CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-400

Administrative Documents

Section 14 – Patent Certification

All investigators relied upon by Bayer in this NDA were conducted by or for Bayer using drug substance and drug product in accordance wit the patents listed in the Patent Information Section.

Please refer Section 13, Patent Information.

Section 13: The following information is hereby provided pursuant to 21 C.F.R. § 314.53(c):

Patent Number:	Not yet assigned. (Notice of Allowance for application serial number 09/554,162 mailed from U.S. Patent and Trademark Office on July 25, 2001. Issue Fee was paid August 9, 2001.)
Expiration Date:	October 31, 2018
Type of Patent:	drug substance, drug product, method of use
Name of Patent Owner:	Bayer Aktiengesellschaft
Agent:	Applicant (Bayer Corporation), residing in the U.S.

The undersigned declares that the patent application having serial number 09/554,162 to be issued as U.S. Patent Number (Not yet assigned) covers the formulation, composition and method of use of vardenafil. This product is the subject of this application for which approval is being sought.

Mary Taylor
Director, Regulatory Affairs
Bayer Corporation

EXCLUSIVITY SUMMARY for NDA # 21-400

Trade Name Levitra® Generic Name vardenafil hydrochloride

Applicant Name Bayer Corporation _____ HFD- 580

Approval Date August 19, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/__x_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_x__/

      If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /__x_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_x_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_x__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_x__/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_x__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_x__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

Eufrecina DeGuia — August 18, 2003
Signature of Preparer — Date

Title: Regulatory Health Project Manager

(See appended electronic signature page)

Daniel Shames, M.D. — August 18, 2003
Signature of Division Director — Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Daniel A. Shames
8/18/03 03:58:02 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-400 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: February 17, 2003 Action Date: August 19, 2003

HFD 580 Trade and generic names/dosage form: Levitra® (vardenafil hydrochloride)

Applicant: Baver Corporation Therapeutic Class: 1S

Indication(s) previously approved: treatment of erectile dysfunction

Number of indications for this application(s): 1

Indication #1: treatment of erectile dysfunction

Is there a full waiver for this indication (check one)?

- ■ Yes: Please proceed to Section A.
- ❑ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ Products in this class for this indication have been studied/labeled for pediatric population
- ■ Disease/condition does not exist in children (This drug is indicated only for men with erectile dysfunction.)
- ❑ Too few children with disease to study
- ❑ There are safety concerns
- ❑ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for partial waiver:

- ❑ Products in this class for this indication have been studied/labeled for pediatric population
- ❑ Disease/condition does not exist in children
- ❑ Too few children with disease to study
- ❑ There are safety concerns
- ❑ Adult studies ready for approval
- ❑ Formulation needed
- ❑ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____ kg____ mo.____ yr.____ Tanner Stage_____
Max____ kg____ mo.____ yr.____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ■ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): TBD (Development plan and study protocol will be submitted to FDA by December 2003.

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS

Section D: Completed Studies

Age/weight range of completed studies:

Min ____ kg____ mo.____ yr.____ Tanner Stage_____
Max____ kg____ mo.____ yr.____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

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

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: N/A

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ___Partial Waiver ___Deferred ___Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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/s/

Eufrecina deGuia
8/18/03 08:59:25 AM

Pediatric Studies Waiver Request

Pursuant to 21 CFR § 314.55(c), Bayer Corporation Pharmaceutical Division requests a full waiver of the assessment of the efficacy and safety of vardenafil tablets in pediatric population. This class of drug product does not represent therapeutic benefit for pediatric patients.

Section 16: Debarment Certification

Bayer hereby certifies under FD&C Act, Section 306 (k) (1) that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Mary Taylor, Director
Regulatory Affairs
Bayer Corporation

NDA 21-400

Supervisory Medical Officer's Memorandum

From:	George S. Benson, MD Medical Team Leader, DRUDP
To:	Flo Houn, MD Office Director, ODE-3
Through:	Donna Griebel, MD Deputy Director, DRUDP
Review completed:	August 18, 2003
Regarding:	Recommendation for regulatory action – NDA 21-400
Sponsor:	Bayer Pharmaceutical Division Bayer Corporation 400 Morgan Lane West Haven, CT. 06516

Date of original submission:	September 24, 2001
Date received:	September 27, 2001
Date of approvable letter outlining deficiencies:	July 23, 2002
Date of complete response to approvable action:	February 17, 2003
Date received:	February 19, 2003

Drug:	vardenafil hydrochloride
Tradename:	Levitra
Route of administration:	oral
Dosage form and strength:	2.5, 5, 10, and 20 mg tablets
Drug class:	type 5 phosphodiesterase inhibitor
Indication:	treatment of erectile dysfunction
Related IND's:	IND# [redacted] (vardenafil hydrochloride for erectile dysfunction)

Table of Contents

1. Materials Used in Conducting the Review
2. Executive Summary
3. Clinically Relevant Issues from Other Disciplines Reviews
4. Review of Specific Trials
   A. Trial 10929 (QT)
   B. Trials 100480 and 100481 (alpha-blocker DDI)
5. Summary Comment of Efficacy
6. Integrated Review of Safety
7. Dosing and Administration
8. Labeling Recommendations

1. Materials used in conducting the review

Minutes of the Cardiovascular and Renal Drug Advisory Committee (May 29, 2003)
Ophthalmology consultation
Medical Officer Review of Complete Response to Approvable Action
Trial 10929 (QT study)
Trials 100480 and 100481 (alpha blocker DDI studies)
Integrated Summary of Safety
DMETS Review of Tradename
DDMAC Consult

2. Executive Summary

Recommendation:

In my opinion, vardenafil hydrochloride in doses of 2.5, 5, 10, and 20 mg taken no more often than once daily should be approved for the indication "treatment of erectile dysfunction." The risks associated with the use of this drug are acceptable and can be adequately managed with labeling. Four phase 4 commitments should be required: 1) repeated dose studies evaluating the effect of vardenafil on retinal function 2) a study to evaluate the impact on QT interval prolongation of combining vardenafil with another drug with a similar QT effect size 3) a study (ies) to evaluate the pharmacokinetic/pharmacodynamic drug-drug interaction between vardenafil 2.5 mg and alpha-blockers used for BPH and 4) a study to evaluate the pharmacokinetic/pharmacodynamic drug-drug interaction between vardenafil and the alpha-blocker alfuzosin.

The reasons for this decision are as follows:

A. The clinical effectiveness of vardenafil (defined by the appropriate endpoints of Erectile Function Domain of the International Index of Erectile Function and SEP questions 2 and 3) was demonstrated in 4 placebo-controlled trials in appropriate patient populations.
B. The overall clinical safety database, collected in adequate controlled and uncontrolled human trials, demonstrates an acceptable adverse event profile consistent with the

drug's pharmacological effect (type 5 phosphodiesterase inhibition) with no other significant safety signals noted. The risks associated with the use of this drug can be managed adequately with labeling.

C. Following the initial review of NDA 21-400, an approvable action was taken on July, 23, 2002. The following seven deficiencies were noted:

i) "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 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."

In response to the approvable letter issue dealing with the QT interval the sponsor submitted the results of Trial 10929. Trial 10929 is discussed in greater detail in Section 4.A. of this memorandum. The protocol was approved by Cardio-Renal and the Reproductive and Urologic Drug Products Divisions. This 6-way crossover study evaluated vardenafil 10 and 80 mg, sildenafil 50 and 400 mg, moxifloxacin (positive control) 400 mg, and placebo. The primary endpoint was the change in QTc Fridericia from baseline at 1 hour post-dose. An individually corrected QT interval (Qtci) was also measured. The results are summarized in Tables 1 and 2.

Table 1: Change from baseline in QTcF (msec) at 1 hour post-dose

Regimen	Means[1] (s.e.)	Comparison	Point Estimate[2]	90%CI
Placebo	0 (0.7)			
Primary Comparison:				
80 mg vardenafil	10 (0.7)	80 mg vardenafil Placebo	10	(8, 11)
Secondary Comparison:				
10 mg vardenafil	8 (0.7)	10 mg vardenafil Placebo	8	(6, 9)
50 mg sildenafil	7 (0.7)	50 mg sildenafil Placebo	6	(5, 8)
400 mg Sildenafil	9 (0.7)	400 mg sildenafil Placebo	9	(8, 11)
400 mg moxifloxacin	8 (0.7)	400 mg moxifloxacin Placebo	8	(6, 9)

1 represents adjusted arithmetic mean 2 represents difference between arithmetic means Note: above results are rounded to the nearest integer. Source: Study report 10929. Table 12, page 60.

Table 2::Change from Baseline in QTci (msec) at 1 hour post-dose

Regimen	Means[1] (s.e.)	Comparison	Point Estimate[2]	90% CI
Placebo	2 (0.7)			
Primary Comparison:				
80 mg vardenafil	8 (0.7)	80 mg vardenafil Placebo	6	(4, 7)
Secondary Comparison:				
10 mg vardenafil	6 (0.7)	10 mg vardenafil Placebo	4	(3, 6)
50 mg sildenafil	6 (0.7)	50 mg sildenafil Placebo	4	(2, 5)
400 mg Sildenafil	7 (0.7)	400 mg sildenafil Placebo	5	(4, 7)
400 mg moxifloxacin	9 (0.7)	400 mg moxifloxacin Placebo	7	(5, 8)

1 represents adjusted arithmetic mean 2 represents difference between arithmetic means
Note: above results are rounded to the nearest integer (accounts for apparent discrepancies between means and point estimates and asymmetry of CI). Source: Study report 10929. Table 13, page 61.

