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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-400

Medical Review(s)

NDA 21-400 Amendment to Pending NDA

Date submitted: February 17, 2003
Date received: February 19, 2003
Review completed: August 19, 2003

Medical Officer Review

Sponsor:	Bayer Pharmaceutical Division Bayer Corporation 400 Morgan Lane West Haven, CT 06516-4175
Drug:	vardenafil hydrochloride
Proposed tradename:	Levitra
Route of administration:	oral
Dosage form:	tablets
Strength:	2.5, 5, 10, and 20 mg
Proposed indication:	treatment of erectile dysfunction
Related IND's:	[redacted]

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Executive Summary

I. Recommendations

In the opinion of this reviewer, from a clinical standpoint, vardenafil, at doses of 2.5, 5, 10 and 20 mg, should be approved for the indication "treatment of erectile dysfunction." The risks associated with the use of this drug are acceptable and can be managed adequately with labeling.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Vardenafil is a phosphodiesterase Type 5 inhibitor proposed for the "treament of erectile dysfunction." The recommended starting dose is 10 mg with up or down titration to 5 mg or 20 mg. The 2.5 mg dose is reserved for patients on concomitant potent CYP3A4 inhibitors. The 5, 10 and 20 mg doses of vardenafil have been approved in Europe since March 7, 2003. The only approved PDE5 inhibitor in the United States is Viagra® (sildenafil).

The original NDA, submitted September 24, 2001, contained 4 primary efficacy studies (100249, 10128, 100250 and 100285) using either 5, 10, or 20 mg of vardenafil. All four trials were randomized, placebo-controlled, double-blind, parallel-group, multicenter studies. All four trials were at least 12 weeks in duration. Three of the trials were conducted in North America and the fourth in Europe. The intent-to-treat population in these 4 trials combined was 2400 subjects. 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 NDA contained several deficiencies that were outlined in the "approvable" letter dated July 23, 2003:

1) QT issues
   - Provide evidence to rule out QT prolongation due to vardenafil
   - Characterize the vardenafil plasma concentration relationship for QT interval prolongation
   - Evaluate the degree of QT prolongation at plasma concentrations following maximal potential interaction between vardenafil and CYP3A4 inhibitors using an active control
2) Alpha-blocker interaction
   - Provide data from drug-drug interaction studies to support labeling for concomitant use of vardenafil with an alpha-blocker used for BPH
3) Nitrate interaction for the 20 mg vardenafil dose
   - Provide a study in patients treated with doses of vardenafil of 20 mg or higher with administration of nitrates at various times following the dose of

vardenafil to determine at what point after vardenafil dosing there is no apparent blood pressure interaction. This study should include elderly subjects (who may have higher exposure than younger patients).

- Propose a plan for patient and physician education regarding nitrate contraindication and nitrate interaction.

4) Aspirin interaction for the 20 mg vardenafil dose

- Provide data from a drug-drug interaction study to support labeling regarding interactions of vardenafil 20 mg and aspirin

5) CMC issues – for the 2.5 mg vardenafil dose

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

6) Back pain for new and ongoing studies

- Sponsor 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.

7) Eye effects

- Provide data for labeling the quantitative effects of Levitra on retinal function following repeat dosing with Levitra. We recommend that you submit your proposed protocol(s) so that DRUDP and the Division of Anti-Inflammatory, Analgesic, and Opthalmological Drug Products (DAAOP) can assess the acceptability of the protocol to fulfill this requirement.

8) Safety update

- Update the NDA by submitting all safety information regarding the drug.

A complete response to the "approvable" action was submitted February 17, 2003, to address these deficiencies. The amendment contains data from 3 completed Phase III studies and 9 completed clinical pharmacology studies (See Table 1).

Table 1: Newly Completed Studies Included in the Amendment

	Trial #	Descriptor	Region
Phase III completed			
	10867	1 month time to onset	N.A.
	10194	6 month flexible dose extension to 10128	Non N.A.
	10769	3 month flexible dose	Non N.A.
Clinical Pharmacology -completed			
	10720	Nitrate interaction	N.A.
	10929	Cardiac repolarization	N.A.
	100408	VAR 20 mg ETT	N.A.
	100478	High dose safety vs SIL and placebo	N.A.
	100480	Terazosin interaction	N.A.
	100481	Tamsulosin interaction	N.A.
	100482	Aspirin interaction	N.A.
	100512	Ritonavir interaction	N.A.
	10503	RigiScan VAR vs SIL	Non N.A.

Source: Study report Tables 2-1, 2-3, pages 8 and 10

B. Efficacy

In the original NDA review, the statistical reviewer concluded that "all doses [5, 10, and 20 mg] of vardenafil were statistically superior to placebo in all 4 trials. None of the pivotal studies was designed to specifically compare the 10 and 20 mg doses of vardenafil. Both the 2.5 and 5 mg doses of vardenafil were statistically significantly more effective than placebo in terms of all 3 primary endpoints. Vardenafil 5 mg was statistically significantly better than the 2.5 mg dose with respect to penetration and maintenance of erection." The sponsor believed that the increases measured by the primary endpoints with the 2.5 mg dose were not clinically meaningful and since the 2.5 mg dose had a lack of an obvious safety advantage over the 5 mg dose, the development of the 2.5 mg dose was not pursued. In the complete response, the 2.5 mg dose has been added for use in patients taking concomitant potent CYP3A4 inhibitors.

C. Safety

At the time of the NDA Amendment submission, 4436 patients with erectile dysfunction had been treated in Phase IIb and Phase III trials. In all completed Phase III trials, a total of 3825 patients have been exposed to vardenafil 5, 10 or 20 mg, 777 (20%) completed up to 12 weeks of exposure, 840 (22%) completed between 12 and 24 weeks of exposure, 1328 (35%) completed between 24 and 48 weeks of exposure, and 880 (23%) completed more than 48 weeks of exposure.

Significant adverse events:

Deaths: A total of 18 deaths have been reported during drug development. 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. None of these 7 deaths occurred in studies which appear to be placebo-controlled. Two deaths occurred prior to study drug administration due to sudden death (100446-302-003) and electrocution (10806-016-003), respectively. One death (10869-023-352) occurred 10 days after randomization to vardenafil 20 mg. This

57 year-old,Caucasian male with a history of diabetes (on insulin), hypertension, hyperlipidemia, peripheral vascular disease on alpha-lipoic acid, ramipril/HCTZ, amlodipine, simvastatin, and aspirin was found dead at home 10 days after randomization. It is unknown how many doses of study drug he had taken. Empty bottles of alcohol were found next to the body and death was presumed to be "hypoglycemia due to alcohol intake." The remaining 4 deaths occurred in the ongoing, blinded study 10573 in which subjects were randomized to receive either vardenafil 10 mg or 20 mg. The causes of death include presumed ischemic cardiomyopathy, suicide, posterolateral myocardial infarction and severe CAD. See section 7.6.5 for further details.

The overall incidence of serious adverse events and the nature of individual adverse events in the updated pools do not suggest a specific risk pattern and no new safety concerns were identified.

Frequent adverse events:

Fifty-nine percent (59%) of patients in all placebo controlled and uncontrolled trials reported adverse events. For almost all body systems, the incidence rates of treatment-emergent adverse events in the vardenafil treatment group was greater than in the placebo group. Adverse events that occurred at least twice as often on vardenafil than on placebo were headache, flushing, rhinitis, sinusitis, dyspepsia, nausea, and dizziness. The incidence of treatment-emergent adverse events reported by ≥2% of patients taking vardenafil is shown in Table 2.

Table 2. 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.

Other Significant Safety Issues:

1) Effect of vardenafil on cardiac depolarization/QT interval

Study 10929 was designed to rule out a greater than 10 msec effect of a single 80 mg dose of vardenafil on QTc interval compared to placebo. An individual correction method (QTci) was also used. The primary endpoint (QTc Fridericia) showed a 10 msec (90% CI:8, 11) increase for vardenafil 80 mg compared to placebo. The magnitude of QTci was less [(mean 8 msec) 90% CI: 4,7] (see Section 7.1 in the Clinical Review and Appendix

A). The Cardiovascular and Renal Advisory committee meeting held on May 29, 2003, voted that this change was not clinically meaningful (vote: 8-No, 1-Yes, 1-Maybe, and 3-Abstain). Data concerning QT changes seen with vardenafil will be added to the Clinical Pharmacology and Precautions sections of the label.

2) Vardenafil/ alpha-blocker interaction

Studies 100480 and 100481 were designed to compare changes in blood pressure of vardenafil 10 and 20 mg compared to placebo when subjects were on terazosin or tamsulosin, respectively. The combination of terazosin 10 mg and vardenafil 10 or 20 mg given simultaneously produced pronounced decreases in SBP by as much as 23 mm Hg (all values are placebo-subtracted, mean maximum change), DBP by as much as 9 mm Hg and HR increases of 9 bpm. When dosing of the two drugs was separated by 6 hours (corresponding to a Cmax separation of 6 hours), the changes were not as dramatic but were still significant (mean maximum change- 11 mm Hg, 7 mm Hg, and 7 bpm, respectively). The combination of tamsulosin 0.4 mg and vardenafil 10 or 20 mg given with simultaneous Cmax also produced pronounced decreases in SBP by as much as 8 mm Hg, DBP by as much as 7 mm Hg and HR increases by as much as 3 bpm. When Cmax was separated by 6 hours, the changes were not as dramatic but were still significant (mean maximium change- 8 mm Hg, 4 mm Hg, and 6 mm Hg, respectively). The separation of the doses did not negate the effect of concomitant treatment.

With simultaneous dosing of LEVITRA 10 mg and terazosin 10 mg, 6 out of 8 patients experienced a standing systolic blood pressure of less than 85 mm Hg. With simultaneous dosing of LEVITRA 20 mg and terazosin 10 mg, 2 out of 9 patients experienced a standing systolic blood pressure of less than 85 mm Hg. When LEVITRA dose dosing was separated from terazosin 10 mg by 6 hours, 7 out of 28 patients who received 20 mg of LEVITRA experienced a decrease in standing systolic blood pressure below 85 mm Hg. Similar studies with tamusulosin 0.4 mg showed significant reductions in standing systolic blood pressure but the decreases were less pronounced and occurred in a lower percentage of patients. Based on these data and the fact that there is no information available regarding the concomitant use of alpha-blockers and doses of LEVITRA less than 10 mg, LEVITRA should be contraindicated in patients on alpha-blocker therapy.

