levitra have different dosage forms (crystalline powder vs. tablets), route of administration (intravenous, intramuscular, rectal vs. oral), dosing intervals (one time vs. as needed with a maximum of once daily), and patient populations (inpatient vs. outpatient). Additionally, the products are provided in different strengths (500 mg vials, 2.5 grams vials, 5 gram vials vs. 2.5 mg, 5 mg, 10 mg, and 20 mg). The numerical digits of 2.5 and 5 could potentially be misinterpreted if the units of measure (grams vs. mg) are not clearly scripted. However, the products do not have overlapping doses [1 to 1.5 mg/kg (intravenous), 6.6 to 10 mg/kg (intramuscular), 25 mg/kg (rectally) vs. 2.5 mg, 5 mg, 10 mg, 20 mg]. Overall the product differences and the conditions of use will decrease the potential for name confusion between Brevital and Levitra.

Brevital Levitra

2. The root name for Flextra 650 and Flextra DS may look like Levitra when scripted. Flextra is a combination analgesic and antipyretic used to treat pain, headache, and fever. The beginning letters (F vs. L) may look similar depending upon how they are scripted (see below), especially if the modifier is omitted. Both names share the same ending letters (tra) which increases the look-alike similarities. There are product differences between the two products, which decrease the potential for name confusion. Flextra and Levitra have different dosing schedules [every 4 hours (650), every 6 hours (DS) vs. as needed with a maximum of once daily]. The prescribing strength for Levitra and either Flextra product do not overlap. Additionally, the strength must be noted on Levitra prescriptions whereas

Levitra

Flextra

Flextra prescriptions may be distinguished using the strength or the modifiers, 650 or DS. The different strengths and the dosing schedules help to decrease the potential for medication errors between Flextra and Levitra.

3. Lustra and Levitra may look alike depending upon how they are scripted. The names begin and end with the same letters (L__tra) which contributes to the look alike similarities. There are differences between the two products, which help to minimize the potential for name confusion. They have different dosage forms (cream vs. tablets) and dosing intervals (two times a day vs. as needed with a maximum of once daily). Additionally, prescriptions for Levitra will require that a strength be noted whereas prescriptions for Lustra can be ordered without indicating a strength. The differences in strength decrease the potential for name confusion between Lustra and Levitra. ●
4. Levora and Levlen are both oral contraceptives. Levora and Levlen may look like Levitra when scripted. All three names begin with the same three letters (Lev) which increases the name similarity. However, the endings of the names are different. The strengths will also help to differentiate Levora/Levlen from Levitra. Both Levora/Levlen are only available in a single strength (ethinyl estradiol 30 mcg and levonorgestrel 0.15 mg) which means they may be prescribed without indicating a strength. Levitra is available in three strengths, thus requiring that a strength be indicated when prescribed. Additionally, the ordering quantity for the products may help to distinguish them. For example, the oral contraceptives will be prescribed in multiples of 21 or 28 (tablets) or single quantities of 1, 2, etc (months or packages). However, Levitra will be packaged in unit-of-use blister packages that could potentially be ordered as '#one (referring to boxes). If a prescription for 'Levitra UD #1' is misinterpreted as 'Levora UD #1' the practitioner would need to clarify if the patient takes 21 or 28 tablets. In contrast, if the Levora prescription is misinterpreted as Levitra the practitioner would have to clarify the prescribing strength of Levitra. Although the oral contraceptives Levora and Levlen may look similar to Levitra the endings of the names and the product characteristics help to decrease the potential for name confusion.
5. Levoxyl and Levotabs are both proprietary names for levothyroxine sodium tablets. Levoxyl and Levotabs have look-alike similarities with Levitra, especially since the names begin with the same three letters. However, the letters in the last two syllables of each name are different (oxyl vs. otabs vs. itra). Additionally, Levoxyl has a letter downstroke and Levotabs has two upstrokes which helps to differentiate the names from Levitra. Moreover, the letter upstrokes in the endings of each name are in different positions. The dosage range for Levoxyl and Levotabs is 25 mcg to 200 mcg given once daily. The dosages for "Levitra" are 5 mg, 10 mg, and 20 mg. The doses do not overlap; however the numerical strengths are similar (5 mg, 10 mg, 20 mg vs. 50 mcg, 100 mcg, 200 mcg respectively). The "Levitra" strength may be misinterpreted as a Levoxyl or Levotab strength, if the "Levitra" dose is written with a trailing zero (e.g., 5.0 vs. 50), an undistinguished decimal point and the units (mg vs. mcg) are not clearly written. Overall, the differences in the endings of the names minimize the potential for name confusion between Levitra and Levoxyl or Levotabs.
6. Levulan and Levitra may look alike when scripted. Although both names begin with the same letters, the endings are different (ulan vs. itra). Other differences include the dosage form (topical solution vs. tablet) and dosing interval (single application vs. as needed with a maximum of once daily). The specific conditions of use for Levulan will also help to differentiate the products. Levulan must be used in conjunction with a blue light and