a) The mean change from baseline at one hour post-dose was 8 msec (6,9; 90% CI) for the 10 mg vardenafil dose and 10 msec (8,11; 90% CI) for the 80 mg vardenafil dose. These changes were similar to those observed for the positive control moxifloxacin and for the sildenafil arms; the study, however, was not powered to detect differences between the various treatment arms. The QTc values measured by the individual correction formula Qtci were smaller (4 msec for the 10 mg vardenafil dose and 6 msec for the 80 mg vardenafil dose).
b) The 80 mg vardenafil dose is sufficient to cover C_{max} values seen with maximum inhibition of CYP 3A4 (i.e. with the concomitant administration of ritonavir).
c) Outlier analyses showed no patient with either 10 or 80 mg of vardenafil who had a QTcF > 450 msec or a QTcF increase of > 60 msec.
d) No signal for arrhythmogenic risk was seen in the controlled or uncontrolled clinical trials.
e) No signal for arrhythmogenic risk was found in a limited post-marketing data base in Europe.
f) No definitive QT studies are available for other type 5 phosphodiesterase inhibitors. No cases of Torsades de Pointes are reported, however, in a large post-marketing experience for sildenafil.
g) An Advisory Committee meeting was held on May 29, 2003, to discuss evaluation of the QT interval in general and the findings of the vardenafil study in particular. The Advisory Committee was unable to determine which QT correction method most accurately estimated QTc. The committee was asked, "Do these data demonstrate a clinically relevant QT prolongation associated with vardenafil?" In response to this question, the majority of the committee voted "no" (8 votes "no", 1 vote "yes", 3 abstained and 1 member could not vote). Several committee members, however, expressed the opinion that information concerning the effect of vardenafil on the QT interval and a description of patients who might be at risk for Torsades should be included in labeling.
h) *Based on the above, I believe that the risk of Torsades de Pointes in patients taking vardenafil is low to very low and is acceptable. Nevertheless, information regarding the effect of vardenafil on the QT interval should be included in the "Clinical Pharmacology" section of the label and the "Precautions" section of the label should include*

information concerning the use of vardenafil in patients with congenital prolongation of the QT interval and patients taking Class 1A (e.g. quinidine and procainamide) or Class III (e.g. amiodarone and sotalol) antiarrhythmic medications.

ii) "It is expected that many men who seek treatment with Levitra for ED will require concomitant treatment for symptoms of benign prostatic hyperplasia (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."

In response to the approvable letter issue dealing with the possible **drug-drug interaction of Levitra and alpha-blockers used for the treatment of benign prostatic hyperplasia**, the sponsor submitted the results of **Trials 100480 and 100481**. Trial 100480 evaluated the drug-drug interaction with terazosin and Trial 100481 the drug-drug interaction with tamsulosin. These trials are reviewed in greater detail in Section 4.B. of this memorandum.

In Trial 100480, vardenafil (10mg and 20mg) and placebo were given both 6 hours after a dose of 10 mg terazosin in Part 1 and simultaneously with teraosin 10 mg in Part 2. Trial 100481 is an identical trial except for the fact that tamsulosin 0.4mg instead of terazosin was evaluated and vardenafil (10 mg and 20 mg) were given either at 4 or 10 hours after tamsulosin (giving vardenafil 4 hours after tamsulosin results in the C_{max} values of both drugs occurring at the same time).

In both trials, a significant number of patients experienced standing systolic blood pressures less than 85 mmHg (Tables 3 and 4).

Table 3. Terazosin (Trial 100480): Summary of Part I and Part II patients with standing systolic BP < 85 mmHg:

	Run-in or prior to treatment	Placebo	Vardenafil 10 mg	Vardenafil 20 mg
Part I	1/30	1/28	3/29	7/28
Part II		0/9	6/8	2/9

The combination of vardenafil 10 or 20 mg with terazosin 10 mg at steady state caused hypotension (standing SBP < 85) in 3 of 29 subjects with the 10 mg dose of vardenafil and in 7 of 28 patients with the 20 mg dose of vardenafil with dose separation. The 3 patients in the 10 mg dose group were all asymptomatic.

When 10 or 20 mg vardenafil was dosed simultaneously with terazosin 10 mg, a significant proportion of patients experienced significant hypotension and this portion of the study was terminated.

Table 4. Tamsulosin (Trial 100480): Summary of Part I and Part II patients with standing systolic BP < 85 mmHg:

Patients with systolic blood pressure < 85 mmHg

	Placebo	Vardenafil 10 mg	Vardenafil 20 mg
Part I	0/21	0/21	1/24
Part II	0/15	2/16	0/13

In the terazosin study, healthy volunteers were up-titrated to 10 mg terazosin. Although it can be argued that the design of this study resulted in patients who were on high doses of terazosin who were, therefore, prone to significant lowering of blood pressure, subsequent dosing with vardenafil resulted in further decreases of blood pressure to unacceptable levels.

In Part 1 of the tamsulosin study, 5 patients dosed with 10 mg vardenafil had standing systolic blood pressures < 100 mmHg and 4 patients dosed with 20 mg had standing systolic blood pressures < 100 mmHg (one had a BP of 80/60). In Part 2, 2 patients had standing SBP < 85 mmHg following 10 mg vardenafil (BP's = 80/42 and 80/58) and 5 patients had a SBP < 100 following 20 mg vardenafil. Based on the results of these 2 studies, I believe that vardenafil (at least at doses of 10 and 20 mg) should be contraindicated in patients taking alpha blockers.

In response to a labeling discussion with the sponsor concerning the use of 5 mg vardenafil with alpha blockers, the sponsor cited a study report that had not yet been submitted. DRUDP requested that this study report be submitted to the NDA. On August 17, 2003, the sponsor submitted this abbreviated study report for Trial 100535. This study was designed to evaluate the expected additive BP lowering effect of 5 mg vardenafil compared to placebo when administered on a background of stable chronic alpha blocker therapy (terazosin or tamsulosin) in patients with BPH. Vardenafil 5 mg was dosed either simultaneously with the alpha blocker or with a 6 hour separation from the alpha blocker. Two cohorts of 21 subjects were evaluated.

In patients on terazosin 5 mg, one patient had a BP of 99 when dosed simultaneously with 5 mg vardenafil and one patient had a BP of 98 when dosed at 6 hours with vardenafil. In those patients on 10 mg terazosin, 1 of 9 patients had a BP of < 85 mmHg when dosed simultaneously and 1 of 9 patients had a BP of 93 when dosed at 6 hours. In the tamsulosin group dosed simultaneously, 2 of 20 patients had a systolic BP < 85 mmHg and when

doses were separated by 6 hours, 2 of 20 patients also had a BP of < 85 mmHg.

The narrative for patient # 4012 is as follows:

A 15-Day adverse event safety report documenting dizziness and hypotension was submitted on April 28, 2003, on patient 100535-4012. A 62-year-old man in the vardenafil 5mg or placebo + terazosin trial experienced hypotension, dizziness and lightheadedness 1 hour following simultaneous administration of vardenafil 5 mg + terazosin 10 mg. His blood pressure was 80/60 and HR of 74. Blood pressure prior to dosing was 126/79. He had a history of hyperlipidemia, HTN, BPH, and seasonal allergies. Concomitant medications were terazosin, calcium, proscar, and ginko biloba.

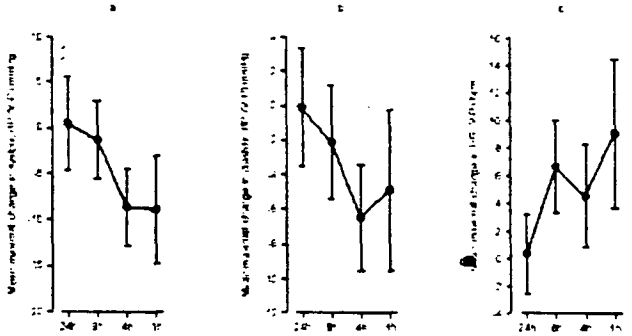
The results of this trial using 5 mg vardenafil do not support the safe use of this dose in patients taking alpha blockers. Until further data with the 2 lowest doses of vardenafil are available, I believe that vardenafil should be contraindicated in patients taking alpha blockers.

iii) "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). 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.

In response to the approvable letter issue dealing with the possible **drug-drug interaction of Levitra and nitrates,** the sponsor submitted the results of **Trial 10720.** In this trial, the pharmacodynamic (blood pressure and heart rate) interaction between vardenafil (20mg) and a standard dose of 0.4 mg sublingual nitroglycerin with separation of the 2 drugs by 24 hours, 8 hours, 4 hours, and 1 hour was evaluated. Eighteen (18) healthy male subjects (age 40-69) were included in the study. Mean age was 53 years.

The results of this study are shown in Figure 1.

Figure 1. Point estimates of a) SBP, b) DBP, and c) HR treatment effects of pre-dosing with vardenafil with 90% CI (0-2 hr data)



Source: Figure 11-2, study report p. 2-20.

Twenty-four hours of separation of the doses of vardenafil and NTG results in NTG effects that are similar to NTG alone. Dosing with vardenafil 20 mg eight hours prior to NTG resulted in a significant effect on HR and small effects on blood pressure. The effect of vardenafil 20 mg, 4 or 1 hour prior to NTG, produced a mean additional reduction of about 9 mmHg on systolic BP, about 6 mmHg on diastolic BP and 5 to 9 bpm increase on HR.

Although the concomitant use of vardenafil and nitrates is contraindicated, these results provide useful information for decisions regarding nitrate use in patients who are taking vardenafil and experience emergency cardiac problems.

iv) "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 10 mg. 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.

In response to the approvable letter issue dealing with the possible **drug-drug interaction of Levitra (20 mg) and aspirin,** the sponsor submitted the results of **Trial 100482.** This drug-drug interaction study evaluated the effect of vardenafil 20 mg on bleeding time at one and four hours on a background of aspirin 162 mg/day.

Vardenafil alone did not affect bleeding time and bleeding time was not significantly altered in subjects receiving aspirin in combination with vardenafil 20 mg.

v) "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 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 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."

The chemistry reviewer recommended approval of NDA 21-400 based on a review of chemistry, maufacturing, and control issues that pertain to the drug product Levitra (vardenafil HCl) Tablets of all requested dosage strengths including the 2.5 mg tablet (2.5, 5.0, 10, and 20 mg).

vi) "Significant back pain was reported by subjects administered Levitra 40 mg 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. 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, rhabdomyolysis, and other inflammatory processes."