3) Vardenafil/ nitrate interaction

Study 10720 was designed to evaluate the pharmacodynamic interaction between vardenafil 20 mg and NTG 0.4 mg. A 24-hour separation caused no additional change in SBP, DBP or HR (compared to placebo). An 8-hour separation caused minor changes in SBP and DBP (1-2 mmHg) but HR increased approximately 7 bpm. A 4-hour separation caused SBP to decrease by 8 mmHg, DBP to decrease by 7 mm Hg and HR to increase by 5 bpm. A 1-hour separation caused SBP to decrease by 8-9 mmHg, DBP to decrease by 5 mm Hg and HR to increase by 9 bpm. This information is adequately presented in the label.

4) Vardenafil/ ritonavir interaction

Study 100512 was designed to evaluate the pharmacokinetic interaction between vardenafil 5 mg and ritonavir 600 mg bid. Increases of 13-, 49- and 108- fold were observed in vardenafil mean Cmax, AUC_{0-24} and $AUC_{0-\infty}$, respectively, when 5 mg vardenafil was administered with ritonavir vs 5 mg vardenafil alone. The ritonavir mean Cmax and AUC_{0-12} decreased by 22% and 20%, respectively, following concomitant administration with vardenafil 5 mg. Based on these data, the sponsor proposes to limit the dose of vardenafil to 2.5 mg in a 72-hour period. This is acceptable to the clinical pharmacology reviewer and I agree.

5) Vardenafil/ aspirin interaction

Study 100482 studied the effects of vardenafil 20 mg on bleeding time and the effects of vardenafil 20 mg on aspirin-induced prolongation of bleeding time. Bleeding time was not altered in subjects receiving vardenafil 20 mg in combination with aspirin or when given alone.

6) Incidence of Back pain

In phase III trials, there have been 6 new cases of back pain, one in the placebo group and 5 in vardenafil groups and one new case of myalgia (in the placebo group). Overall, the incidence of back pain is 2.0% in the vardenafil group and 1.7% in the placebo group. In single dose studies, up to the maximum recommended dose of vardenafil 20 mg, the incidence of back pain and myalgia was the same as or less than with placebo. Single doses of vardenafil 40 mg or higher, demonstrate a dose-response for the incidence of back pain and myalgia and were more likely to be more severe. In multiple-dose Clinical Pharmacology studies, there was a clear dose-response and dose-frequency-response. The tolerability at the 20 mg/qd and 40 mg/qod dose levels was similar. The back pain/myalgia incidence was lower at the 20 mg/qd dose level than at the 40 mg/qd dose level and it was much lower than that at the 40 mg/bid dose level. The 40 mg/bid dose level treatment was discontinued after Day 4 due to poor tolerability in all subjects receiving that dose regimen.

7) Ophthalmology adverse events

The Updated Pool 3 and Pool 4 datasets show very little change in the total number of patients with reportable adverse events and showed no change in the total percentage of patients affected. Color vision change was reported rarely (<0.1%) with vardenafil treatment in all clinical studies. Collectively, these updated data are consistent with all previous reports of visual events. The ophthalmology reviews states that minimal information is available from the submitted studies. However, no significant differences in comparision to other PDE5 inhibitors can be determined.

There were 6 new cases of visual disturbance (coded as abnormal vision [4], amblyopia [1], and photobia [1]) in the vardenafil group and none in the placebo group. There were 3 special senses adverse events that led to premature discontinuation in the vardenafil

group compared to none in the placebo group These events were abnormal vision (1), conjunctivitis (1), and lacrimation disorder (1). In ongoing trials, there was one patient in the vardenafil arm (20 mg) with a serious adverse event related to vision. Patient 10573-906-300 was discontinued after 2 occurrences of blurred vision and retina pigmentary alterations that were considered as possibly related to study drug by the principal investigator. His blurred vision has fully recovered.

D. Dosing

The recommended starting dose is 10 mg with up or down titration to 5 mg or 20 mg. The 2.5 mg dose is reserved for patients on concomitant potent CYP3A4 inhibitors.

With respect to the high end of the proposed doses, in 3 of the 4 major trials submitted with the original NDA, the dose of 20 mg was not clinically or statistically superior to 10 mg. In Trial 100250 (diabetic patients with erectile dysfunction), the difference between 20 mg and 10 mg for the EF domain of the IIEF was statistically different in favor of the 20 mg dose. The data for SEP 2 and SEP 3 were marginally numerically superior for the 20 mg dose in this trial, but the differences did not reach statistical significance. None of the major studies was designed to specifically compare the 10 and 20 mg doses of vardenafil.

Reviewer's comment: The reviewer believes that, based on efficacy, the proposed doses are acceptable.

E. Special Populations

Gender: Vardenafil is indicated only for the treatment of men with erectile dysfunction.

Age: There was >50% increase in AUC and >30% increase in Cmax in patients greater than 65 years of age. In phase III clinical trials involving more than 834 elderly patients, there were no differences in safety or effectiveness of vardenafil 5, 10, or 20 mg in the elderly patients as compared to younger patients. However, due to increased vardenafil concentrations in the elderly, the clinical pharmacology reviewer suggests that a starting dose of 5 mg LEVITRA in patients ≥65 years be considered and I agree.

Race/ethnicity: The vast majority of patients in both the vardenafil and placebo treatment groups were Caucasian. The number of patients in racial sub-groups other than Caucasians was too small to detect any meaningful differences in the rates of adverse events in vardenafil treated patients across racial subgroups.

Pediatric population: Vardenafil is indicated only for men with erectile dysfunction. The sponsor has requested and been granted a pediatric waiver.

Renal impairment: Renal impairment does not have a significant effect on vardenafil exposure, and the clinical pharmacology reviewer believes that dose adjustment is not required in renal impairment. This reviewer agrees. Vardenafil has not been studied in patients on dialysis.

Hepatic impairment: Based on the results showing increase in drug exposure (approximately 2 ½ times the AUC and Cmax), the clinical pharmacology reviewer believes that the starting dose of vardenafil in the moderately hepatic impaired (Child-Pugh B) patient should be 5 mg which may be increased to a maximum of 10 mg based on tolerability and efficacy (not 20 mg as recommended in the proposed label). Exposure in patients with moderate hepatic impairment given a 20 mg dose would be equivalent to a 50 mg dose in patients without hepatic impairment. Patients with severe hepatic impairment (Child-Pugh C) have not been evaluated.

Pregnancy: Vardenafil is not indicated for use in women.

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Clinical Review

1. Introduction and Background

1.1 Proposed Drug

Vardenafil hydrochloride (proposed trade name Levitra) is a Type 5 phosphodiesterase (PDE5) inhibitor proposed for the indication "treatment of erectile dysfunction." The sponsor requests approval for 4 doses (2.5, 5, 10, and 20 mg). The recommended starting dose of vardenafil is 10 mg which may be increased to a maximum recommended dose of 20 mg or decreased to 5 mg based on efficacy and tolerability. The 2.5 mg dose formulation will be available for use in patients concomitantly taking potent CYP3A4 inhibitors. The sponsor has requested and been granted a pediatric waiver.

1.2 Milestones in Product Development

The original NDA was submitted September 24, 2001. An "approvable" letter was issued July 23, 2002, stating the following deficiencies/requirements:

1) QT issues
   - Provide evidence to rule out QT prolongation due to vardenafil
   - Characterize the vardenafil plasma concentration relationship for QT interval prolongation
   - Evaluate the degree of QT prolongation at plasma concentrations following maximal potential interaction between vardenafil and CYP3A4 inhibitors using an active control

2) Alpha-blocker interaction
   - Provide data from drug-drug interaction studies to support labeling for concomitant use of vardenafil with an alpha-blocker used for BPH

3) Nitrate interaction – for the 20 mg vardenafil dose
   - Provide a study in patients treated with doses of vardenafil of 20 mg or higher with administration of nitrates at various times following the dose of vardenafil to determine at what point after vardenafil dosing there is no apparent blood pressure interaction. This study should include elderly subjects (who may have higher exposure than younger patients).
   - Propose a plan for patient and physician education regarding nitrate contraindication and nitrate interaction.

4) Aspirin interaction – for the 20 mg vardenafil dose
   - Provide data from a drug-drug interaction study to support labeling regarding interactions of vardenafil 20 mg and aspirin

5) CMC issues – for the 2.5 mg vardenafil dose
   - Submit chemistry, manufacturing and controls information to support approval of the 2.5 mg strength. This must include manufacturing

information on three (3) batches with accompanying stability data in the proposed market container closure system. This information may be submitted with three months accelerated and room temperature data with a commitment to update the stability data with an additional three (3) months of data when available. However, if the formulation and manufacturing process differ significantly from the 5, 10, and 20 mg strengths, more stability data will be necessary to establish an acceptable shelf life.

6) Back pain – for new and ongoing studies

- Sponsor 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.

7) Eye effects

- Provide data for labeling the quantitative effects of Levitra on retinal function following repeat dosing with Levitra. We recommend that you submit your proposed protocol(s) so that DRUDP and the Division of Anti-Inflammatory, Analgesic, and Opthalmological Drug Products (DAAOP) can assess the acceptability of the protocol to fulfill this requirement.

8) Safety update

- Update the NDA by submitting all safety information regarding the drug.

1.3 Active Issues

1) The sponsor had previously performed a retrospective analysis of the ten studies that involved QT data (studies 94, 10006, 10104, 10229, 10010, 10011, 100195, 100196, 10006 and 196). These studies were submitted and reviewed within the original NDA. Two of the studies did not include a placebo control group and in two studies the first ECGs were obtained 2 ½ hours post-vardenafil dosing which exceeds the Tmax. Only 5 patients were studied at the maximum dose of 80 mg. Consequently, the data were not felt to be compelling to rule out an arrhythmogenic potential. Study 10929 was submitted with the amendment to address this deficiency.