administered by a healthcare practitioner. Additionally, Levulan is only available in one strength whereas Levitra will be available in three strengths. The different strengths and conditions-of-use between Levulan and Levitra will help to decrease the potential for name confusion.

7. Lexapro and Levitra may look similar when scripted. The beginning letters 'Lex vs. Lev' and the ending letters 'ro vs. ra' look similar. The products also have overlapping strengths (10 mg and 20 mg) and may have overlapping dosing intervals (daily). However, Lexapro has a downstroke (p) in the same position as the upstroke (t) in Levitra when scripted or printed. This difference may help to differentiate the names. There are additional differences that may help to distinguish the two products. The indication of use is different. Levitra prescriptions will likely be written using directions such as 'use as directed' or 'as needed' whereas the directions for Lexapro prescriptions, since it is an antidepressant, will not usually be as ambiguous. Furthermore, practitioners may add additional information to Levitra prescriptions which may help to distinguish the two products (e.g., Do not use more than 1 per day or every other day or Take 1 hour prior to intercourse, etc). The majority of the Lexapro prescriptions will most likely state 'daily' or 'every day' as the directions, with a prescribing quantity of 30 or 28 (representing a month's supply). Since the sponsor is packaging Levitra as a unit-of-use blister package containing six tablets, it is likely that Levitra may be prescribed in quantities less than 30 tablets. Due to the packaging configuration practitioners are more likely to prescribe multiples of 6 tablets in lieu of the usual 30 days/tablets. DMETS acknowledges that Levitra will also be marketed in bottles of 30 tablets and that larger quantities may be prescribed. However, the cost of the drug and lack of coverage by insurers will also contribute to practitioners prescribing smaller quantities. Although Lexapro and Levitra look similar when scripted.

Levitra 10mg
Lexapro 10mg

8. Levaquin and Levitra share look-alike similarities. The first four letters of each name look similar to each other when scripted (leva vs. levi) which increases the look alike characteristics. However, the products have different prescribing strengths that do not overlap between the two products (250 mg, 500 mg, 750 mg vs. 5 mg, 10 mg, and 20 mg). The products share similar dosing intervals (daily vs. as needed with a maximum of once daily). The differences in the prescribing strengths help to decrease the potential for confusion between Levaquin and Levitra.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the "Levitra" container label and carton labeling DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL (30 TABLETS)

1. Relocate the net quantity statement so that it is not presented in close proximity to the strength. Revise accordingly.
2. Consider using a different background color for either the 2.5 mg tablets or the 20 mg tablets, since the colors are similar. See below.

B. BLISTER LABEL (6 TABLET PACKAGE)

DMETS notes that the sponsor did not qualify the strength on the blister label. Since the strength is based on the active moiety and not the salt, the strength should be qualified (e.g., ...5 mg* or equivalent to 5 mg Vardenafil) on all labels and labeling. Revise accordingly.

C. CARTON LABELING (6 TABLET PACKAGE)

1. The various strengths (i.e., 2.5 mg, 5 mg, 10 mg, and 20 mg) should be differentiated using contrasting color, boxing, etc. Revise accordingly.
2. Consider using a different background color and contrasting font for easier legibility. The current presentation (i.e., orange on purple and vice versa) is difficult to read. Revise accordingly.

APPEARS THIS WAY
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IV. RECOMMENDATIONS:

- A. DMETS has no objections to the use of the proprietary name Levitra. This is considered a final decision; however if the approval of the NDA is delayed beyond 90 days of the date of this review, the name with its associated labels and labeling must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.
- B. DMETS also recommends implementation of the labeling revisions outlined in Section III of this review.
- C. DDMAC finds the proprietary names Levitra acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

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Denise P. Toyer, Pharm.D.
Safety Evaluator Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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this page is the manifestation of the electronic signature.