The possible mechanisms underlying back pain/myalgia associated with vardenafil were evaluated. These findings revealed: 1) myalgia and back pain were not associated with any clinically significant CK changes even in subjects where these events caused discontinuation; 2) isolated myalgia of the long muscles in the back and in the legs without any muscle weakness or neurological deficits, as assessed by consultant neurologist's evaluation, and; 3) no evidence for an underlying pathophysiological mechanism from a battery of immunological and virological tests. Testing included C-reactive protein, P-ANCA, anti-ds DNA, Anti-Jo-1, anti-SSA, anti-SSB, anti-centromere Ab, anti-PM Scl, and anti-histone. In the clinical studies a total of 9 subjects reported back pain events (10720-001-1024, 100478-001-1027, 100478-002-2044, 100478-002-2022, 100478-002-2039, 100478-002-2010, 100478-002-2035, Subject 022 in Study 100480, and Subject 1007 in Study 100481). Seven subjects were in the vardenafil group, 1 in placebo, and 1 in the sildenafil group).

The etiology of back pain seen with vardenafil exposure is unknown. This adverse event appears to a "drug class effect" of PDE5 inhibitors. The back pain generally subsides within 48 hours of discontinuing the drug. There is no associated significant CK increase. Back pain is associated with high doses of

vardenafil and, in the Phase 3 controlled clinical trials, the incidence of back pain was not different from placebo.

vii) "Levitra can inhibit phosphodiesterase Type 6 in the retina as evidenced by color vision 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. 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 Ophthalmological Drug Products (DAAOP) can assess the acceptability of the protocol to fulfill this requirement."

The ophthalmology consultant reviewed clinical studies 10197, 100196, and 10125, the safety update, and the proposed label. From an ophthalmologic prospective, the consultant "found no objection to the approval of this NDA provided that the labeling is consistent with other phosphodiesterase inhibitors." The consultant also found "many events listed in the Safety Update which deserve further follow-up." The consultant's comments and questions will be sent to the sponsor. The consultant also recommended that Phase 4 studies be required ("repeated dose studies evaluating the effect of vardenafil on retinal function be conducted and submitted for review"). The consultant also revised the ophthalmological portions of the label. I agree with the consultant's recommendations.

3. Clinically relevant issues from other discipline's reviews

A. Chemistry

The chemistry reviewer recommended approval of NDA 21-400 based on a review of chemistry, maufacturing, and control issues that pertain to the drug product Levitra (vardenafil HCl) Tablets of all requested dosage strengths including the 2.5 mg tablet (2.5, 5.0, 10, and 20 mg).

B. Pharmacology-toxicology

No additional pharmacology-toxicology data were submitted in the "complete response to approvable action."

C. Clinical Pharmacology

The clinical pharmacology reviewer recommended that this NDA was "acceptable."

Vardenafil is metabolized primarily CYP 3A4. The T_{max} is approximately 1 hour and the terminal half-life is approximately 4 to 5 hours.

I agree with the following recommendations which have been made by the clinical pharmacology reviewer:

Geriatric dosing: In a healthy volunteer study of elderly males (>65 years) and younger males (18-45 years), mean C_{max} and AUC values were 34% and 52% higher, respectively, in the older males. Consequently, a lower starting dose of vardenafil (5 mg) in patients > 65 years of age should be considered.

Renal insufficiency: In volunteers with mild renal impairment (CLcr =50-80 ml/min), the pharmacokinetics of vardenafil were similar to those observed in a control group with normal renal function. In the moderate (CLcr = 30-50 ml/min) , or severe (CLcr <30 ml/min), renal impairment groups, the AUC of vardenafil was 20-30% higher compared to those observed in a control group with normal renal function (CLcr >80 ml/min). No dose adjustment in patients with mild, moderate, and severe renal impairment is required. Vardenafil has not been evaluated in patients on renal dialysis.

Hepatic impairment: For patients with mild hepatic insufficiency (Child-Pugh A), no dose adjustment is required. Vardenafil clearance is reduced in patients with moderate hepatic impairment (Child-Pugh B) and a starting dose of 5 mg vardenafil is recommended. The maximum dose in patients with moderate hepatic impairment should not exceed 10 mg. Vardenafil has not been evaluated in patients with severe hepatic impairment (Child-Pugh C).

Concomitant medications: For ritonavir, a single dose of 2.5 mg vardenafil should not be exceeded in a 72-hour period. For indinavir, ketoconazole 400 mg and itraconazole, a single dose of 2.5 vardenafil should not be exceeded in a 24-hour period. For ketoconazole 200 mg daily and erythromycin, a single dose of 5 mg vardenafil should not be exceeded in a 24-hour period.

D. Statistics

The statistician reviewed the statistical analysis of the QT trial 10929. None of the other materials submitted in the complete response to approvable action required statistical consultation.

4. Review of specific trials

A. Trial 10929: In response to the approvable letter issue dealing with the QT interval the sponsor submitted the results of Trial 10929. The primary objective of this study was to rule out a greater than 10 msec effect (i.e. to demonstrate lack of effect) of a single 80 mg oral dose of vardenafil on QTc interval as compared to placebo, as measured by the change from baseline at the 1 hour post-dose time point. The 80 mg dose was chosen because the sponsor believed that maximum plasma concentrations achieved with this dose were above the maximum plasma

levels achieved with 5 mg vardenafil and potent CYP 3A4 inhibition (with ritonavir). (The to be marketed doses of vardenafil are 2.5, 5, 10, and 20 mg). The one hour time point was chosen because this approximates T_{max}. Secondary objectives were to: 1) characterize the effect of a single 80 mg oral dose of vardenafil on QTc interval as compared to placebo, as measured by the change from baseline at the time of maximum concentration (T_{max}). 2) to characterize the effect of a single oral dose of 400 mg of moxifloxacin on QTc interval relative to placebo. 3) characterize the effect on QTc relative to placebo of single oral doses of 10 mg of vardenafil and of 50 and 400 mg of sildenafil. 4) characterize the effect on QT and HR relative to placebo of single oral doses of 400 mg of moxifloxacin, 10 and 80 mg of vardenafil and of 50 and 400 mg of sildenafil. 5) characterize the pharmacokinetics of vardenafil, sildenafil and moxifloxacin. 6) explore the relationship between vardenafil, sildenafil and moxifloxacin exposure versus ECG parameters (QTc, QT intervals and HR).

The trial was a double-blind, randomized, single dose, 6-way crossover, period-balanced study in healthy adult males. Each subject participated in 6 study sessions separated by a minimum washout period of at least 3 days. Each subject received the following six regimens in a randomized crossover fashion (AFBECD, BACFDE, CBDAEF, DCEBFA, EDFCAB, or FEADBC). (Table 5)

Table 5. Regimen description

Regimen	Regimen Description
A	Vardenafil 10 mg
B	Vardenafil 80 mg
C	Sildenafil 50 mg
D	Sildenafil 400 mg
E	Moxifloxacin 400 mg
F	Placebo

Source: Study report 10929, page 11.

The study population consisted of healthy adult men between 45 and 60 years of age. Sixty men were enrolled and one man withdrew prior to dosing. Data from 59 subjects are included in the statistical analysis.

Six 12-lead EKGs taken approximately 1 minute apart were obtained at specified times (-0.5, -0.25, predose, 1, 1.5, 2.5, and 4 hours). Conduction intervals from the 12-lead EKGs were manually read and confirmed by an external cardiologist. All EKGs were read blinded. The final conduction intervals entered into the database were those generated by the over-reading cardiologist. Patients were not dosed if the pre-dose ECG showed either PR interval > 240 msec or ≤ 110 msec; or QTc > 440 msec. Blood samples for pharmacokinetic analysis of vardenafil, sildenafil and moxifloxacin were collected from each subject at times 0, 0.5, 1, 1.5, 2.5, and 4 hours following single oral administration on Day 1 of each period.

The primary endpoint was the change in Fridericia's correction formula ($QTcF=QT/RR^{1/3}$) from baseline at 1 hour post-dose. QTc at 1 hour post-dose was determined from the average of the 6 replicate measurements taken at 1 hour post-dose and baseline QTc was determined from the average of all 18 pre-dose measurements. Secondary endpoints included change from baseline at the time of maximum concentration (T_{max}), raw QT intervals and heart rate, and individually corrected QT intervals (QTci). QTci is calculated using the formula QTci = QT + [b*(1-RR)]. The variable "b" was obtained from fitting each subject's data into the linear regression model QT= a + b * RR, where RR=60/HR. Based on median values, T_{max} occurred at approximately 1.2 hour postdose following oral 10 and 80 mg vardenafil. Exploratory endpoints included maximum change from baseline and time averaged change from baseline.

The change in heart rate at one hour post-dose is shown in Table 6.

Table 6. Change from Baseline in HR (bpm) at 1 hour post-dose

Regimen	Means[1] (s.e.)	Comparison	Point Estimate[2]	90% CI
Placebo	-3 (0.5)			
Primary Comparison:				
80 mg vardenafil	3 (0.5)	80 mg vardenafil Placebo	6	(5, 7)
Secondary Comparison:				
10 mg vardenafil	2 (0.5)	10 mg vardenafil Placebo	5	(4, 6)
50 mg sildenafil	1 (0.5)	50 mg sildenafil Placebo	4	(3, 5)
400 mg Sildenafil	2 (0.5)	400 mg sildenafil Placebo	5	(4, 6)
400 mg moxifloxacin	-1 (0.5)	400 mg moxifloxacin Placebo	2	(1, 3)

1 represents adjusted arithmetic mean 2 represents difference between arithmetic means
Note: above results are rounded to the nearest integer (accounts for apparent discrepancies between means and point estimates and asymmetry of CI). Source: Study report 10929. Table 15, page 62.

Change in QTcF and Qtci at one hour:

Change in QTcF:

Point estimates and 90% confidence intervals for change from baseline at 1 hour post-dose for QTc corrected using Fridericia's formula and QTCi are provided in Tables 7 and 8.