2) Two subjects in two different trials (10125 and 10029) experienced fainting or syncope on the same day or one day following, respectively, his last dose of terazosin and on the same day as taking vardenafil. Further evaluation was requested regarding the pharmacodynamic interaction (hypotension) between alpha-blockers and vardenafil. Studies 100480 (using terazosin 10 mg) and 100481 (using tamsulosin 0.4 mg) were submitted to address this deficiency.

3) Vardenafil is contraindicated for patients on continuous or intermittent nitrate therapy. In the subset of patients with cardiovascular events who may require emergency nitrate use, information regarding the blood pressure effects of Levitra, specifically, the time when no blood pressure interaction is seen should be determined. The sponsor had previously submitted study 100304 using 10 mg vardenafil and found no hemodynamic interaction. The maximum proposed dose (20 mg) was not studied. Study 10720 was submitted with the supplement to address this deficiency using the 20 mg vardenafil dose.

4) Vardenafil can affect the phosphodiesterase Type 5 in platelets. Study 100396 showed no clinically meaningful anticoagulant interaction between aspirin and 10 mg of vardenafil. The maximum proposed dose (20 mg) was not studied. Study 100482 was submitted with the supplement to address this deficiency using the 20 mg vardenafil dose.

5) Back pain: Significant back pain was reported by subjects administered vardenafil 40 mg twice daily in one clinical trial. The etiology in this setting is unclear.

6) Eye changes: Vardenafil can inhibit phosphodiesterase Type 6 in the retina as evidenced by color vision changes in controlled studies and clinical adverse event reports in Phase III trials. Minimal information was submitted with the original NDA.

1.4 Foreign Approval

Since the approvable action to the original NDA, vardenafil (5, 10, and 20 mg) was approved in Europe on March 7, 2003, for the treatment of erectile dysfunction.

1.5 Important Issues with Pharmacologically Related Agents

Safety concerns with PDE5 inhibitors include pharmacodynamic interaction with nitrates, visual adverse events, and a frequent adverse event profile which includes headache, flushing, rhinitis, and dyspepsia. In addition, there have been reports of death and myocardial infarction in the post-marketing period in patients who have taken sildenafil. The actual etiology of these events remains unclear.

Since the original NDA approvable action, sildenafil, the only approved PDE 5 inhibitor in the U.S., has made several updates to its labeling regarding:

- Alpha-blocker administration
- Post-marketing cardiovascular events
- Risk of sexual activity

- Patients who were not studied in clinical trials – CVA/MI within 6 mo, significant hypotension or hypertension, history of cardiac failure or CAD causing unstable angina, retinitis pigmentosa
- Priapism

2. Clinically Relevant Findings from Chemistry, Toxicology, Microbiology, Biopharmaceutics, Statistics and/or other reviews

Ophthalmology Consult: From an ophthalmologic prospective, there is no objection to the approval of this NDA provided that the labeling is consistent with other phosphodiesterase inhibitors. There were no major labeling issues. It is recommended that repeated dose Phase IV studies evaluating the effect of vardenafil on retinal function be conducted and submitted for review.

3. Human Pharmacokinetics and Pharmacodynamics

Vardenafil C_{max} is achieved within 1 hour of dosing. The half-life is approximately 4 hours. Vardenafil has 1 major metabolite (M1) and 2 minor metabolites (M4 and M5). All of the metabolites are a result of degradation of the piperazine ring of vardenafil. M1 is the most active among the 3 metabolites against PDE5, and has about 25% of the activity of the parent. M1 levels are approximately 25-50% of that of the parent. Vardenafil is almost entirely excreted in the feces (>90% of the dose and the majority as metabolites). The drug shows linear pharmacokinetics between 5 and 20 mg but shows non-linear pharmacokinetics beyond 40 mg. Both vardenafil and the major metabolite are 93-95% bound to plasma proteins. Please see Clinical Pharmacology review for further details.

Effect of impaired renal function: Renal impairment does not have a significant effect on vardenafil exposure, and the clinical pharmacology reviewer believes that dose adjustment is not required in renal impairment. This reviewer agrees. Vardenafil has not been studied in patients on dialysis.

Effect of hepatic impairment: Based on the results showing increase in drug exposure, the clinical pharmacology reviewer believes that the starting dose of vardenafil in the moderately hepatic impaired patient should be 5 mg, and such patients should not be given doses higher than 10 mg. This reviewer agrees and believes that the current proposed labeling of "a starting dose of 5 mg vardenafil which may subsequently be increased to 10 mg and then 20 mg, based on tolerability and efficacy" should be changed to reflect a maximum dose of 10 mg in these patients. (Exposure in patients with moderate hepatic impairment given a 20 mg dose would be equivalent to a 50 mg dose in patients without hepatic impairment. Limited safety information exists on this level of exposure.) Vardenafil has not been evaluated in patients with severe hepatic impairment.

Effect of age: There was a >50% increase in AUC and a >30% increase in Cmax in patients older than 65 years. In phase III clinical trials involving more than 834 elderly patients, there were no differences in safety or effectiveness of vardenafil 5, 10, or 20 mg

in the elderly patients as compared to younger patients. However, due to increased vardenafil concentrations in the elderly, the clinical pharmacology reviewer suggests that a starting dose of 5 mg LEVITRA in patients ≥65 years be considered and I agree.

Drug-Drug interaction studies: Drug interaction studies including warfarin, digoxin, antacids, cimetidine/ranitidine, glyburide, and nifedipine trials did not show any significant potential for drug interaction requiring dosing recommendations.

Other issues: Several other significant PK/PD interactions are discussed in the safety section of this review (section 7) and in the attached appendices.

Cardiac depolarization: Study 10929 (Appendix A)

Nitrate interaction: Study 10720 (Appendix B)

Alpha-blocker interaction: Studies 100480 and 100481 (Appendix C and D)

Ritonavir interaction: Study 100512

Aspirin interaction: Study 100482

4. Description of Clinical Data and Sources

The following materials were reviewed: NDA supplement including 1) Studies 10929, 10720, 100480, 100481, 100512, 100482, 10867; 2) integrated safety summary; 3) integrated efficacy summary; 4) 3-Month safety update; and 5) 15-Day safety reports.

4.1 Tables listing Clinical Trials

In support of NDA 21400, the sponsor submitted, in the original NDA, the results of 4 primary efficacy studies (Trials 100249 and 10128 in the general erectile dysfunction population, Trial 100250 in patient 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. These trials are outlined in Table 3.

In addition to the 4 primary efficacy studies submitted with the original NDA, the sponsor submitted Trial 100199 (a Phase 2b study) and Trial 10232 (a Phase 3 trial using doses of 2.5 and 5 mg vardenafil). Updated safety data includes all studies submitted with the original NDA through the amendment which includes three completed Phase III trials (10867, 10194, 10769), nine ongoing Phase III trials (10566, 10786, 10806, 10454, 10563, 10573, 10775, 10869, 100446), nine completed clinical pharmacology trials (10720, 10929, 100408, 100478, 100480, 100481, 100482, 100512, 10503), and eight ongoing clinical pharmacology trials (10618, 10804, 10151, 10601, 10634, 10687, 10864, and 10865).

Overall, vardenafil was administered to 4436 patients with erectile dysfunction (Phase IIb and Phase III trials). The mean duration of treatment was between 180-189 days.

Table 3. 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	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 mg Vard 20	137/97 139/114 147/119	Post-radical prostatectomy	93 99 87	60 (47-72) 61 (44-77) 60 (45-74)

Source: Original NDA review, Table 1, page 20.

4.2 Post-marketing Experience

The WHO database was searched on April 2, 2003. Two adverse event cases were found – cholelithiasis and a suicide attempt.

4.3 Literature review

The European Commission scientific discussion of vardenafil was reviewed.

5. Clinical Review Methods

5.1 Conduct of Review

The NDA Amendment was entirely electronically submitted. The following studies were reviewed in detail:

10929 (Cardiac depolarization) (see Appendix A)
10720 (Nitrate interaction) (see Appendix B)
100480 (Interaction with terazosin 10 mg) (see Appendix C)
100481 (Interaction with tamsulosin 0.4 mg) (see Appendix D)

Other trials were reviewed in less depth and not included in the appendices:
100512 (Ritonavir interaction)
100482 (Aspirin interaction)
10867 (Time to onset)

5.2 Overview of Methods Used to Evaluate Data Quality and Integrity

An inspection was not required for the amendment.

5.3 Financial Disclosure

Of the studies reviewed, financial disclosure information was submitted on study 10867 and is adequate. All other financial disclosures referenced ongoing Phase III trials.

6. Integrated Review of Efficacy

6.1 Efficacy Conclusions

In the opinion of this reviewer, the 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.

6.2 Approach to Review of Efficacy

In the original NDA review, four major efficacy trials (100249, 10128, 100250, and 100285) were reviewed in detail (see Appendices A, B, C, and D of the original review). Trials 100199 and 10232 were also reviewed.

6.3 Review of Trials

- Trial 100249: to assess the efficacy and safety of the PDE5 inhibitor vardenafil in the treatment of men with erectile dysfunction
- Trial 10128: to assess the efficacy and safety of the PDE5 inhibitor vardenafil, tested for 3 months at doses versus placebo, in men with erectile dysfunction. A secondary comparison versus 50 mg sildenafil was also performed.
- Trial 100250: to assess the efficacy and safety of the PDE5 inhibitor vardenafil in the treatment of diabetic men with erectile dysfunction.
- Trial 100285: to assess the efficacy and safety of the PDE5 inhibitor vardenafil in the treatment of men with erectile dysfunction following radical prostatectomy.

6.3.1 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.

Reviewer's comment: These 3 primary endpoints are currently accepted as the endpoints for all studies involving erectile dysfunction.

6.3.2 Results

The results of the primary efficacy analyses of the 4 major efficacy trials are shown in Tables 4, 5, 6, and 7 below.