/s/

Denise Toyer
8/15/03 03:43:34 PM
PHARMACIST

Carol Holquist
8/15/03 03:44:33 PM
PHARMACIST

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8/18/03 09:42:15 AM
DIRECTOR

NDA 21-400
Levitra® (vardenafil hydrochloride) Tablets
Bayer Healthcare

Final re-evaluation from DMETS will be given to the Div on Monday, 8/18. See email from Denise Toyer of DMETS.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: April 10, 2002	DUE DATE: June 26, 2002	ODS CONSULT #: 01-0149-3
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TO: Dan Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Eufrecina DeGuia
Project Manager
HFD-580

PRODUCT NAME:
Levitra
(Vardenafil Hydrochloride Tablets)
5 mg, 10 mg, and 20 mg

NDA: 21-400

NDA SPONSOR:
Bayer Corporation

SAFETY EVALUATOR: Denise P. Toyer, Pharm.D.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), ODS conducted a review of the proposed proprietary name "Levitra" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:
DMETS has no objections to the use of the proprietary name, Levitra.

This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

/s/	/s/
Carol Holquist, R.Ph. Deputy Director Division of Medication Errors and Technical Support Phone: (301) 827-3242 Fax: (301) 443-5161	Jerry Phillips, R.Ph. Associate Director Office of Drug Safety Center for Drug Evaluation and Research Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: June 27, 2002
NDA # 21-400
NAME OF DRUG: Levitra
(Vardenafil Hydrochloride) 10 mg, 20 mg, 40 mg
NDA HOLDER: Bayer Corporation
Pharmaceutical Division

*****NOTE:** This review contains proprietary and confidential information that should not be released to the public.***

This review also contains information that is provided by ims health national prescription audit plus (on-line) and is not to be used outside of the fda without prior clearance by ims health. A minimum of 2 weeks is required for clearance by ims health.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580) for assessment of the proposed proprietary name Levitra. ODS reviewed the sponsor's first choice—Nuviva—and did not recommend use of this proprietary name (see ODS consult 01-0149). The primary concerns were related to potential name confusion between Nuviva and Norvasc or Navane. Bayer submitted a rebuttal to support the proposed name Nuviva on February 5, 2002 and additional supporting information on April 18, 2002. The latter submission also contained a proposal for a *Nuviva Medication Error Risk Management Program* to support the acceptability of the proprietary name. DMETS' subsequent review of the two submissions concluded that none of the data submitted (i.e., supporting information nor the proposed Nuviva Medication Error Risk Management Program) alleviated the concerns relating to potential confusion between Nuviva and Norvasc or Navane (see ODS consults 01-149-1, and 01-0149-2). Therefore, DMETS did not recommend use of the proprietary name, Nuviva. On May 21, 2002, Bayer also submitted a summary of study in support of the proposed name, Nuviva. DMETS' review of the summary notes that this study (1) involved more pharmacists (proposed) than previous studies (360 vs. 100), (2) pharmacists only interpreted one Nuviva prescription (whereas in the previous study two were interpreted), and (3) the study included both drugs of concern (Norvasc and Navane). However, the results of the study indicate that name confusion continues between Norvasc and Navane (two misinterpretations of Navane handwritten prescriptions for Norvasc) and there is potential name confusion between Nuviva and Norvasc (one misinterpretation of Nuviva handwritten prescription for Norvasc). Based on these data and the previous DMETS consults, we do not recommend use of the proposed proprietary name, Nuviva.

On May 24, 2002, Bayer submitted three proprietary names for review— _____ and Levitra. _____ are both phonetically and alphabetically similar to Nuviva. Therefore, the concerns relating to name confusion with Nuviva would not be addressed by the proposed names _____ and _____. Thus, this review will only address the proposed proprietary name Levitra.

DMETS notes that during the first review (ODS consult 01-0149) the unit dose container labels, unit dose carton labeling, container labels (30s), and package insert of Nuviva were reviewed for safety issues relating to possible medication errors. DMETS identified several areas of possible improvement that might minimize potential user error and recommended labeling changes. Revised labels and labeling were not submitted with this consult.