Table 7: Change from baseline in QTcF (msec) at 1 hour post-dose

Regimen	Means[1] (s.e.)	Comparison	Point Estimate[2]	90%CI
Placebo	0 (0.7)			
Primary Comparison:				
80 mg vardenafil	10 (0.7)	80 mg vardenafil Placebo	10	(8, 11)
Secondary Comparison:				
10 mg vardenafil	8 (0.7)	10 mg vardenafil Placebo	8	(6, 9)
50 mg sildenafil	7 (0.7)	50 mg sildenafil Placebo	6	(5, 8)
400 mg Sildenafil	9 (0.7)	400 mg sildenafil Placebo	9	(8, 11)
400 mg moxifloxacin	8 (0.7)	400 mg moxifloxacin Placebo	8	(6, 9)

1 represents adjusted arithmetic mean 2 represents difference between arithmetic means Note: above results are rounded to the nearest integer. Source: Study report 10929. Table 12, page 60.

Table 8: Change from Baseline in QTci (msec) at 1 hour post-dose

Regimen	Means[1] (s.e.)	Comparison	Point Estimate[2]	90% CI
Placebo	2 (0.7)			
Primary Comparison:				
80 mg vardenafil	8 (0.7)	80 mg vardenafil Placebo	6	(4, 7)
Secondary Comparison:				
10 mg vardenafil	6 (0.7)	10 mg vardenafil Placebo	4	(3, 6)
50 mg sildenafil	6 (0.7)	50 mg sildenafil Placebo	4	(2, 5)
400 mg Sildenafil	7 (0.7)	400 mg sildenafil Placebo	5	(4, 7)
400 mg moxifloxacin	9 (0.7)	400 mg moxifloxacin Placebo	7	(5, 8)

1 represents adjusted arithmetic mean 2 represents difference between arithmetic means
Note: above results are rounded to the nearest integer (accounts for apparent discrepancies between means and point estimates and asymmetry of CI). Source: Study report 10929. Table 13, page 61.

QTcF and QTci were also determined at Tmax and the difference for each drug and dose in comparison to placebo and are shown in Tables 9 and 10.

Table 9. Change from baseline in QTcF (msec) at Tmax post-dose

Regimen	Comparison	Point Estimate[1]	90% CI
Primary Comparison:			
80 mg vardenafil	80 mg vardenafil Placebo	9	(8, 11)
Secondary Comparison:			
10 mg vardenafil	10 mg vardenafil Placebo	7	(5, 9)
50 mg sildenafil	50 mg sildenafil Placebo	6	(5, 8)
400 mg Sildenafil	400 mg sildenafil Placebo	6	(4, 7)
400 mg moxifloxacin	400 mg moxifloxacin Placebo	8	(7, 10)

1 represents difference between arithmetic means Source: Study report 10929. Table 16, page 63.

Table 10. Change from baseline in QTci (msec) at Tmax post-dose

Regimen	Comparison	Point Estimate[1]	90% CI
Primary Comparison:			
80 mg vardenafil	80 mg vardenafil Placebo	6	(5, 8)
Secondary Comparison:			
10 mg vardenafil	10 mg vardenafil Placebo	3	(2, 5)
50 mg sildenafil	50 mg sildenafil Placebo	3	(2, 5)
400 mg Sildenafil	400 mg sildenafil Placebo	5	(3, 6)
400 mg moxifloxacin	400 mg moxifloxacin Placebo	7	(6, 9)

1 represents difference between arithmetic means Source: Study report 10929. Table 17, page 63.

Outlier analysis for vardenafil:

There were no uncorrected QT values > 500 msec.

QTcF

QTcF > 450 msec:
There were no QTcF values > 450 msec in any of the drug groups, including moxifloxacin.

QTcF increase > 60 msec:
There were no mean differences (average of 6 recordings) greater than 60 msec for any subject or drug.

QTcF increase > 30 msec:
There was 1 subject with a mean difference (average of 6 recordings) of QTcF > 30 msec in the change from baseline following sildenafil 400 mg at 1 hr post-dose.

Qtci

QTci > 480 msec:
There were no occurrences of QTCi > 480 msec.

QTci >450 msec:
There were 24 out of 16749 (0.14%) occurrences of QTci greater than 450 msec (but less than or equal to 480 msec). These 24 occurrences were seen in 3 out of 58 subjects. Out of these 24 data points, 3 were in 80 mg vardenafil group (range 450-461 msec), 19 were in 50 mg sildenafil group (range 450-461 msec) and 2 were in 400 mg moxifloxacin group (range 451-458 msec).

QTci > 60 msec:
There were no mean differences (average of 6 recordings) greater than 60 msec at 1 hr post-dose.

See comments concerning QT study in Executive Summary.

B. Trials 100480 and 100481: In response to the approvable letter issue dealing with the possible drug-drug interaction of Levitra and alpha-blockers used for the treatment of benign prostatic hyperplasia, the sponsor submitted the results of Trials 100480 and 100481. Trial 100480 evaluated the drug-drug interaction with terazosin and Trial 100481 the drug-drug interaction with tamsulosin.

Trial 100480 ("A randomized, double-blind, placebo-controlled, period-balanced, two-part, three period crossover drug interaction study of vardenafil (10 mg and 20 mg) and terazosin (10 mg) in healthy males aged 45 to 75 to evaluate changes in blood pressure") was a PK/PD study which evaluated the effect of administration of Levitra 10 and 20 mg given either together with or with a dose separation of 6 hours from terazosin 10 mg. (The Tmax of both vardenafil and terazosin is approximately 1 hour.)

Objectives: The primary objective was to compare changes in blood pressure, induced by vardenafil (10 mg and 20 mg) and placebo, in healthy male subjects when administered to subjects receiving the alpha-blocker terazosin (10 mg) at steady state.

Design and conduct summary: This was a Phase I, single-center, two part, randomized, period balanced, placebo-controlled, double-dummy, three-way

crossover study. Parts I and II of the study were double-blind with respect to placebo, 10 mg vardenafil and 20 mg vardenafil. Terazosin was given in open-label fashion.

Non-hypertensive subjects were uptitrated to a final dose of terazosin 10 mg during days 1 through 14 and continued to received 10 mg terazosin at 7 a.m. throughout Parts I and II of the study. On day 15, subjects began Part I, in which they were randomized to receive one of the following regimens over three sessions: (A) a single oral dose of 10 mg vardenafil; (B) a single oral dose of 20 mg vardenafil, (C) a single dose of vardenafil-matched placebo. At each session, vardenafil or placebo was dosed 6 hours after terazosin dosing (at approximately 1 p.m.) to achieve Cmax separation of six hours. There was a 48-hour washout period between study regimens.

Comment: Terazosin was uptitrated to 10 mg in all patients. Lower doses of terazosin were not evaluated.

All subjects were to participate in Part II beginning approximately 60 hours after the final dose of study medication in Part I. On day 22, subjects began Part II (7 a.m. vardenafil/placebo dosing *simultaneously* with terazosin to achieve simultaneous Cmax), in which they were randomized to receive one of the following regimens over three sessions (in addition to terazosin 10 mg): (D) a single oral dose of a vardenafil-matched placebo; (E) a single oral dose of 10 mg vardenafil; (F) a single oral dose of 20 mg vardenafil. Terazosin dosing and vardenafil or placebo dosing occurred at the same time (approximately 07:00). There was a 48-hour washout period between study regimens.

Table 11. Dosing regimens (Source- study report text, page 59)

Regimen	Study Drug-single dose	Timing
A	Placebo	6 hours after terazosin
B	Vardenafil 10 mg	6 hours after terazosin
C	Vardenafil 20 mg	6 hours after terazosin
D	Placebo	simultaneous with terazosin
E	Vardenafil 10 mg	simultaneous with terazosin
F	Vardenafil 20 mg	simultaneous with terazosin

The terazosin titration consisted of one mg on days 1-3, two mg on days 4-6, five mg on days 7-10 and ten mg on days 11-14. Orthostatic hypotension was defined as a reduction of systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of at least 10 mm Hg within 3 minutes of standing.

Study population: Healthy male subjects between 45 and 75 years of age were eligible for the study. Thirty subjects were enrolled (mean age=58).

Run-in Phase (Days 1 to 14):
The following table (Table 12) summarizes standing and supine mean (SE) blood pressure and heart rate prior to terazosin treatment and on Day 15 of terazosin

treatment in the entire study population (n=30). There was a reduction in mean blood pressure values in subjects after terazosin alone.

Table 12. Standing and supine mean (SE) blood pressure and heart rate prior to terazosin treatment and on Day 15 of terazosin treatment in the entire study population (n=30)

Parameter	Day 1	Day 15	
		Pre- terazosin a.m. dose	6 h post-terazosin a.m. dose
Standing Systolic BP (mm Hg)	138 (3.5)	120 (2.4)	113 (2.3)
Supine Systolic BP (mm Hg)	130 (3.1)	120 (2.2)	122 (2.3)
Standing Diastolic BP (mm Hg)	80 (1.9)	75 (1.4)	67 (1.5)
Supine Diastolic BP (mm Hg)	74 (1.5)	71 (1.3)	69 (1.4)
Standing HR (bpm)	71 (1.4)	75 (1.6)	75 (2.1)
Supine HR (bpm)	64 (1.3)	63 (1.4)	60 (1.6)

Source: Study report, page 19

Following terazosin titration only, standing SBP decreasedby 18 mm Hg. All patients were uptitrated to 10 mg terazosin and no lower doses of terazosin were evaluated.