Table 4. Study 100249 – Results for Primary Efficacy Parameters

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	13.8	12.5	13.4	12.8
LS mean value (SE)	15.0 (0.7)	18.4 (0.6) P<0.0001	20.6 (0.6) P<0.0001	21.4 (0.6) 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) P<0.0001	75.5 (2.4) P<0.0001	80.5 (2.5) 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) P<0.0001	64.5 (2.6) P<0.0001	64.5 (2.7) P<0.0001

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

*The P value is for the comparison of the vardenafil groups with placebo

Source: Original NDA review, Table 3, page 26.

Table 5. Study 10128 – Results for Primary Efficacy Parameters

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	14.80	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

*The *P* value is for the comparison of the vardenafil groups with placebo

Source: Original NDA review, Table 4, page 26.

Table 6. Study 100250 – Results for Primary Efficacy Parameters

	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

*P value is for comparison of the vardenafil groups with placebo

Source: Original NDA review, Table 5, page 27.

Table 7. Study 100285 –Results

	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

*The *P* value is for the comparison of the vardenafil groups with placebo

Source: Original NDA review, Table 6, page 27.

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 8.

Table 8. Study 10232 –Results

	Placebo	Vardenahl 2.5 mg	Vardenahl 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	16.81
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
* The P value is for the comparison of the vardenafil groups with placebo

Source: Original NDA review, Table 7, page 28.

In the original NDA review, the statistical reviewer concluded that "all doses [5, 10, and 20 mg] of vardenafil were statistically superior to placebo in all 4 trials. None of the pivotal studies was designed to specifically compare the 10 and 20 mg doses of vardenafil. Both the 2.5 and 5 mg doses of vardenafil were statistically significantly more effective than placebo in terms of all 3 primary endpoints. Vardenafil 5 mg was statistically significantly better than the 2.5 mg dose with respect to penetration and maintenance of erection. The sponsor believed that the increases measured by the primary endpoints with the 2.5 mg dose were not clinically meaningful and since the the 2.5 mg dose had a lack of an obvious safety advantage over the 5 mg dose, the development of the 2.5 mg dose was not pursued." Since then, the 2.5 mg dose has been developed for use in patients on concomitant potent CYP3A4 inhibitors.

6.3.3 Statistical Plan

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."

6.4 Efficacy Conclusions

In the opinion of this reviewer, the 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.

7. Integrated Review of Safety

7.1 Cardiac Depolarization

Study 10929 was designed to rule out a greater than 10 msec effect of a single 80 mg dose of vardenafil on QTc interval compared to placebo. QTc Fridericia was

the primary endpoint and an individual correction method (QTci) was also used. Results are shown below in Table 9 and Table 10.

Table 9: 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 10. 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.

Results: The primary endpoint (QTcF) showed a 10 msec (90% CI:8, 11) increase for vardenafil 80 mg compared to placebo. The magnitude of QTCi was less [(mean 8 msec) 90% CI: 4,7]. The Cardiovascular and Renal Advisory committee voted that this change was not clinically meaningful (vote: 8-No, 1-Yes, 1-Maybe, and 3-Abstain).

7.2 Alpha-blocker interaction studies

Studies 100480 and 100481 were designed to compare changes in blood pressure of vardenafil 10 and 20 mg compared to placebo when subjects were on terazosin or tamsulosin, respectively. In Part I, vardenafil was dosed to achieve a 6 hour separation from terazosin or tamsulosin and in Part II, vardenafil and terazosin/tamsulosin were dosed to achieve simultaneous Cmax. Results are shown in Table 11 and Table 12.

Table 11: Terazosin results

	Part I Mean Max Δ	Point Est	95% CI		Part II Mean Max Δ	Point Est	95% CI
SBP -placebo	-10			SBP -placebo	-14		
vard 10 mg	-17	-7	(-10, -3)	vard 10 mg	-37	-23	
vard 20 mg	-21	-11	(-14, -7)	vard 20 mg	-28	-14	
DBP -placebo	-5			DBP -placebo	-11		
vard 10 mg	-9	-4	(-6, -1)	vard 10 mg	-20	-9	
vard 20 mg	-12	-7	(-9, -4)	vard 20 mg	-20	-9	
HR -placebo	4			HR -placebo	19		
vard 10 mg	11	7	(3, 10)	vard 10 mg	24	5	
vard 20 mg	11	7	(3, 10)	vard 20 mg	28	9	

Table 12: Tamsulosin results

	Part I Mean Max Δ	Point Est	95% CI		Part II Mean Max Δ	Point Est	95% CI
SBP -placebo	-9			SBP -placebo	-11		
vard 10 mg	-13	-4	(-8, -1)	vard 10 mg	-19	-8	(-14, -2)
vard 20 mg	-17	-8	(-11, -4)	vard 20 mg	-19	-8	(-14, -1)
DBP -placebo	-8			DBP -placebo	-7		
vard 10 mg	-11	-3	(-6, 0)	vard 10 mg	-14	-7	(-12, -2)
vard 20 mg	-12	-4	(-7, 0)	vard 20 mg	-13	-7	(-12, -1)
HR -placebo	7			HR -placebo	12		
vard 10 mg	11	4	(-2, 10)	vard 10 mg	9	-3	(-8, 2)
vard 20 mg	13	6	(0, 12)	vard 20 mg	9	-2	(-8, 3)

Reviewer's comment: The combination of terazosin 10 mg and vardenafil 10 or 20 mg given simultaneously produced pronounced mean decreases in SBP by as much as 23 mm Hg, DBP by as much as 9 mm Hg and mean HR increases of 9 bpm. When separated by 6 hours, the changes were not as dramatic but were still significant (mean maximum change- 11 mm Hg, 7 mm Hg, 7 bpm, respectively). The combination of tamsulosin 0.4 mg and vardenafil 10 or 20 mg given with simultaneous Cmax also produced pronounced mean decreases in SBP by as much as 8 mm Hg, DBP by as much as 7 mm Hg and mean HR increases by as much as 3 bpm. When Cmax was separated by 6 hours, the changes were not as dramatic but were still significant (mean maximium change- 8 mm Hg, 4 mm Hg, 6 mm Hg, respectively). The separation of the doses did not negate the effect of concomitant treatment. The outlier data are presented in Table 13 and Table 14.

Table 13.Terazosin Outliers (subjects)

	run-in or prior to treatment	placebo	vardenafil 10 mg	vardenafil 20 mg
Standing SBP < 85 mm Hg				
Part I	1/30	1/28	3/29	7/28
Part II		0/9	6/8	2/9

Table 14.Tamsulosin Outliers (subjects)

		placebo	vardenafil 10 mg	vardenafil 20 mg
Standing SBP < 85 mm Hg				
Part I		0/21	0/21	1/24
Part II		0/15	2/16	0/13

Based on the degree of blood pressure response and the outlier data, this reviewer believes that vardenafil should be contraindicated in patients taking alpha-blockers.

7.3 Nitrate interaction

Study 10720 was designed to evaluate the pharmacodynamic interaction between vardenafil 20 mg and NTG 0.4 mg.

A 24-hour separation caused no additional change in SBP, DBP or HR (all values are placebo-subtracted point estimates of mean maximal change). An 8-hour separation caused minor changes in SBP and DBP (1-2 mmHg) but HR increased by about 7 bpm. A 4-hour separation caused SBP to decrease by 8 mmHg, DBP to decrease by 7 mm Hg and HR to increase by 5 bpm. A 1-hour separation caused SBP to decrease by 8-9 mmHg, DBP to decrease by 5 mm Hg and HR to increase by 9 bpm.

Reviewer's comment: In an emergency situation, nitrates can be safely administered in subjects who have taken doses up to and including vardenafil 20 mg after a 24-hour wash-out period.

7.4 Ritonavir interaction

Study 100512 was designed to evaluate the pharmacokinetic interaction between vardenafil 5 mg and ritonavir 600 mg bid.

Increases of 13-, 49- and 108- fold were observed in vardenafil mean Cmax, AUC_{0-24} and $AUC_{0-\infty}$ when 5 mg vardenafil was administered with ritonavir vs 5 mg vardenafil alone. The ritonavir mean Cmax and AUC_{0-12} decreased by 22% and 20%, respectively, following concomitant administration with vardenafil 5 mg.

Reviewer's comment: Patients who are on ritonavir or other potent CYP3A4 inhibitors should be restricted to use of a single vardenafil 2.5 mg dose in a 72-hour period.

7.5 Aspirin interaction

Study 100482 was a study on the effects of vardenafil 20 mg on bleeding time and the effects of vardenafil 20 mg on aspirin-induced prolongation of bleeding time.

Bleeding time was not altered in subjects receiving vardenafil 20 mg in combination with aspirin or when given alone.

7.6 Update of Integrated Safety Summary

7.6.1 Introduction and patient exposure

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. The mean duration of treatment was between 180-189 days. Table 15 lists the vardenafil exposure in the clinical pharmacology program and Table 16 lists the patients valid for safety in the "Updated Integrated Safety Pools."

Table 15. Vardenafil Exposure at Different Doses in Clinical Pharmacology Program

Vardenafil Dose	Original NDA Number of Subject Exposure Periods[a]	Nine Studies Since the NDA Number of Subject Exposure Periods[a]	Total (NDA plus nine Studies since NDA) Number of Subject Exposure Periods[a]
2.5 mg	24	0	24
5 mg	54	20	74
10 mg	234 (+19)[b]	132	366 (+19)[b]
20 mg	348 (+22)[b]	204	552 (+22)[b]
40 mg	134	2	136
80 mg	5	8	5
120 mg	0	8	8
Total	**799 (+41)[b]**	**451**	**1291**

a - Subjects are counted once at each dose level they were exposed to; exposure could have been once or more than once at each dose level.
b – Additional subjects not included in the original NDA Pool (from completed studies 100396 and 10298 submitted in the 4-Month Update).
Source: ISS, Table 5-1, page 15.