PRODUCT INFORMATION

Levitra the active ingredient vardenafil hydrochloride, which is a highly selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). Levitra is an oral therapy for the improvement of erectile function in men with erectile dysfunction. The recommended starting dose of Nuviva is 10 mg taken 25 to 60 minutes before sexual activity. The recommended dose frequency is a maximum of once per day as desired. The dose may be increased to a maximum recommended dose of 20 mg or decreased to 5 mg based on efficacy and tolerability. A maximum dose of 5 mg should not be exceeded when used in combination with potent cytochrome P450 3A4 inhibitors ketoconazole, itraconazole, indinavir, and ritonavir. Concomitant use of these products can produce elevated plasma levels of vardenafil. However, a maximum dose of 10 mg should not be exceeded when use in combination with the cytochrome P450 3A4 inhibitor, erythromycin. Consistent with the effects of PDE5 inhibition of the nitric oxide/cyclic guanosine monophosphate pathway, PDE5 inhibitors may potentiate the hypotensive effects of nitrates, and therefore co-administration of vardenafil with nitrates and nitric oxide donors is contraindicated. Levitra will be supplied as 5 mg, 10 mg, and 20 mg tablets.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to "Levitra" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted.⁴ The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies, for each proposed proprietary name, consisting of two written

¹ MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁵ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Levitra." Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

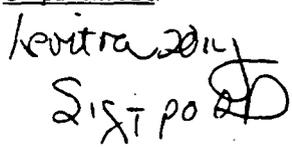
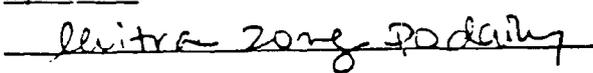
1. The Expert Panel identified Levatol, — , Levlite, Evista, Arixtra, Bicitra, and Kaletra as names that could have the potential for confusion with "Levitra." These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.
2. DDMAC did not have concerns about the name "Levitra" with regard to promotional claims.

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Levitra	Vardenafil Tablets 5 mg, 10 mg, and 20 mg	10 mg once daily up to a maximum of 20 mg daily.	
Levatol	Penbutolol Sulfate Tablets 20 mg	1 tablet once daily	*LA
Levlite	Levonorgestrel and Ethinyl Estradiol Tablets, (0.1 mg /0.03 mg)	1 tablet once daily	LA
Evista	Raloxifene Hydrochloride Tablets 60 mg	60 mg once daily	S/A
Arixtra	Fondaparinux Injection 2.5 mg	2.5 mg subcutaneously approximately 6 hours postoperative and daily for up to 11 days	*S/A and L/A
Bicitra	Sodium Citrate Dihydrate 500 mg and Citric Acid Monohydrate 334 mg	10 mL to 30 mL taken up to four times a day or as a single dose depending upon indication	*SA
Kaletra	Lopinavir 133.3 mg and Ritonavir 33.3 mg Capsules	3 capsules two times a day	*S/A and L/A
* Frequently used, not all-inclusive. ** L/A (look-alike), S/A (sound-alike) ***Pending Approval			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology for Levitra:

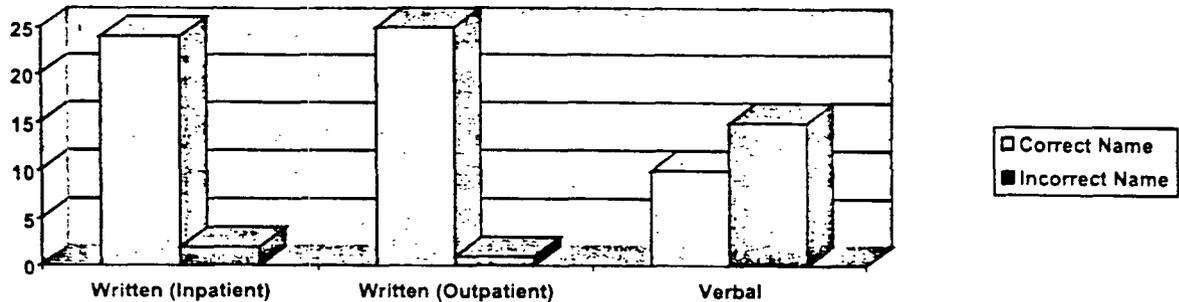
Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of "Levitra" with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 108 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for "Levitra" (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient prescription was recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretation and review. After receiving either the written or verbal prescription orders, the participants sent their interpretation of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p>Outpatient RX:</p> 	<p>... and the last prescription is Levitra 20 mg He's to take 1 of those every day Dispense #30</p>
<p>Inpatient RX:</p> 	

2. Results for Levitra:

The results are summarized in Table II.