Part I (vardenafil/placebo administered 6 hours after 10 mg of terazosin): Following single doses of both 10 mg and 20 mg vardenafil, standing and supine, systolic and diastolic blood pressures were lower when compared to placebo. Additionally, the magnitude of the effect for all parameters appeared to increase with increasing dose of vardenafil. A summary of the comparisons of interest for maximal change from baseline in standing blood pressure and heart rate are provided in the Table 13 below:

Table 13 Maximal change from baseline in standing blood pressure and heart rate- Part I

Parameter	Regimen	Means[1](SE)	Comparison	Point Estimate[2]	95% CI
Primary PD Parameter					
Standing Sys BP (mm Hg)[3]	A	-10(1.40)			
	B	-17(1.40)	B - A	-7	(-10,-3)
	C	-21(1.40)	C - A	-11	(-14,-7)
Secondary PD Parameter					
Standing Diastolic BP (mm Hg)[3]	A	-5(0.96)			
	B	-9(0.95)	B - A	-4	(-6, -1)
	C	-12(0.96)	C - A	-7	(-9, -4)
Standing HR (bpm)[4]	A	4(1.61)			
	B	11(1.60)	B - A	7	(3, 10)
	C	11(1.60)	C - A	7	(3, 10)

1 represents adjusted arithmetic mean from ANCOVA model
2 represents difference between adjusted arithmetic means
3 maximal change from baseline (minimum baseline)
4 maximal change from baseline (maximum baseline)
Note: above results are rounded to the nearest integer. (accounts for apparent discrepancies between means and point estimates and asymmetry of CI)
Regimen Key: A Placebo; B 10 mg Vardenafil; C 20 mg Vardenafil
Source: Study report, page 20

An additional 7 mmHg (95% CI: -10, 3) and 11 mmHg (95% CI; -14, -7) decreases in standing SBP were seen for vardenafil 10 mg and vardenafil 20 mg, respectively, when given 6 hours after terazosin.

Subjects with standing systolic blood pressures less than 85 mmHg in Part 1:

In Part 1, there were twelve subjects with a standing SBP < 85 mmHg (1 with terazosin alone at steady state, 1 following terazosin + placebo, 3 following terazosin + vardenafil 10 mg, and 7 following terazosin + vardenafil 20 mg.

Vardenafil 10 mg group

Patient number	Lowest blood pressure (mmHg)	Comments
5	83/41	asymptomatic – 15 hours post vardenafil dose (patient also had a standing BP of 84/60 15 hours after a dose of placebo)
8	76/62	asymptomatic
15	84/54	asymptomatic

Vardenafil 20 mg group

Patient	Lowest blood pressure (mmHg)	Comments
3	78/58	asymptomatic
8	82/67	asymptomatic
11	82/51	asymptomatic
15	64/45	asymptomatic
18	71/40	asymptomatic (patient also had a standing BP of 82/61 following 10 mg terazosin dose without vardenafil)
24	82/54	asymptomatic
25	73/41	BP = 78/54 6 hours after 10 mg terazosin, but before vardenafil. No symptoms were reported.

Part II (vardenafil/placebo administered concurrently with 10 mg of terazosin):

THIS PORTION OF THE STUDY WAS TERMINATED BECAUSE OF THE HIGH RATE OF SIGNIFICANT HYPOTENSION.

The summary statistics for primary and secondary endpoints for Part II are provided below in Table 14.

Table 14. Summary statistics for primary and secondary endpoints are provided below

	Placebo n = 9	Vardenafil 10 mg n = 8	Vardenafil 20 mg n = 9
Standing SBP (mm Hg)			
Baseline	122 (13.7)	118 (13.9)	118(13.8)
Minimum	108 (6.5)	82 (10.0)	90 (6.6)
Max Change from Baseline	-14 (13.1)	-37 (9.0)	-28 (14.5)
Mean Change from Baseline	4 (6.9)	-2 (8.0)	-4 (7.1)
Standing DBP (mm Hg)			
Baseline	77 (6.8)	71 (7.0)	75 (4.8)
Minimum	66 (6.5)	50 (7.5)	54 (4.7)
Max Change from Baseline	-11(6.9)	-20 (5.8)	-20 (5.6)
Mean Change from Baseline	4 (6.4)	-0 (4.6)	-2 (5.6)
Standing Heart Rate (bpm)			
Baseline	75 (6.5)	76 (12.1)	72 (11.5)
Maximum	95 (8.8)	100 (18.7)	100 (12.8)
Max Change from Baseline	19 (5.2)	24 (10.3)	28 (11.7)
Mean Change from Baseline	-6 (6.9)	-3 (8.1)	-3 (7.7)
Supine SBP (mm Hg)			
Baseline	132 (13.9)	118 (13.0)	120 (8.1)
Minimum	117 (9.6)	97 (9.9)	98(4.0)
Max Change from Baseline	-15 (10.1)	-22 (5.6)	-22(10.2)
Mean Change from Baseline	2 (8.1)	-2 (6.7)	-4 (7.7)
Supine DBP (mm Hg)			
Baseline	76 (5.5)	68 (8.3)	71 (4.8)
Minimum	65 (5.9)	54 (8.4)	54 (6.3)
Max Change from Baseline	-11 (4.4)	-14 (5.2)	-16 (6.6)
Mean Change from Baseline	4 (5.6)	0 (5.1)	-3 (4.3)
Supine Heart Rate (bpm)			
Baseline	70 (7.4)	65 (7.8)	64 (8.7)
Minimum	77 (5.4)	80 (11.0)	82 (8.2)
Max Change from Baseline	7 (7.4)	16 (9.5)	17 (6.4)
Mean Change from Baseline	-6 (5.5)	-4 (7.0)	-2 (4.9)
Orthostatic SBP (mm Hg)			
Baseline	-10 (13.1)	-0 (5.5)	-2 (7.5)
Minimum	-18 (6.4)	-24 (12.2)	-24 (10.9)
Max Change from Baseline	-8 (12.8)	-24 (10.2)	-22 (13.1)
Mean Change from Baseline	2 (8.4)	0 (8.8)	-0 (7.7)
Orthostatic DBP (mm Hg)			
Baseline	1 (5.8)	3 (2.1)	4 (4.4)
Minimum	-5 (3.2)	-10 (7.1)	-8 (5.3)
Max Change from Baseline	-6 (5.1)	-13 (8.0)	-12 (7.6)
Mean Change from Baseline	-0 (5.4)	-0 (5.1)	1 (4.6)

Source: Study report, page 22.

In Part II, similar trends as for Part I were observed for standing and sitting blood pressures and heart rates, with the magnitude of the effect appearing to be larger than that observed for Part I.

The trends in Part II are similar but the magnitude of affect is larger. Vardenafil 10 mg caused a 23 mmHg greater decrease compared to placebo in standing SBP in Part II compared to 7 mmHg in Part I. Vardenafil 20 mg caused a 14 mmHg greater decrease in standing SBP in Part II compared to 11 mmHg in Part I. Heart rate increased by 5 and 9 bpm, with vardenafil 10 and 20 mg, respectively, in Part II, compared to 7 bpm with both 10 and 20 mg of vardenafil in Part I.

The lowest blood pressures in the two groups of patients (10 and 20 mg) are shown below.

Vardenafil 10 mg and terazosin 10 mg given simultaneously

Patient number	Lowest systolic BP (mmHg)	Comments
3	84/62	asymptomatic
8	81/51	asymptomatic
14	73/48	asymptomatic
22	75/53	asymptomatic except lower back pain
23	69/42	asymptomatic
30	82/45	No symptoms reported

Vardenafil 20 mg and terazosin given simultaneously

Patient number	Lowest systolic BP (mmHg)	Comments
6	81/67	Dizziness after phlebotomy
27	82/52	Site "unable to obtain a BP reading while standing" – dizziness, sweating, and treated with IV saline

Summary of Part I and Part II patients with BP < 85 mmHg:

	Run-in or prior to treatment	Placebo	Vardenafil 10 mg	Vardenafil 20 mg
Part I	1/30	1/28	3/29	7/28
Part II		0/9	6/8	2/9

The combination of vardenafil 10 or 20 mg with terazosin 10 mg at steady state caused hypotension (SBP < 85) in 3 of 29 subjects with the 10 mg dose of vardenafil and in 7 of 28 patients with the 20 mg dose of vardenafil with dose separation. The 3 patients in the 10 mg dose group were all asymptomatic.

When 10 or 20 mg vardenafil was dosed simultaneously with terazosin 10 mg, a significant proportion of patients experienced significant hypotension and this portion of the study was terminated.

A 15-Day adverse event safety report documenting dizziness and hypotension was submitted on April 28, 2003, on patient 100535-4012. (At that time, the trial was an ongoing study of the drug-drug interaction of 5 mg vardenafil in patients with symptomatic BPH on stable doses of terazosin and tamsulosin. A 62-year-old man experienced hypotension, dizziness and lightheadedness 1 hour following simultaneous administration of vardenafil 5 mg + terazosin 10 mg. His blood pressure was 80/60 and HR of 74. Blood pressure prior to dosing was 126/79. He had a history of hyperlipidemia, HTN, BPH, and seasonal allergies. Concomitant medications were terazosin, calcium, proscar, and ginko biloba.

Trial 100481 ("A randomized, double-blind, placebo-controlled, period-balanced, two-part, three period crossover drug interaction study of vardenafil (10 mg and 20 mg) and tamsulosin (0.4 mg) in healthy males aged 45 to 75 to evaluate changes in blood pressure" was a PK/PD study which evaluated the effect of administration of Levitra 10 and 20 mg given either 4 or 10 hours after the tamsulosin dose to achieve either simultaneous C_{max} of both drugs or a 6 hour separation of C_{max} respectively.

Design and conduct summary: This was a Phase I, two center, two part, randomized, period balanced, placebo-controlled, double-dummy, three way crossover study. Parts I and II of the study were double-blind with respect to placebo, 10 mg vardenafil and 20 mg vardenafil. Tamsulosin 0.4 mg was given in open-label fashion.

Subjects received tamsulosin 0.4 mg at 7 a.m. during days 1 through 5 to reach steady-state and continued tamsulosin throughout Parts I and II of the study. On day 6, subjects began Part I, in which they were randomized to receive one of the following regimens over three sessions: (A) a single oral dose of placebo; (B) a single oral dose of 10 mg vardenafil, (C) a single dose of 20 mg vardenafil. At each session, vardenafil or placebo was dosed 10 hours after tamsulosin dosing to achieve C_{max} separation of six hours. There was a 48-hour washout period between study regimens.

All subjects were to participate in Part II beginning approximately 60 hours after the final dose of study medication in Part I. On day 13, subjects began Part II (vardenafil/placebo) dosing 4 hours post tamsulosin to achieve simultaneous C_{max}), in which they were randomized to receive one of the following regimens over three sessions (in addition to tamsulosin 0.4 mg): (D) a single oral dose of a vardenafil-matched placebo; (E) a single oral dose of 10 mg vardenafil; (F) a single oral dose of 20 mg vardenafil. There was a 48-hour washout period between study regimens.