Table 16. Patients Valid for Safety Updated Integrated Safety Pools (See Pooling section)

Study Number/Descriptor	Pool 3: All PC Studies of Vardenafil 5, 10 and 20 mg		Pool 4: All Studies of Vardenafil 5, 10, or 20 mg
	Placebo	Vardenafil	Vardenafil
100250 (Diabetes)	143	296	296
100249 (6 month pivotal)	182	580	580
10128 (3 month pivotal)	160	479	479
100285 (prostatectomy)	140	287	287
10232 (2.5/5 mg 3 mo)	168	170	170
10769 (3 month flexible dose)	**164**	**157**	**157**
10867 (1 month time to onset)	**242**	**234**	**234**
100312 (extension 100250)			98
10125 (One Year safety)			1023
10152 (6 month 20 mg open label)			239
10194 (6 month flexible dose extension to 10128)			**262**
Total	1199	2203	3825

New studies added to the Safety Pool in this amendment are in bold characters. Source: ISS, Table 5-2, page 16

This review includes 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**. 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).

7.6.2 Listing of studies

The sources of safety data in this submission include three completed Phase III trials, nine ongoing Phase III trials, nine completed clinical pharmacology trials, and eight ongoing clinical pharmacology trials.

Table 17. Listing of studies submitted in current safety update

	Trial #	Descriptor	Region
Phase III completed			
	10867	1 month time to onset	N.A.
	10194	6 month flexible dose extension to 10128	Non N.A.
	10769	3 month flexible dose	Non N.A.
Phase III ongoing			
	10566	Crossover of VAR 20 mg vs SIL 100mg	N.A.
	10786	Open-label, VAR flexible dose, ethnicity study	N.A.
	10806	VAR vs SIL flexible dose	N.A.
	10454	3 month comparison to PLA and SIL	Non N.A.
	10563	Open label, VAR 20 mg	Non N.A.
	10573	1 year extension to 10125	Non N.A.
	10775	Open label, VAR flexible dose	Non N.A.
	10869	Crossover of VAR 20 mg vs SIL 100 mg	Non N.A.
	100446	VAR vs SIL flexible dose	Non N.A.
Clinical Pharmacology -completed			
	10720	Nitrate interaction	N.A.
	10929	Cardiac repolarization	N.A.
	100408	VAR 20 mg ETT	N.A.
	100478	High dose safety vs SIL and placebo	N.A.
	100480	Terazosin interaction	N.A.
	100481	Tamsulosin interaction	N.A.
	100482	Aspirin interaction	N.A.
	100512	Ritonavir interaction	N.A.
	10503	RigiScan VAR vs SIL	Non N.A.
Clinical Pharmacology- ongoing			
	10618	RigiScan- VAR vs placebo	N.A
	10804	Time to onset, RigiScan- VAR vs placebo	N.A.
	10151	intranasal	Non N.A.
	10601	intranasal	Non N.A.
	10634	Dose escalation – Korea	Non N.A
	10687	Dose escalation – China	Non N.A
	10864	intranasal	Non N.A
	10865	intranasal	Non N.A

Source: Study report Tables 2-1, through 2-4, pages 8-10.

7.6.3 Pooling

Safety data were pooled to better assess the safety profile of vardenafil

- "NDA Pool 3" (the original NDA) is comprised of all Phase III placebo-controlled studies using vardenafil 5 mg, 10 mg or 20 mg
- "Updated Pool 3" represents the original NDA Pool 3 plus new safety data for Phase III placebo-controlled studies within this amendment.
- "NDA Pool 4" comprised all controlled and uncontrolled Phase III studies submitted with the original NDA.
- "Updated Pool 4" represents the original NDA Pool 4 plus new trials (controlled and uncontrolled) submitted within this amendment.

The 2.5 mg dose data were excluded from the pooling since approval for this dose was not being sought at the time of the original NDA.

Reviewer's comment: The 2.5mg dose studies are not included in the safety review but is a proposed dose for a special population.

Table 18. Safety Population in NDA and Updated Pools 3

	Placebo	5 mg	10 mg	20 mg	Flexible	Total vardenafil
NDA Pool 3	793	520	650	642	0	1812
Updated Pool 3	1199	520	650	876	157	2203

Source: Study text, ISS, table 4-1 page 13

7.6.4 Demographics:

The demographic, medical history and baseline concomitant medication characteristics between NDA pool 3 and the Updated NDA pool 3 were similar.

Reviewer's comment: This review will focus on Updated Pool 3 unless specifically stated.

7.6.5. Deaths

Table 19. 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

Source: ISS, Table 6-22, page 52.

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 are listed below.

Patient #100446-302-003: A 40 year-old Caucasian male with no previous medical history with a normal screening ECG who during the non-medicated phase suddenly collapsed and died of an expected ruptured aortic aneurysm. An autopsy was performed but the results were not available at the time of submission. He had previously been on sildenafil.

Reviewer's comment: No study drug was administered.

Patient 10806-016-003: A 59 year-old Caucasian male with history of reflux, headaches, and DJD of left shoulder who was found dead, prior to drug dispensing, on his boat presumably due to electrocution while repairing the motor of the boat. No additional information is available.

Reviewer's comment: No study drug was administered.

Patient 10869-023-352: A 57 year-old Caucasian male with history of diabetes, hypertension, hyperlipidemia, peripheral vascular disease on insulin, alph-lipoic acid, ramipril/HCTZ, amlodipine, simvastatin, and aspirin had received vardenafil 20 mg. He was found dead at home 10 days after randomization. It is unknown how many doses he had taken. Empty bottles of alcohol were found next to the body and death was presumed to be hypoglycemia due to alcohol intake.

Reviewer's comment: The number of pills dispensed was not given. A causal relationship can not be ruled out.

Patient 10573-106-006: A 69 year-old male with history of hypertension, hypercholesterolemia, borderline diabetes, CAD s/p CABG on digoxin, amlodipine, potassium, fosinopril, furosemide, lovastatin, aspirin, calcium and vitamin E was randomized to receive vardenafil 10 or 20 mg. One year and 10 months later, he was found dead in the bathroom. No autopsy was perfomed. The cause of death was given as ischemic cardiomyopathy.

Reviewer's comment: Temporal relationship between drug intake and death has not been ruled out. Cause of death has not been confirmed but ischemic etiology is likely based on patient's medical history. The treatment remains blinded.

Patient 10573-017-024: A 58 year-old male whose drug intake remains blinded had cause of death listed as suicide. A case report form was not available for review.

Reviewer's comment: A full case report form was not available for review.

Patient 10573-037-003: 81 year-old Caucasian male with a history of asthma, and hypertension on cortisone, furosemide, carvedilol, diltiazem was randomized to vardenafil 10 or 20 mg. Three weeks after last study drug intake, he presented with unstable angina and progressed to a posterolateral myocardial infarction with cardiogenic shock and subsequent death. No autopsy was performed.

Reviewer's comment: No temporal relationship exists between study drug and event. The treatment remains blinded.

Patient 10573-037-006: A 59 year-old Caucasian male with history of diabetes and BPH on metformin, doxazosin, and normoprost compuesto was randomized to vardenafil 10 or 20 mg. Three and ½ weeks after last dose of study drug, he presented with angina and underwent angioplasty due to severe CAD. He deteriorated during the admission and died. No autopsy was performed.

Reviewer's comment: No temporal relationship exists between study drug and event. The treatment remains blinded.

7.6.6. Adverse events

Fifty-nine percent (59%) of patients in all placebo controlled and uncontrolled trials reported adverse events. For almost all body systems, the incidence rates of treatment-emergent adverse events in the vardenafil treatment group was greater than in the placebo group. See Table 20.

Table 20. Incidence Rates (%) of Treatment-Emergent Adverse by Body System[a]

	NDA Pool 3		Updated Pool 3	
Body System	Placebo n = 793	Vardenafil n = 1812	Placebo n = 1199	Vardenafil n = 2203
Any Adverse Event	39.7	57.6	32.9	53.4
Body as a whole	16.5	27.2	13.2	25.1
Cardiovascular	4.8	16.4	4.4	15.4
Digestive	6.8	12.1	5.6	11.2
Hemic and Lymphatic	0.8	0.7	0.5	0.6
Metabolic and nutritional	3.4	5.6	3.3	5.3
Musculoskeletal	3.3	4.6	2.3	4.1
Nervous	4.5	6.9	3.7	6.3
Respiratory	9.3	17.5	6.9	15.6
Skin and appendages	1.3	2.7	1.1	2.5
Special senses	1.6	4.5	1.3	4.1
Urogenital	3.0	3.5	2.3	3.0

a - Reported for systems where the incidence rates for vardenafil exceed those for placebo in Updated Pool 3.

Adverse events that occurred at least twice as often on vardenafil than on placebo were headache, flushing, rhinitis, sinusitis, dyspepsia, nausea, and dizziness. See Table 21.

Table 21. 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.

Effect of age on adverse events:

In the >65 years of age subgroup, a total of 254 patients received placebo and 489 patients received vardenafil in the placebo-controlled studies. The incidence rates for adverse events in the >65 year vardenafil subgroup were similar to that for the ≤65 year vardenafil subgroup (53% vs 54%). The adverse events of abnormal vision, back pain, dyspepsia, headache, rhinitis and sinusitis occurred

less frequently in the >65 year age vardenafil treatment group compared to the ≤65 year age vardenafil treatment group. The incidence of flushing was similar in both age categories among vardenafil treated patients.

Reviewer's comment: These data suggest that older patients do not experience adverse events with higher frequency than younger patients. However, discontinuations due to treatment-emergent adverse events were greater compared to the ≤65 age group (3.9% vs 3.0%). (See discontinuation section).

Effect of race on adverse events:

The majority of patients in both the vardenafil and the placebo groups were Caucasian. Although the adverse event profile for vardenafil was consistent across subgroups by race, the number of patients within racial subgroups other than Caucasians was too small to detect any meaningful differences in the rates of adverse events across racial subgroups.

Effect of BMI on adverse events:

The majority of patients in the treatment groups had a BMI of ≤ 29 kg/m^2. Regardless of BMI, the odds ratios of vardenafil compared to placebo were increased for the adverse events of dyspepsia, headache, rhinitis, sinusitis and flushing, and were similar to those in the original NDA. Cardiovascular adverse events were infrequent and similar in both ≤ 29 kg/m^2 and >29 kg/m^2 BMI categories of Updated Pool 3 vardenafil treated patients.

Effect of medical history on adverse events:

There were no changes in the incidence rates of adverse events among the medical history subgroups of alcohol consumption, smoking history, pulmonary disease, hyperlipidemia, diabetes mellitus, history of prostatectomy or history of previous sildenafil use.