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	39	26 (66%)	24	2
Written Outpatient	36	26 (72%)	25	1
Verbal	33	25 (76%)	10	15
Total	108	77 (71%)	59	18



In the verbal study 15 of 25 (60%) participants interpreted "Levitra" incorrectly. The majority of the incorrect name interpretations involved the names Lavetra (4), Lovitra (3), and Lovetra (2). Six other single misinterpretations included Abitro, Lanitra, Lavedra, Lavietra, Lavita, and Levetra. All of the responses except two (Abitro and Lanitra) are phonetic equivalents of Levitra. None of the misinterpretations was an approved product.

Among the two written studies, 3 of 52 (6%) participants interpreted the name incorrectly. The misinterpretations included Levitia, Elvitra, and Levitran.

C. AERS SEARCHES

The Orange Book was searched for all approved proprietary names beginning with the prefix 'Lev.' This search revealed the following proprietary names: Levulan, Levlite, Levora, Levaquin, Levoxyl, and Levatol. Next, the Adverse Event Reporting System (AERS) was searched for all post-marketing safety reports of medication errors associated with the aforementioned proprietary names. The AERS search identified two medication error reports (one for Levoxyl and one for Levaquin) which may have been related to name confusion. The first report involved a potential error of a prescription written for Lovenox 500 mg but upon clarification the prescription was for Levaquin 500 mg. The other report involved a prescription of Lanoxin 0.125 mg filled with Levoxyl 0.125 mg. See Attachment One for details of the two cases. DMETS did not identify any pattern of name confusion between products that begin with the prefix 'Lev.' We do not feel that there is a concern at this time with the number of proprietary names beginning with the prefix 'Lev;' however, we will continue to monitor these medication error reports.

*****NOTE: This review contains proprietary and confidential information that should not be released to the public. *****

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Levitra" the primary concerns raised were related to sound-alike and look-alike names that already exist in the U.S. marketplace and one name that is currently under review. The products considered having the greatest potential for confusion include Levatol, Levlite, Arixtra, Bicitra, Kaletra, Evista, and _____

Levatol is a beta-blocker used to treat hypertension. The usual recommended dose of Levatol is 20 mg daily, whereas the maximum daily dose of "Levitra" is 20 mg. These products have overlapping strengths (20 mg), dosage forms (tablets), and dosing intervals (daily). "Levitra" and Levatol may be stored next to each other in pharmacies. Both "Levitra" and Levatol are seven

letter, three syllable words. They have the same first syllable, 'Le' and the second syllables, 'vi' and 've,' may look similar. Although, the names look similar when scripted the last syllable is different (see page 7). An additional difference between these products is that Levitol may be prescribed without a strength, since it is only available in one strength whereas "Levitra" will be available in 5 mg, 10 mg, and 20 mg strengths (and will require a strength on the prescription). Additionally, "Levitra" may also be ordered on an 'as needed' basis whereas Levitol will always be ordered on a scheduled regimen. Despite these differences DMETS is concerned about potential name confusion due to the overlapping strength and dosing interval. However, use data from IMS Health was obtained to help to determine the potential market share of Levitol. The IMS HEALTH projected number of prescriptions dispensed for calendar years, _____ through _____ is _____. The number of projected prescriptions has steadily decreased since the launch date (_____ to _____). Based on the IMS data relating to the limited market share of Levitol, the differences between the two products, and the differences in the last syllable of both names; DMETS feels that the potential risk of name confusion is decreased.

LEVITRA

LEVITOL

Levitra Levitol

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LEVITRA

Levitra : _____

Levlite is the proprietary name for an oral contraceptive containing ethinyl estradiol and levonorgestrel. The dose is one tablet every day. Prescriptions for Levlite may contain directions of use that state 'one tablet daily' or 'use as directed.' "Levitra" may also be written in this format but may also include additional information indicating that the medication is to be used on an 'as needed' basis. A strength is not required for Levlite prescriptions; however, the prescription must contain a '21 or 28' notation indicating the days supply. "Levitra" prescriptions will be required to contain the strength (5 mg, 10 mg, or 20 mg). Although, Levlite prescriptions will generally include the numbers '21 or 28' (representing the days supply), the

majority of the prescriptions will also include a dispensing quantity (e.g., 1 month, 1 package, #1, etc) which corresponds to the SLIDECASE dispenser (packaging configuration). "Levitra" and Levlite both begin with the same prefix 'Lev' and thus look similar when scripted (see below). However, the endings of these names are different. The differences in packaging configuration and strength should also help to decrease the potential risk of medication errors due to name confusion.