Table D.1 Dosing regimens (Source- study report text, page 23)

Regimen	Study Drug-single dose	Timing
A	Placebo	Cmax 6 hour separation
B	Vardenafil 10 mg	Cmax 6 hour separation
C	Vardenafil 20 mg	Cmax 6 hour separation
D	Placebo	simultaneous Cmax
E	Vardenafil 10 mg	simultaneous Cmax
F	Vardenafil 20 mg	simultaneous Cmax

Study population: Healthy male subjects between 45 and 75 years of age. A total of 31 subjects were randomized to treatment and enrolled in the study.

Endpoints:
Pharmacodynamic: Pharmacodynamic endpoints consisted of standing and supine systolic and diastolic blood pressures and standing and supine heart rates.

Run-in Phase:
Mean BP and HR values prior to tamsulosin treatment on Day 1 and Day 6 are shown in Table 15.

Table 15. Standing and supine mean (SE) blood pressure and heart rate prior to tamsulosin treatment on Day 1 and Day 6

Parameter	Day 1	Day 6	
	Pre-dose	Pre-dose	2 h post- dose
Standing Systolic BP (mm Hg)	126 (3.2)	122 (3.0)	121 (2.8)
Standing Diastolic BP (mm Hg)	83 (1.6)	83 (1.2)	82 (1.7)
Supine Systolic BP (mm Hg)	126 (3.0)	121 (2.6)	123 (2.5)
Supine Diastolic BP (mm Hg)	78 (1.7)	80 (1.5)	81 (1.4)
Standing HR (bpm)	69 (1.8)	74 (2.1)	71 (1.7)
Supine HR (bpm)	62 (1.8)	66 (2.3)	65 (1.9)

Source: study report page 71 table 22.

Part I: vardenafil/placebo administration 10 hours after 0.4 mg tamsulosin

Mean maximal reduction of standing systolic blood pressure was, on average, 4 mmHg and 8 mmHg greater following single doses of 10 mg and 20 mg vardenafil, respectively, relative to placebo. The average maximal reduction from baseline following placebo was 9 mmHg. Additionally, the magnitude of the effect appeared to increase with increasing doses of vardenafil. See table 16.

Table 16. Maximal change from baseline in standing blood pressure and heart rate- Part I (n=20)

Parameter	Regimen	Means[1](SE)	Comparison	Point Estimate[2]	95% CI
Primary PD Parameter					
Standing Sys BP (mm Hg)[3]	A	-9 (2.1)			
	B	-13 (2.1)	B - A	-4	(-8, -1)
	C	-17 (2.1)	C - A	-8	(-11,-4)
Secondary PD Parameter					
Standing Diastolic BP (mm Hg)[3]	A	-8 (1.4)			
	B	-11 (1.4)	B - A	-3	(-6, 0)
	C	-12 (1.4)	C - A	-4	(-7, 0)
Standing HR (bpm)[4]	A	7 (2.1)			
	B	11(2.2)	B - A	4	(-2, 10)
	C	13 (2.2)	C - A	6	(0, 12)

1 represents adjusted arithmetic mean from ANCOVA model
2 represents difference between adjusted arithmetic means
3 maximal change from baseline (minimum minus baseline)
4 maximal change from baseline (maximum minus baseline)
Regimen Key: A Placebo; B 10 mg Vardenafil; C 20 mg Vardenafil

Lowest blood pressures after 10 and 20 mg dose of vardenafil in Part I

Patient #	lowest BP after 10 mg vardenafil in Part I "B"	lowest BP after 20 mg vardenafil in Part I "C"
201		**80/60**
202	120/60	105/65
203		100/60
204		
205	104/82	102/82
206	**98/60**	
207	**90/60**	**98/60**
208	**98/70**	100/70
209	**98/78**	100/60
210	102/62	**90/62**
211	100/80	102/78
212	110/64	104/60
213		
215		
1001	120/76	118/70
1002	104/62	104/60
1003	128/84	122/83
1004	126/90	110/80
1005	110/80	108/80
1006	**96/80**	106/68
1007	118/80	122/80
1008	110/72	104/66
1009	100/70	**98/70**
1010		120/94
1011	100/70	110/74
1012	112/96	110/88
1013	122/72	118/80

Part II. Vardenafil/placebo dosing 4 hours after tamsulosin 0.4mg

Mean maximal reduction in standing systolic blood pressure was, on average, 8 mmHg greater following single doses of both 10 and 20 mg vardenafil relative to placebo. The average maximal reduction from baseline following placebo was 11 mmHg. See Table 17.

Table 17. Maximal Change from Baseline- Part II

Parameter	Regimen	Means[1]	Comparison	Point Estimate[2]	95% CI
Primary PD Parameter					
Standing Sys BP (mmHg)	D	-11 (2.6)			
	E	-19 (2.5)	E-D	-8	(-14, -2)
	F	-19 (2.7)	F-D	-8	(-14, -1)
Secondary PD Parameter					
Standing Dia BP mmHg	D	-7 (2.5)			
	E	-14 (2.4)	E-D	-7	(-12, -2)
	F	-13 (2.5)	F-D	-7	(-12, -1)
Standing HR bpm	D	12 (3.0)			
	E	9 (3.0)	E-D	-3	(-8, 2)
	F	9 (3.1)	F-D	-2	(-8, 3)
Supine Sys BP (mm Hg)[3]	D	-12 (2.2)			
	E	-17 (2.2)	E-D	-5	(-9, -2)
	F	-15 (2.3)	F-D	-3	(-7, 0)
Supine Diastolic BP (mm Hg)[3]	D	-6 (1.7)			
	E	-10 (1.6)	E-D	-3	(-6, 0)
	F	-10 (1.7)	F-D	-4	(-7, -1)
Supine HR (bpm)[4]	D	8 (2.6)			
	E	6 (2.5)	E-D	-2	(-8, 3)
	F	9 (2.7)	F-D	1	(-5, 7)
Orthostatic Sys BP (mm Hg)[3]	D	-9 (2.1)			
	E	-11 (2.0)	E-D	-2	(-7, 2)
	F	-10 (2.1)	F-D	-1	(-6, 4)
Orthostatic Diastolic BP (mm Hg)[3]	D	-9 (1.5)			
	E	-10 (1.4)	E-D	-1	(-5, 3)
	F	-9 (1.6)	F-D	0	(-5, 4)

1 represents adjusted arithmetic mean from ANCOVA model
2 represents difference between adjusted arithmetic means
3 maximal change from baseline (minimum minus baseline)
4 maximal change from baseline (maximum minus baseline)
Regimen Key: A Placebo; B 10 mg Vardenafil; C 20 mg Vardenafil Source: Study report,table 25 page 75.

Serious adverse events:

There were no SAEs reported by the principal investigator during the study, however post hoc, the sponsor considered any episode of standing systolic blood pressure less than or equal to 85 mmHg, symptomatic hypotension and hypotension requiring treatment to be a serious adverse event. Three subjects qualified for this post hoc definition and are shown in Table 18.

Table 18. Subjects with Standing Systolic Blood Pressures < 85 mmHg

Subject	Period	Regimen	Day	Time*	Standing Sys BP (mmHg)	Standing Dia BP (mmHg)	Standing HR (bpm)
201	2	C	1	8	80	60	60
205	6	E	1	0.75	80	42	72
	6	E	1	1	80	38	80
209	5	E	1	1.5	80	58	120

C: 20 mg Vardenafil (Part I)
E: 10 mg Vardenafil (Part II)
* In relation to dosing of study medication (vardenafil/placebo) in hours

Narratives:
Subject 201: 53-year-old Caucasion male who experienced postural hypotension approximately 8 hours following his first dose of vardenafil 20 mg and 18 hours following dosing with tamsulosin 0.4 mg. Symptoms included lightheadedness, dizziness, and altered vision. The supine BP was 124/70 (HR 70) and standing BP was 80/60 (HR 60). He was treated with 550 cc intravenous normal saline with symptom resolution after 12 hours. The subject was withdrawn from the study.

Subject 205: 51-year-old Caucasion male who experienced orthostatic hypotension approximately 45 minutes following vardenafil 10 mg and approximately 4 hr and 45 minutes following tamsulosin 0.4 mg. He was asymptomatic and had a supine BP of 102/62 (HR 88) and standing BP of 80/42 (HR 72) with subsequent BP 80/38 (HR 80). His blood pressure returned to pre-vardenafil levels after 1 hour. The subject was withdrawn from the study.

Subject 209: 47-year-old Caucasion male who experienced asymptomatic orthostatic hypotension 1.5 hours following vardenafil 10 mg and 5.5 hours following tamsulosin. Standing BP was 80/58 (HR 120). The duration of the event was 30 minutes.

Patients with systolic blood pressure < 85 mmHg

	Placebo	Vardenafil 10 mg	Vardenafil 20 mg
Part I	0/21	0/21	1/24
Part II	0/15	2/16	0/13

Lowest blood pressure after vardenafil 20 mg in part II

Patient number	lowest BP after var 20 mg Part II
202	110/60
208	98/62
210	92/70
1001	90/60
1002	90/60
1004	126/84
1005	104/80
1006	100/74
1007	106/78
1008	92/70
1011	100/72
1012	110/82
1013	118/84

See comments concerning Trials 100480 and 100481 in the executive summary. I believe that vardenafil at doses of 10 and 20 mg should be contraindicated in patients taking alpha blockers.

5. **Summary comments on efficacy**

In the opinion of this reviewer, the 2.5, 5, 10, and 20 mg doses of vardenafil are effective for the "treatment of erectile dysfunction." The sponsor proposes to begin patients on the 10 mg dose and this reviewer agrees.