Effect of positive history of cardiovascular disease on adverse events:

The incidence of adverse events expected from this class of drug for patients with or without a history of cardiovascular disease was low and comparable in vardenafil-treated patients. For both the vardenafil and placebo treatment groups, the incidence of selected cardiovascular adverse events (angina, chest pain, atrial arrhythmia, hypotension, myocardial infarction, stroke, syncope) was low regardless of history of cardiovascular disease. See Table 22.

Table 22. Incidence Rates of Selected Cardiovascular Events

Cardiovascular Event	History of CVD	Updated Pool 3 Placebo (%) (No=1093) (Yes=106)	Updated Pool 3 Vardenafil (%) (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.

Effect of concomitant medication on adverse events:

The incidence of adverse events in patients on concomitant medications was similar to the rates in the original NDA.

Anti-hypertensives: The subgroups taking at least one antihypertensive drug concomitantly were older, had a higher BMI, and had a greater proportion of patients with a history of hyperlipidemia, diabetes mellitus and cardiovascular disease than the subgroups not on concomitant antihypertensives. Despite the apparently greater inherent risk in the subpopulation, concomitant use of one or two antihypertensives did not increase the risk of *selected* cardiovascular adverse events during vardenafil treatment.

Reviewer's comment: Hypotension associated with concomitant alpha-blocker use is discussed separately.

CYP3A4 drug interactions:

CYP3A4 Inhibitors: Twenty-seven percent (27%) of both placebo and vardenafil groups used CYP3A4 inhibitors at anytime during treatment.[1] Adverse events common to the PDE5 inhibitor class occurred less frequently in patients who concomitantly used CYP3A4 inhibitors compared with those who did not (dyspepsia 1.9% vs 4.1%, headache 10.9% vs 15.3%, and flushing 8.3% vs 11.6%). The incidence of back pain was greater in the vardenafil treatment group compared to placebo (2.0% vs 1.0%). The incidence of rhinitis was similar.

CYP3A4 substrates: As seen with the inhibitors, the incidence rates of adverse events were less in the vardenafil treatment group when CYP3A4 substrate drugs were used concomitantly compared to when these drugs were not used. There was one exception in the vardenafil treated group,

back pain and sinusitis occurred more frequently in the CYP3A4 substrate users compared to the CYP3A4 substrate non-users.

Reviewer's comment: [1] These numbers differ from the original NDA review. For placebo and vardenafil groups, 7% and 6% was cited as the percentage of CYP34 inhibitor users, respectively (see page 86 of original NDA review). Despite the reported reduced incidence of adverse events, potent CYP3A4 inhibitors have been shown to increase plasma levels of vardenafil substantially and dose adjustment should be recommended.

Adverse events in fixed dose vs flexible dose studies:

The incidence rates of treatment emergent adverse events in the placebo controlled flexible dose Study 10769 (submitted with supplement) were less than those in the NDA Pool 3 fixed dose studies. However, the incidence rates for flu syndrome, back pain and prolonged QT were slightly greater in flexible dose Study 10769 than was observed in the NDA Pool 3 fixed dose studies. The sponsor believes that the slight increased incidence rates for flu syndrome and prolonged QT in this smaller population of the Flexible Dose Study is difficult to interpret.

Reviewer's comment: In study 10769, ECGs were performed at time –4 weeks, 0 weeks, 4 weeks and 12 weeks. Prolonged QT was noted in 1 of 157 patient in the vardenafil groups and 5 of 164 patients in the placebo group. Two narratives were available in the electronic file with a maximum QTc (Bazett) interval of 484 msec, however, both subjects received placebo This reviewer agrees the results are difficult to interpret and no conclusion can be made at this time.

7.6.7. Serious adverse events

The incidence of serious adverse events were greater in the vardenafil group than in the placebo group. The incidence was similar to the original NDA.

There were two new treatment-related events reported with the updated Pool 4- which did not occur in Pool 3 – one report each of anaphylactoid reaction and deafness. The anaphylactoid reaction was judged to be serious and possibly treatment-related and was confounded by amoxicillin administration. The overall incidence does not represent a signal for serious adverse events.

7.6.8 Discontinuations

Overall, discontinuation due to treatment-emergent adverse events was greater in the vardenafil treated group compared to placebo. This was similar to rates in the original NDA pool. The most common adverse events were headache (19 patients), flushing (10 patients), rhinitis (5 patients), tachycardia (4 patients), nausea (5 patients), abnormal liver function tests (4 patients), and dizziness, hypesthesia, abdominal pain and palpitations (3 patients each).

In the vardenafil treated ≥65 age group, discontinuations due to treatment-emergent adverse events were greater compared to the ≤65 age group (3.9% vs 3.0%). In both groups the incidence of discontinuations was highest in the vardenafil 20 mg treatment group.

7.6.9 Laboratory Abnormalities

The updated Pool 3 datasets included two additional placebo-controlled studies with 20 cases of laboratory abnormalities and no overall change in the conclusions.

There was one additional case of ALT>3xULN identified in the placebo group (10769-20-0014) and one in the vardenafil group (10769-27-0008) in the Updated Pool 3 data sets. There was also one additional AST>3xULN identified in the placebo group (10867-904-011) in the Updated Pool 3 datasets. There were 6 additional CK>3xULN identified in the placebo group and 8 in the vardenafil group, with 2 additional CK>10xULN in the placebo group (10769-36-0020, 10769-18-0004) and 1 additional CK>10xULN in the vardenafil group (10769-39-0005) identified in the Updated Pool 3 datasets. The incidence of these laboratory abnormalities remain overall unchanged compared to the NDA Pool 3 dataset.

Table 23. Incidence Rates of Treatment-Emergent Potentially Significant Chemistry Laboratory Abnormalities [n (%)]

	Lab Variable	NDA Pool 3 Placebo n=793	NDA Pool 3 Vardenafil n=1812	Updated Pool 3 Placebo n=1199	Updated Pool 3 Vardenafil n=2203
CK	>3xULN	16/746 (2.1%)	50/1745 (2.9%)	22/1125 (2.0%)	58/2118 (2.7%)
	>5xULN	8/752 (1.1%)	18/1762 (1.0%)	11/1133 (1.0%)	20/2138 (0.9%)
	>10xULN	2/753 (0.3%)	5/1764 (0.3%)	4/1136 (0.4%)	6/2143 (0.3%)
SGOT/AST	>3xULN	2/753 (0.3%)	4/1760 (0.2%)	3/1135 (0.3%)	4/2139 (0.2%)
	>5xULN	1/753 (0.1%)	3/1764 (0.2%)	1/1136 (0.1%)	3/2144 (0.1%)
	>10xULN	0/754 (0%)	2/1765 (0.1%)	0/1137 (0%)	2/2145 (0.1%)
SGPT/ALT	>3xULN	8/752 (1.1%)	4/1760 (0.2%)	9/1134 (0.8%)	5/2139 (0.2%)
	>5xULN	2/753 (0.3%)	2/1764 (0.1%)	2/1135 (0.2%)	2/2144 (0.1%)
	>10xULN	0	0	0	0

Source: ISS, Table 7-2, page 56.

In the case of CK elevation (> 3xULN), there were no cases of elevated CK-MB fraction of >2.5% of total CK. No new cases of myalgia were reported.

Reviewer's comment: This reviewer was unable to locate the line listings for the new cases of ALT/AST and CK elevations.

7.6.10. Special safety

Cardiovascular

a) Hemodynamic: Due to vardenafil's vasodilatory actions, particular attention is given to serious adverse events which may have a hemodynamic basis.

Alpha-blockers and Nitrates interaction: Pharmacodynamic studies were performed with alpha blockers (terazosin 10 mg and tamsulosin 0.4 mg), and with nitrates (0.4 mg sublingual). The combination of terazosin 10 mg and vardenafil 10 or 20 mg given simultaneously produced pronounced decreases in SBP/DBP and HR increases resulting in termination of the study. When separated by 6 hours, the changes were not as dramatic but were still significant. The combination of tamsulosin 0.4 mg and vardenafil 10 or 20 mg given with simultaneous Cmax also produced pronounced decreases in SBP/DBP and HR increases. When Cmax was separated by 6 hours, the changes were not as dramatic but were still significant.

Concomitant use of nitrates with vardenafil is contraindicated. However, based on the nitrate interaction study, separation by 24 hours caused no additional change in SBP, DBP or HR.

Dizziness: Dizziness was reported in more patients receiving vardenafil (2.2%) compared to patients receiving placebo (0.9%). See Table 24.

Table 24. Incidence Rates of Dizziness

	Placebo n (%)	Vardenafil n (%)
Treatment-emergent	11/1199 (0.9)	48/2203 (2.2)
Drug-related	6/1199 (0.5)	43/2203 (2.0)

Source: ISS, Table 8-6, page 75.

Twenty-five out of the 48 (52%) vardenafil patients with treatment-emergent dizziness experienced at least one BP reduction episode (defined as SBP<90 mmHg or decrease ≥20 mmHg from baseline visit and/or DBP < 50 mm Hg or decrease ≥15 mmHg from baseline visit) during a scheduled visit compared to 6 out of 11 in the placebo group. In those patients with treatment-emergent dizziness, 6 out of the 11 in the placebo group also received antihypertensive medications compared to 24 out of the 48 in the vardenafil receiving antihypertensive medications.

Reviewer's comment: Dizziness was more frequent in the vardenafil treated group and >50% of episodes corresponded to low blood pressures.

In review of the 15-Day safety reports, an additional case of dizziness with hypotension was found (patient 100535-4012 - serial #347). This 62 year-old male in the vardenafil 5 mg/ 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, ginko biloba.

Reviewer's comment: This case is likely study drug-related.

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.

Reviewer's comment: Only one of these cases showed a temporal relationship of study drug to the event. Patient 10566-030-30008 was a 64 year-old male with a history of hypertension, gout, diabetes and heartburn maintained on atenolol, terazosin, allopurinol, glipizide, sulindac, rabeprazole and aspirin. Approximately 4 hours after his last dose of study medication (sildenafil 100 mg or vardenafil 20 mg) he experienced a syncopal episode while rising from a chair.