LEVITRA

LEVLITE

Levitra Levlite

Arixtra is indicated for the treatment of deep vein thrombosis that may lead to pulmonary embolism in patients undergoing hip fracture or replacement surgery and knee replacement surgery. Arixtra was identified as a potential sound-alike to "Levitra." Both "Levitra" and Arixtra are three syllable words. The last syllable in each name is identical--'tra.' Thus the latter part of the names sound identical. However, the beginning sounds are quite different 'Levi' and 'Arix.' Arixtra is prescribed as a 2.5 mg once daily subcutaneous injection. The usual recommended duration is five to nine days. Although, the dosing intervals (daily) overlap between Arixtra and "Levitra," they have different recommended doses (2.5 mg vs. 5 mg, 10 mg, or 20 mg), routes of administration (subcutaneous vs. oral), and dosage formulations (injection vs. tablet). The differences noted between "Levitra" and Arixtra would decrease the potential risk of medication errors.

Bicitra is an alkalinizing agent used when maintenance of alkaline urine is required and to alleviate chronic metabolic acidosis. The Expert Panel thought that "Levitra" and Bicitra may sound-alike. The usual recommended dose of Bicitra is 15 mL as a single dose or 15 mL to 30 mL four times a day. Bicitra is different from "Levitra" in the dosing interval (QID vs. QD), formulation (tablet vs. liquid), and usual dose (15 mL to 30 mL). Both names contain three syllables and the last syllable is identical--'tra.' However, the first two syllables are quite different--'Levi' and 'Bici.' Overall, the differences (dosage forms, directions of use, and usual dose) between "Levitra" and Bicitra would decrease the potential risk of medication errors.

Kaletra was identified as a potential sound-alike for "Levitra." The ending syllable of both products is identical--'tra.' In comparison, the remaining portions of the two names are different. The first two syllables are 'Kale' vs. 'Levi.' Kaletra is a combination product used in the treatment of HIV(+) patients. Each capsules contains lopinavir 133.3 mg and ritonavir 33.3 mg. The dosing interval of Kaletra is three capsules two times a day. Differences between "Levitra" and Kaletra include the dosing interval (BID vs. QD) and formulation (capsule vs. tablet). Additionally, Kaletra is usually co-administered with efavirenz or nevirapine and should be taken with food. The differences in the first two syllables, formulation, and dosing interval should minimize the potential risk of medication errors due to name confusion.

Evista is a selective estrogen receptor modulator (SERM) used in the treatment and prevention of osteoporosis in postmenopausal women. The dosing interval (QD) and formulation (tablets) of "Levitra" and Evista overlap. Evista is only available in one strength (60 mg) whereas "Levitra" is available in three strengths (5 mg, 10 mg, and 20 mg). Thus prescriptions for Evista may be written without a strength noted; however, "Levitra" prescriptions will require a strength. Additionally, the available strengths for the two products do not overlap. "Levitra" and Evista share three letters—"evi"—that contribute to the sound-alike characteristics. However, "Levitra" begins with the letter 'l' and ends with the letters 'tra.' These additional letters at the beginning and end of "Levitra" lessen the sound-alike characteristics of "Levitra" and Evista. Although, "Levitra" and Evista share the same formulation and dosing intervals the other differences should decrease the potential of name confusion between the two products.

III. RECOMMENDATIONS:

DMETS has no objections to the use of the proprietary name Levitra. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

/s/

Denise P. Toyer, Pharm.D.
Safety Evaluator Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Attachment One

ISR #	FDA Receipt Date	Summary of Case Narrative
3874947-9	2/27/2002	A 90 year old man with a diagnosis of pneumonia was ordered Lovenox 500 mg QD. Pharmacist called and clarified that the order was for Levaquin 500 mg QD.
3303960-5	7/14/1999	A 58-year old female received a refill for a prescription that was labeled Lanoxin 0.125 mg three times a day. The patient indicated that the pills were different and did not take them. The bottle contained 90 tablets of Levoxyl 0.125 mg.

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