In support of the original NDA submission, the sponsor submitted the results of 4 primary efficacy studies (Trials 100249 and 10128 in the general erectile dysfunction population, Trial 100250 in patients with diabetes, and Trial 100285 in patients with erectile dysfunction following radical prostatectomy). The intent-to-treat population in these 4 trials combined was 2400. In addition to the 4 primary efficacy studies, the sponsor submitted Trial 100199 (a Phase 2b study enrolling generally healthier patients than the 4 major efficacy trials) and **Trial 10232 (a Phase 3 trial evaluating 2.5 and 5 mg doses).**

The 4 major efficacy trials are summarized in Table 19.

Table 19. Major efficacy trials.

Study # (Country)	Duration of treatment	Treatment groups	Number of patients ITT/ completer	ED population	Caucasian (%)	Mean age (range)
100249 (North America)	26 weeks	Placebo Vard 5 mg Vard 10 Vard 20	177/91 190/128 196/151 186/138	General (excluded radical prostatectomy)	77 77 80 82	57 (26-76) 58 (29-82) 57 (27-83) 58 (20-79)
10128 (Europe)	12 weeks	Placebo Vard 5 mg Vard 10 Vard 20 Sildenafil 50 mg	160/140 156/146 157/148 163/137 162/147	General (excluded radical prostatectomy)	68 66 68 67 68	56 (23-78) 57 (21-78) 55 (26-75) 56 (25-74) 56 (22-81)
100250 (North America)	12 weeks	Placebo Vard 10 Vard 20	140/121 149/131 141/127	Diabetics (Excluded radical prostatectomy)	79 82 78	57 (35-74) 58 (33-81) 57 (34-78)
100285 (North America)	12 weeks	Placebo Vard 10 Vard 20	137/97 139/114 147/119	Post-radical prostatectomy	93 99 87	60 (47-72) 61 (44-77) 60 (45-74)

Overall Trial Design

All 4 study designs were similar. All four trials were randomized, placebo-controlled, double-blind, parallel-group, multicenter studies and are outlined in Table 1 above. Three of the trials were conducted in North America and the fourth in Europe.

Population and Procedures

All of the studies enrolled men (18 years of age or older) with erectile dysfunction, as defined by the NIH Consensus Panel on Impotence, for six months or longer.

Patients were required to make at least 4 attempts at sexual intercourse on 4 separate days during the untreated 4-week baseline period and at least 50% of these attempts had to be unsuccessful (inability to achieve an erection, failed penetration, or failed maintenance of an erection).

Patients with the following cardiovascular risk factors were excluded from the efficacy trials (because PDE5 inhibitors should "be used with caution in these patients (class labeling) or "because in these patients sexual activity is inadvisable"): unstable

angina pectoris, history of recent myocardial infarction, stroke, electrocardiographic ischemia (except stable angina), life-threatening arrhythmia within the previous six months, atrial tachyarrhythmia with a heart rate of >100 bpm at screening, resting or orthostatic hypotension (in all 4 major Phase 3 trials, patients were excluded if they had a resting systolic blood pressure of <90 mmHg or symptomatic postural hypotension within 6 months of screening), uncontrolled hypertension, and patients taking nitrates or nitric oxide donors, and patients with retinitis pigmentosa. Diabetics with hemoglobin A_{1c} <12% were allowed in all studies except 100199 and 100285.

To "address the potential bias from selection of sildenafil responders or over-recruitment of patients having failed sildenafil therapy, sildenafil failures were excluded from one of the major efficacy studies (Trial 100249) and allowed to enroll in the other major efficacy study (Trial 10128)." Patients who had previously failed sildenafil therapy were excluded from all other trials, except 10128 and 10232 (a Phase 3 trial evaluating the 2.5 and 5 mg doses).

Evaluations/Endpoints

The primary efficacy endpoints for all 4 major efficacy trials were identical. Three primary efficacy endpoints were used. All 3 primary efficacy endpoints were required to show significance so no adjustment to alpha level for multiple endpoints was necessary.

The 3 primary efficacy endpoints were:

1) The Erectile Function Domain of the International Index of Erectile Function Questionnaire (IIEF). This score is calculated as the sum of scores from questions 1 to 5 and 15 at week 12, using the last-observation-carried-forward (LOCF) method to account for missing data. In each study, the responses were analysed by analysis of covariance (ANCOVA) adjusting for baseline, presenting the least squares (LS) means post-randomization together with the standard error for the LS means for each treatment.
2) Success in penetration (Sexual Encounter Profile – Question 2 (SEP2)) – "Were you able to insert your penis into your partner's vagina?" according to the patient's diary from randomization to Week 12 using the per-patient overall success rate.
3) Success in maintaining erection during intercourse (SEP3) – "Did your erection last long enough for you to have successful intercourse?" according to the patient's diary from randomization to Week 12 using the per-patient overall success rate.

These 3 primary endpoints are currently accepted as the endpoints for all studies involving erectile dysfunction.

Statistical Plan and Results

The statistical reviewer concluded that "all doses of vardenafil were statistically superior to placebo in all 4 trials. There are no technical statistical issues which need to be addressed in this review since there are no realistic issues concerning Type 1 error or bias."

Results

The results of the primary efficacy analyses of the 4 major efficacy trials are shown in Tables 20, 21, 22, and 23 below.

Table 20. Trial 100249

Table 4-1: Study 100249—Results[a] for Primary Efficacy Parameters: IIEF EF Domain, Success in Penetration, and Maintenance of Erection (ITT Population)

Variable	Placebo	Vardenafil 5 mg	Vardenafil 10 mg	Vardenafil 20 mg
IIEF domain: EF at Week 12 LOCF				
N	170	188	195	183
LS mean baseline	13.6	12.5	13.4	12.8
LS mean value (SE)	15.0 (0.7)	18.4 (0.6)	20.6 (0.6)	21.4 (0.6)
		P<0.0001	P<0.0001	P<0.0001
Week 12 overall per-patient diary: success in penetration (% yes)				
N	171	189	194	182
LS mean baseline	46.0	42.8	45.4	40.9
LS mean value (SE)	51.7 (2.5)	65.5 (2.4)	75.5 (2.4)	80.5 (2.5)
		P<0.0001	P<0.0001	P<0.0001
Week 12 overall per-patient diary: maintenance of erection for successful intercourse (% yes)				
N	171	188	194	182
LS mean baseline	14.9	14.0	14.6	14.7
LS mean value (SE)	32.2 (2.7)	50.6 (2.6)	64.5 (2.6)	64.5 (2.7)
		P<0.0001	P<0.0001	P<0.0001

Source: Tables 14.2/1.1 and 14.2/1.2, Study 100249

[a] The P value is for the comparison of the vardenafil groups with placebo

Table 21. Trial 10128

Table 4-8: Study 10128—Results[a] for Primary Efficacy Parameters: IIEF EF Domain, Success in Penetration, and Maintenance of Erection (ITT Population)

Variable	Placebo	Vardenafil 5 mg	Vardenafil 10 mg	Vardenafil 20 mg	Sildenafil 50 mg
IIEF domain: EF at Week 12 LOCF					
N	158	150	155	158	156
LS mean baseline	13.01	13.19	13.05	13.25	13.33
LS mean value (SE)	13.23 (0.62)	19.76 (0.63)	20.91 (0.62)	21.49 (0.62)	21.27 (0.62)
		P<0.0001	P<0.0001	P<0.0001	P<0.0001
Week 12 overall per-patient diary: success in penetration (%)					
N	152	152	151	156	156
LS mean baseline	41.72	47.80	43.92	43.77	45.81
LS mean value (SE)	45.35 (2.57)	71.75 (2.56)	76.43 (2.56)	79.48 (2.54)	78.74 (2.54)
		P<0.0001	P<0.0001	P<0.0001	
Week 12 overall per-patient diary: maintenance of erection for successful intercourse (%)					
N	151	152	151	156	156
LS mean baseline	15.91	14.60	15.95	15.31	16.59
LS mean value (SE)	24.95 (2.92)	54.88 (2.89)	61.58 (2.90)	63.92 (2.87)	64.93 (2.87)
		P<0.0001	P<0.0001	P<0.0001	P<0.0001

Source: Tables 14.2/1.1-14.2/1.2, Study 10128

[a] The P value is for the comparison of the vardenafil groups with placebo

Table 22. Trial 100250

Table 4-12: Study 100250—Results[a] for Primary Efficacy Parameters: IIEF EF Domain at LOCF and Overall Per-Patient Diary Results for Penetration and Maintenance Questions (ITT Population)

	Placebo	Vardenafil 10 mg	Vardenafil 20 mg
IIEF domain: erectile function at LOCF			
LS mean baseline	11.2	11.0	12.4
LS mean value (SE)	12.6 (0.7)	17.1 (0.7)	19.0 (0.7)
		$P = 0.0001$	$P = 0.0001$
Overall per-patient diary: success in penetration (% yes)			
LS mean baseline	33.2	30.9	41.1
LS mean value (SE)	36.4 (2.8)	61.2 (2.8)	63.8 (2.8)
		$P = 0.0001$	$P = 0.0001$
Overall per-patient diary: maintenance of erection for successful intercourse (% yes)			
LS mean baseline	11.3	9.4	15.4
LS mean value (SE)	23.0 (3.1)	49.2 (3.1)	54.2 (3.1)
		$P = 0.0001$	$P = 0.0001$

Source: Tables 14.2.1.1 and 14.2.1.2, Study 100250

[a] P value is for comparison of the vardenafil groups with placebo

Table 23. Trial 100285

Table 4-18: Study 100285—Results[a] of IIEF EF Domain at LOCF and Overall Per-Patient Diary Results for Penetration and Maintenance Questions (ITT Population)

	Placebo	Vardenafil 10 mg	Vardenafil 20 mg
IIEF domain: EF at LOCF			
N	135	135	143
LS mean baseline	9.1	9.3	9.2
LS mean value (SE)	9.2 (0.7)	15.3 (0.7)	15.3 (0.7)
		P = 0.0001	P = 0.0001
Overall per-patient diary: success in penetration (% yes)			
N	135	134	142
LS mean baseline	14.2	21.0	18.3
LS mean value (SE)	21.8 (3.4)	46.6 (3.4)	47.5 (3.4)
		P = 0.0001	P = 0.0001
Overall per-patient diary: maintenance of erection for successful intercourse (% yes)			
N	135	134	142
LS mean baseline	6.0	6.6	7.0
LS mean value (SE)	9.9 (3.3)	37.2 (3.3)	34.2 (3.3)
		P = 0.0001	P = 0.0001

Source: Tables 14.2.1.1 and 14.2.1.2, Study 100285

[a] The P value is for the comparison of the vardenafil groups with placebo

1) *Vardenafil doses of 5, 10, and 20 mg are clinically and statistically superior to placebo.*
2) *In 3 of the 4 major trials, the dose of 20 mg is not clinically or statistically superior to 10 mg. In Trial 100250 (diabetic patients with erectile dysfunction), the difference between 20 and 10 mg for the EF domain of the IIEF was*

statistically different in favor of the 20 mg dose. In this same Trial the data for SEP 2 and SEP 3 were marginally numerically superior for the 20 mg dose but the differences did not reach statistical significance. None of the "pivotal" studies was designed to specifically compare the 10 and 20 mg doses of vardenafil.