In review of the 15-Day safety reports, an additional case of syncope was identified (patient 100249-44059 in serial #344). This 61 year-old male experienced a syncopal episode 7 days after starting vardenafil 10 mg and 8 hours after his last dose. He had a second episode while leaving the bathroom that was preceded by nausea, vomiting, left sided paresthesias, chest heaviness and diaphoresis. He was admitted and had a negative work-up. Chronic Hytrin had been discontinued the day before the incident and Proscar had been started the night before the incident.

Reviewer's comment: Causality can not be confirmed in this case.

Accidental injury: There were 8 additional accidental injuries reported, 3 in the placebo group and 5 in the vardenafil group with an overall incidence of 0.4%. None of the accidental injuries were considered drug-related and no relation of these events to changes in hemodynamic parameters could be ascertained.

Reviewer's comment: The study text states that "blood pressure measurements were not obtained at the time of accidental injury" which leaves the data uninterpretable.

Cerebrovascular accident: There were no new reports of CVA in the placebo-controlled Phase III trials or other completed trials. There were 2 cases of CVA and 1 case of TIA reported in ongoing studies.

Reviewer's comment: Subjects with history of CVA were excluded from the trials. Of the 3 cases occurring in ongoing trials, no temporal relationship exists between drug intake and event.

Acute coronary events (myocardial infarction, unstable angina): Eight additional myocardial infarctions have been reported as serious adverse events. Two patients had not received study drug, 2 patients received vardenafil 20 mg, 2 patients received sildenafil 100 mg and 2 patients remain blinded to treatment.

Table 25. Myocardial Infarctions Since NDA submission

Patient Identifier	Treatment	Relation to Tx	Death (Y/N)
10566-038-019	VAR 20 mg	Related	No
10566-047-001	None	None	No
10566-047-013	SIL 100 mg	None	No
10573-037-003	Blinded	None	No
10573-106-006	Blinded	None	Yes
10867-905-004	None	None	No
10869-011-195	VAR 20 mg	None	No
10869-012-036	SIL 100 mg	None	No

Source: ISS, Table 8-11, page 84.

All episodes were considered unrelated to study drug intake except for 10566-038-019, a 62 year-old male with a history of diabetes, MI, PTCA x 2 with stenting, hypertension, hypercholesterolemia, aphasia, tremors and left carotid endarterectomy. One hour after his first dose (and 20 minutes after intercourse), he developed symptoms and was diagnosed with a non Q-wave MI with ventricular tachycardia/cardiac arrest. He underwent CABG and AICD placement.

Reviewer's comment: This event is temporally related to study drug.

In the overall vardenafil program, there have been 22 serious adverse events of definite myocardial infarction and 1 case of presumed myocardial infarction. Of these 23 cases, 4 have resulted in death. Three cases were discussed in the original NDA and the fourth case (10573-106-006) is discussed above in the death section.

Unstable angina: There were 2 additional cases suggestive of unstable angina pectoris reported as serious adverse events (10125-038-015 and 10125-040-006). Descriptions of these 2 patients are given below:

- Patient 10125-38-015, a 69-year-old male with history of hypercholesterolemia, experienced angina and was hospitalized for 24 hours during the study follow up period. This occurred 12 days after the last dose of study medication (vardenafil 10 mg). The event was considered to be not related to the study drug.
- Patient 10125-040-006, a 65-year-old male, experienced angina pectoris 4 days after the last intake of study medication (vardenafil 10 mg) and was hospitalized. The study drug therapy was discontinued and subsequently the patient underwent a PTCA. The event was assessed as not drug-related.

There were 9 more reports of unstable or prolonged angina in ongoing studies. Of these, 2 patients (10806-050-003 and 100446-206-021) did not receive any study medication prior to the event, 2 patients (10869-002-059 and 10566-020-005) had received sildenafil 100 mg, and 1 patient (10869-007-023) had received vardenafil 20 mg.

Four patients (10573-105-360, 10573-037-003, 10573-037-006 and 10573-108-178) are still blinded with respect to study medication but patients received either vardenafil 10 mg or 20 mg. Two patients (10573-037-003 and 10573-037-006) died 2 days after, and on the same day, respectively, after the episode of angina. Patient 10573-037-003 had PTCA performed subsequent to the episode of unstable angina, had an MI 2 days later followed by cardiogenic shock and died. Patient 10573-037-006 was diagnosed as having severe CAD, had a PTCA, and his condition worsened during the hospital stay leading to death. All the events of unstable or prolonged angina were considered by the investigator as unrelated to study medication.

b) Electrocardiographic

The primary endpoint (QTcF) of the QT study (10929) showed a 10 msec (90% CI: 8, 11) increase for vardenafil 80 mg compared to placebo. The magnitude of QTci was less [(mean 8 msec) 90% CI: 4,7]. In exercise tolerance testing studies 100302 (submitted with the NDA) and 100408, the safety of vardenafil 10 and 20 mg, respectively, were assessed in patients with stable exertional CAD. There were no statistically significant differences in mean total time to angina, and in mean total time to 1 mm or greater ST-segment depression between the vardenafil-treated group and the placebo-treated group. Adverse events were reported with greater frequency in the vardenafil group compared to the placebo group. There was one patient (100408-007-002) in the vardenafil group who had serious adverse events of dizziness and hypotension, which began just after completing the ETT. These events were considered likely vardenafil-related. The patient discontinued the study after these events.

Reviewer's comment: Vital sign measurements for patient 100408-007-002 were BP 80/40 and HR 125 at the end of exercise. The subject had relative hypotension prior to stress testingwith BP 90/60 and HR 81-89. Baseline BP was in the 120/76 range with a HR of 60.

Visual safety

Visual safety is assessed by the following parameters: oculomotor balance, conjunctiva examination, slit lamp examination, anterior chamber depth, lens and fundus examination, Amsler grid, best visual acuity, intra-ocular pressure and color vision test (Farnsworth-Munsell 100 Hue test), and electroretinography, in addition to, patient interviews. The Updated Pool 3 and Pool 4 datasets show very little change in the total number of patients with reportable adverse events and no change in the total percents of patients affected. Color vision change was reported

rarely (<0.1%) with vardenafil treatment in all clinical studies. Collectively, these data are consistent with all previous reports of visual events.

There were 6 new cases of visual disturbance (coded as abnormal vision [4], amblyopia [1], and photobia [1]) in the vardenafil group and none in the placebo group. There were 3 special senses adverse events that led to premature discontinuation in the vardenafil group compared to none in the placebo group These events were abnormal vision (1), conjunctivitis (1), and lacrimation disorder (1). In ongoing trials, there is one patient in the vardenafil arm (20 mg) with a serious adverse event related to vision. Patient 10573-906-300 was discontinued after 2 occurrences of blurred vision and retina pigmentary alterations that were considered as possibly related to study drug by the principal investigator. His blurred vision has fully recovered.

Reviewer's comment: The ophthalmology consult believes that, from an eye safety standpoint, that this NDA can be approved with a Phase 4 commitment for repeated dose studies evaluating the effect of vardenafil on retinal function. This reviewer agrees.

Hemostatic Events

There was one new case of epistaxis. Bleeding time was not altered in subjects receiving aspirin in combination with 20 mg vardenafil.

Priapism

As reported in the original NDA, there have been 2 cases of priapism reported in the 31 day multiple dose clinical pharmacology study (100196). No additional cases of priapism have been reported.

Myalgia/Back pain

In phase III trials, there have been 6 new cases of back pain, one in the placebo group and 5 in the vardenafil groups and one new case of myalgia (in the placebo group). The overall incidence of back pain is 2.0% in the vardenafil group and 1.7% in the placebo group.

Table 26. Incidence of Back Pain and Myalgia

	NDA pool 3 Placebo N=793	NDA pool 3 Vardenafil N=1812	Updated Pool 3 Placebo N=1199	Updated pool 3 Vardenafil N=2203
Backpain	19 (2.4%)	39 (2.2%)	20 (1.7%)	43 (2.0%)
Myalgia	2 (0.3%)	12 (0.7%)	3 (0.3%)	12 (0.5%)

Source: ISS, Table 8-36, page 138.

Table 27. Incidence of Back Pain/Myalgia in Pooled Data from Placebo-Controlled Single Dose Clinical Pharmacology Studies of Vardenafil

Adverse Event	Vardenafil 10 mg[a]		Vardenafil 20 mg[b]		Vardenafil 40 mg[c]		Vardenafil 80 mg[d]		Vardenafil 120 mg[e]	
	PLA	VAR	PLA	VAR	PLA	VAR	PLA	VAR	PLA	VAR
n	200	191	365	507	77	78	67	71	4	8
Backpain	2 (1.0%)	2 (1.0%)	2 (0.5%)	3 (0.6%)	1 (1.3%)	6 (7.9%)	1 (1.5%)	6 (8.5%)	1 (25%)	3 (38%)
Myalgia	3 (1.5%)	0	2 (1.3%)	3 (0.6%)	1 (1.3%)	1 (1.3%)	1 (1.5%)	1 (1.4%)	0	0

Source: ISS, Table 8-37, page 139.

- In single dose studies, up to the maximum recommended dose of vardenafil 20 mg, the incidence of back pain and myalgia was the same as or less than with placebo. Single doses of vardenafil 40 mg or higher, demonstrate a dose-response for the incidence of back pain and myalgia and were more likely to be moderate and severe in nature.
- In multiple-dose Clinical Pharmacology studies there was a clear dose-response and dose-frequency-response. The tolerability at the 20 mg/qd and 40 mg/qod dose levels was similar. The back pain/myalgia incidence was lower at these dose levels than at the 40 mg/qd dose level and it was much lower than that at the 40 mg/bid dose level. The 40 mg/bid dose level treatment was discontinued after Day 4 due to poor tolerability in all subjects receiving that dose regimen.
- 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 an extensive 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, anti-histone. In clinical pharmacology studies (10720, 100478, 100480 and 100481), 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).