3) *All 4 studies enrolled large numbers of patients (70%, 59%, 60%, and 80%) who had previously taken sildenafil. Erections had been improved by sildenafil in nearly all of these patients. A "history of unresponsiveness to sildenafil" was an exclusion criterion in Trials 100249, 100250, and 100285. A history of significant side effects with sildenafil use was an exclusion criterion in Trials 100250 and 100285. This reviewer believes that the data presented in this NDA provides sufficient evidence to approve vardenafil at doses of 2.5, 5, 10, and 20 mg from an efficacy standpoint. Despite the exclusion of patients with a history of "significant side effects with sildenafil use in Trials 100250 and 100285," this reviewer believes that there remains a safety data base which is adequate for evaluation.*
4) *There is insufficient efficacy data directly comparing vardenafil to other drugs indicated for the treatment of erectile dysfunction to make meaningful comparisons.*

With regard to the low end of the dose ranging studies, the sponsor also submitted the results of Phase 3 study 10232. Trial 10232 included the same patient population and same primary endpoints as the 4 major efficacy studies but evaluated doses of vardenafil of 2.5 and 5 mg. The efficacy results from Trial 10232 are shown in Table 24.

Table 24. Efficacy results of Trial 10232.

Table 4-30: Study 10232—Results[a] IIEF EF Domain at Week 12 LOCF and Overall Per-patient Diary Results for Penetration and Maintenance of Erection[a] (ITT Population)

		Vardenafil	
	Placebo	2.5 mg	5 mg
IIEF domain: erectile function at LOCF			
N	157	160	163
LS mean baseline	13.61	12.92	13.53
LS mean value±SE at LOCF	15.10±0.70	18.79±0.69	20.31±0.65
		P<0.0001	P<0.0001
Overall per-patient diary: success in penetration (% yes)			
N	164	169	167
LS mean baseline	51.57	53.30	46.88
LS mean value±SE at LOCF	54.74±2.78	65.87±2.68	76.26±2.60
		P = 0.0008	P<0.0001
Overall per-patient diary: maintenance of erection for successful intercourse (% yes)			
N	163	169	167
LS mean baseline	18.57	16.83	16.61
LS mean value±SE at LOCF	28.66±3.07	47.35±2.95	59.02±2.86
		P<0.0001	P<0.0001

Source: Tables 14.2/1.1 and 14.2/1.2, Study 10232
[a] The P value is for the comparison of the vardenafil groups with placebo

Both the 2.5 and 5 mg doses of vardenafil were statistically significantly more effective than placebo in terms of all 3 primary endpoints.

Efficacy conclusions:

I believe that adequate and well-controlled studies have demonstrated that the 5, 10, and 20 mg doses of vardenafil are clinically and statistically effective in the treatment of erectile dysfunction.

6. Update of Integrated review of safety

The sponsor intends to market the 2.5 mg, 5 mg, 10 mg and 20 mg dosage forms of vardenafil. Overall, a total of 4436 patients with erectile dysfunction have been treated with vardenafil in Phase IIb and III trials. In completed Phase III studies, a total of 3825 patients have been exposed to vardenafil 5, 10 or 20 mg, and an additional 173 patients have been exposed to vardenafil 2.5 mg. The remaining 438 subjects were treated in a Phase IIb study with vardenafil 5, 10 or 20 mg.

Safety information from **February 28, 2002, through October 15, 2002** that was provided in the NDA amendment as well as a 3-Month safety update (dated May 16, 2003) that includes information from **October 15, 2003 through January 15, 2003 was reviewed**. The 3-Month safety update summary includes data from one completed study 10786 (an open-label vardenafil flexible dose, ethnicity study) and the remaining ongoing studies (10621, 10473, 10573, 10678, 10690, 10898). The remainder of the safety information was submitted with the original NDA dated September 23, 2001(included data through July 31, 2001), a 4-Month safety update (included data through November 30, 2001) and the 7-Month safety update (included data through February 28, 2002).

Deaths in vardenafil trials are shown in Table 25.

Table 25. Deaths in Vardenafil Trials

Study Number	Treatment Group	Event	Relation	Last Dose	Comments
Death (prior to 31 Jul 2001 and Reported in the original NDA)					
100250-008-026	No drug given	Heart arrest	None	N/A	Age 58 yrs
100250-020-011	No drug given	Chest pain	None	N/A	Age 55 yrs
10125-039-1020	No drug given	Intracerebral hemorrhage	None	N/A	Age 55 yrs
10128-112-040499	No drug given	Ventricular fibrillation	None	N/A	Age 64 yrs
10128-035-040953	Unclear if drug taken	Carcinoma/death	Unlikely	Unknown	Age 62 yrs
10232-027-003	Placebo	Death	None	Unknown	Hx:DM/age 46 yrs
10232-013-004	VAR 2.5 mg	Multiple organ failure	None	11 days prior	Hx:DM,HLP/age 55 yrs
100312-905-004	VAR 10 mg	Death	None	21 days prior	Hx:DM,HTN, CAD/age 67 yrs
10125-110-342	VAR 10 mg	Death	Unlikely	Unknown	Hx:DM,HTN/age 69 yrs
10152-038-590	VAR 20 mg	Suicide	None	12 days prior	Hx:CAD,DM, COPD/age 61 yrs
10128-001-040348	SIL 50 mg	Myocardial infarction/death	Possible	Same day	Hx:DM,HTN, HLP/age 60 yrs
Death (31 Jul 2001 to 15 Oct 2002)					
100446-302-003	No drug given	Sudden death	None	N/A	Age 38 yrs
10806-016-003	No drug given	Electrocution (Fatal)	None	N/A	Age 59 yrs
10869-023-352	VAR 20 mg	Hypoglycemia w/alcohol	None	Unknown	Hx:DM,HTN, HLP/age 57 yrs
10573-106-006	Blinded	Heart attack (fatal)	None	2 1/2 mo prior	Hx:HTN,CAD,HLP/ age 67 yrs
10573-017-024	Blinded	Suicide	None	Unknown	Age 58 yrs
10573-037-003	Blinded	Posterolateral MI/ Cardiogenic Shock	None	25 days prior	Hx:HTN,CAD/ age 79 yrs
10573-037-006	Blinded	Angor (Angina pectoris)	None	24 days prior	Hx:DM/age 57 yrs

There have been a total of 18 deaths reported. Eleven of the deaths occurred prior to July 31, 2001 and were reported in the original NDA submission. The remaining 7 cases were reported since the NDA submission and are included within the amendment. Narratives for these patients are included in the medical officer's review. No new safety concerns have been identified in reviewing the additional safety data submitted with the complete response to approvable or the safety update.

The nature and percentage of adverse events is shown in Table 26. New safety data has not significantly changed these data from those submitted in the original NDA.

Table 26. Incidence rates (%) of Treatment-Emergent Adverse Events Reported by ≥2% of Patients Taking Vardenafil

	Updated Pool 3	
	Placebo	Vardenafil
Adverse Event	n = 1199	n = 2203
Headache	4.2	14.5
Flushing	0.5	11.1
Rhinitis	2.9	9.2
Dyspepsia	0.6	3.7
Accidental injury	1.8	2.9
Sinusitis	0.7	2.6
Pharyngitis	1.8	2.0
Flu syndrome	2.3	2.6
Back pain	1.7	2.0
Dizziness	0.9	2.2
Nausea	0.5	2.0
CK Increased	1.2	2.0
Arthralgia	0.7	1.7

Source: ISS, Table 6-2, page 22.

The incidence rates for selected cardiovascular events are shown in Table 27.

Table 27. Incidence Rates of Selected Cardiovascular Events

		Updated Pool 3	
		Placebo (%)	Vardenafil (%)
Cardiovascular Event	History of CVD	(No=1093) (Yes=106)	(No=2018) (Yes=185)
Angina/Chest Pain	No	1.0	1.4
	Yes	0.9	2.7
Atrial Arrhythmia	No	0.5	0.9
	Yes	0.0	1.6
Hypotension	No	0.0	0.1
	Yes	0.9	0.5
Myocardial Infarct	No	0.1	0.0
	Yes	0.0	0.5
Stroke	No	0.1	0.0
	Yes	–	–
Syncope	No	0.0	0.1
	Yes	0.9	0.5

Source: ISS, Table 6-6, page 29.

Syncope: There were no new reports of syncope in placebo-controlled Phase III trials. The incidence of syncope is reported as <0.1% for all Phase III trials and 0.3% overall.

There were 2 additional cases of syncope in Phase III trials, 1 case in a Phase I trial and 3 cases in ongoing trials.

7. Dosing and administration

The dosing of vardenafil is acceptable and supported by data. The addition of the 2.5 mg dose is justified because of the need to use this dose in conjunction with ritonavir.

8. Labeling recommendations

1. A description of the QT data should be included in the "Clinical Pharmacology" Section and "Precautions Section" of the label.
2. The use of vardenafil in patients taking alpha blockers should be contraindicated.
3. Recommended vardenafil dosing in special populations and with CYP 3A4 inhibitors is discussed in Section 3.C. of this memorandum.

APPEARS THIS WAY
ON ORIGINAL