Reviewer's comment: In review of the 9 back pain cases, only one case (10720-001-1024) had a temporal relationship to dosing occurring 5 minutes after 20 mg vardenafil and NTG was given 1 hour later. There was inconsistency in evaluation regarding the timeliness of CK and inflammatory markers relative to onset of symptoms ranging from laboratory assessment performed at onset through 1 week after onset.

Other adverse events

In the 15-Day safety reports, there was a spontaneous report (# 200310378BFR - serial #367) of a 59 year-old male with history of diabetes for 5-6 years who experienced symptoms following 10 mg of vardenafil and 10 minutes after sexual intercourse. He complained of feeling breathlessness, nausea, throat and eye burning, chest pain and redness of the eye. The following day he experienced bloody vomitus and swelling of the fingers. Symptoms were reported by the patient as "unendurable and he felt a death impression." Concurrent medications were glucophage and amaryl. He had been previously taken sildenafil.

Reviewer's comment: This case is temporally related to study drug.

8. Use in Special Populations

8.1 Effects of Gender, Age, and Race:

Gender: Vardenafil is indicated only for the treatment of men with erectile dysfunction.

Age: There was >50% increase in AUC and >30% increase in Cmax in patients greater than 65 years of age. The clinical pharmacology reviewer recommends that a dose recommendation should be receive a starting dose of 5 mg. Safety data from the clinical studies do not show any increased incidence of adverse events in men >65 years of age compared to those < 65 years of age. Nevertheless, based on the pharmacokinetic data, this reviewer agrees with the clinical pharmacology reviewer and suggests a starting dose of 5 mg be considered for patients ≥65 years.

Race/ethnicity: The vast majority of patients in both the vardenafil and placebo treatment groups were Caucasian. The number of patients in racial sub-groups other than Caucasians was too small to detect any meaningful differences in the rates of adverse events in vardenafil treated patients across racial subgroups.

8.2 Pediatric Program:

Vardenafil is indicated only for men with erectile dysfunction. The sponsor has requested and been granted a pediatric waiver.

8.3 Data Available or Needed in Other Populations Such as Renal or Hepatic Compromised Patients or use in Pregnancy:

Effect of impaired renal function: Renal impairment does not have a significant effect on vardenafil exposure, and the clinical pharmacology reviewer believes that dose adjustment is not required in renal impairment. This reviewer agrees. Vardenafil has not been studied in patients on dialysis.

Effect of hepatic impairment: Based on the results showing increase in drug exposure (approximately 2 ½ times the AUC and Cmax), the clinical pharmacology reviewer

believes that the starting dose of vardenafil in the moderately hepatic impaired patient should be 5 mg, and such patients should not be given doses higher than 10 mg. This reviewer agrees with the clinical pharmacology reviewer in recommending that moderately hepatic-impaired patients not be given doses higher than 10 mg (not 20 mg as recommended in the proposed label). (Exposure in patients with moderate hepatic impairment given a 20 mg dose would be equivalent to a 50 mg dose in patients without hepatic impairment. Limited safety data are available for this dose level). Patients with severe hepatic impairment have not been evaluated.

Pregnancy: Vardenafil is not indicated for use in women.

9. Conclusions and Recommendations

9.1 Conclusions

1) Cardiovascular repolarization: Based on the available data, vardenafil 80 mg exhibits a 10 msec (90% CI: 8, 11) increase in QTcF compared to placebo. The magnitude of the QTci increase was less ([mean 8 msec] 90% CI: 4,7). The magnitude of QTcF changes raises concerns regarding arrhythmogenic potential even though the Cardiovascular and Renal Advisory committee ruled that the results were not clinically meaningful. In the general population, vardenafil at recommended doses has a low arrhythmogenic risk. However, in a conducive clinical environment, vardenafil could potentially cause rare QT-related adverse events. QT data should be presented in the "Clinical Pharmacology" section of the label and also included in the "PRECAUTIONS" section.

2) Nitrate interaction: (1) The co-administration of vardenafil with nitrates should be contraindicated due to a significant drop in blood pressure with concomitant use. (2) In an emergency situation, nitrates can be safely administered in subjects who have taken doses up to and including vardenafil 20 mg after a 24-hour wash-out period.

3) Alpha-blocker interaction: (1) The concomitant use of terazosin 10 mg with vardenafil 10 or 20 mg should be contraindicated. (2) A six-hour separation of doses did not negate the additive hemodynamic effects and concomitant treatment is not clinically acceptable. (3) Based on the current data, the vardenafil 10 mg or 20 mg should not be used concurrently with tamsulosin 0.4 mg. The separation of the doses did not negate the effect of concomitant treatment and is not clinically acceptable.
(4) The sponsor has proposed using vardenafil 5 mg in combination with alpha-blockers without dose/time time modification but no data was initally. During labeling discussion the sponsor agreed to submit study 100535- A Phase I randomized, double-blind, placebo-controlled 4-way crossover evaluation of blood pressure using 5 mg of vardenafil in patients on chronic terazosin (5 or 10 mg) or tamsulosin (0.4 mg) dosed simultaneously and 6 hours apart. In patients on terazosin 5 mg one patient had a BP of 99 when dosed simulatenously with 5 mg vardenfil 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 experienced a standing SBP <85 mmHg when vardenafil 5 mg was dosed simultaneously with terazosin 10 mg and 1 of 9 patients had a BP of 93 when dosed at 6 hours. In the

tamsulosin group, 2 of 20 patients experienced a standing SBP <85 mmHg when vardenafil 5 mg was dosed simultaneously with tamsulosin 0.4 mg and 2 of 20 patients also had a SBP <85 mm Hg when the doses were separated by 6 hours. See Table 28 and 29.

Table 28 Standing Systolic BP in Patients on Terazosin (5 and 10 mg) and Vardenafil 5 mg

Terazosin 5 mg		0 hours			6 hours		
		Baseline	Min Value	Max decrease	Baseline	Min Value	Max Decrease
1002	PLA	112.0	100.0	-12.3	121.0	114.0	-7.0
	VAR	110.0	110.0	0.0	111.0	100.0	-11.0
2001	PLA	112.3	111.0	-1.3	113.3	111.0	-2.3
	VAR	115.0	111.0	-4.0	114.0	111.0	-3.0
2002	PLA	150.7	141.0	-9.7	151.3	147.0	-4.3
	VAR	143.3	141.0	-2.3	141.7	138.0	-3.7
2006	PLA	120.3	117.0	-3.3	118.3	115.0	-3.3
	VAR	118.3	115.0	-3.3	128.3	117.0	-11.3
2009	PLA	133.7	119.0	-14.7	131.7	118.0	-13.7
	VAR	136.7	127.0	-9.7	134.7	128.0	-6.7
2010	PLA	120.3	119.0	-1.3	130.7	126.0	-4.7
	VAR	124.0	114.0	-10.0	119.7	116.0	-3.7
2016	PLA	137.3	126.0	-11.3	135.0	137.0	2.0
	VAR	127.7	115.0	-12.7	132.3	129.0	-3.3
3001	PLA	147.0	123.0	-24.0	121.3	117.0	-4.3
	VAR	144.3	122.0	-22.3	136.7	115.0	-21.7
3002	PLA	133.3	130.0	-3.3	135.3	128.0	-7.3
	VAR	139.7	131.0	-8.7	137.0	124.0	-13.0
3005	PLA	137.7	113.0	-24.7	123.7	117.0	-6.7
	VAR	132.0	114.0	-18.0	119.0	118.0	-1.0
3006	PLA	113.7	108.0	-5.7	110.3	112.0	1.7
	VAR	122.7	99.0	-23.7	117.3	109.0	-8.3
5002	PLA	127.7	112.0	-15.7	122.7	118.0	-4.7
	VAR	131.3	116.0	-15.3	no data	98.0	no data
Terazosin 10 mg							
2004	PLA	139.0	**136.0**	-3.0	138.7	**135.0**	-3.7
	VAR	131.0	**125.0**	-6.0	133.0	**125.0**	-8.0
2007	PLA	129.7	**116.0**	-13.7	126.0	**121.0**	-5.0
	VAR	130.7	**120.0**	-10.7	123.5	**118.0**	-5.5
3007	PLA	160.7	**133.0**	-27.7	132.3	**121.0**	-11.3
	VAR	175.0	**121.0**	-54.0	134.3	**110.0**	-24.3
3008	PLA	145.7	**115.0**	-30.7	119.3	**116.0**	-3.3
	VAR	143.0	**106.0**	-37.0	121.3	**114.0**	-7.3
3017	PLA	139.0	**115.0**	-24.0	118.7	**105.0**	-13.7
	VAR	142.0	**111.0**	-31.0	127.3	**117.0**	-10.3
4005	PLA	143.7	**121.0**	-22.7	127.3	**127.0**	-0.3
	VAR	151.3	**113.0**	-38.3	128.7	**119.0**	-9.7
4007	PLA	104.0	**81.0**	-23.0	107.0	**97.0**	-10.0
	VAR	no data	**no data**	no data	no data	**no data**	no data
4012	PLA	132.0	**91.0**	-41.0	117.7	**110.0**	-7.7
	VAR	123.3	**80.0**	-43.3	113.7	**93.0**	-20.7
5001	PLA	154.3	**126.0**	-28.3	136.7	**125.0**	-11.7
	VAR	139.0	**110.0**	-29.0	128.0	**120.0**	-8.0

Table 29 Standing Systolic BP in Patients on Tamsulosin (0.4 mg) and Vardenafil 5 mg

tamsulosin 0.4mg		0 hours			6 hours		
		Baseline	Min Value	Max Decrease	Baseline	Min Value	Max Decrease
1001	Pla	129.3	110.0	-19.3	113.0	102.0	-11.0
	Var	120.0	122.0	2.0	109.0	101.0	-8.0
1003	Pla	113.3	109.0	-4.3	107.7	104.0	-3.7
	Var	110.3	100.0	-10.3	110.0	89.0	-21.0
2008	Pla	123.0	115.0	-8.0	118.7	115.0	-3.7
	Var	137.7	120.0	-17.7	119.0	115.0	-4.0
2011	Pla	140.0	129.0	-11.0	130.0	134.0	4.0
	Var	135.3	113.0	-22.3	139.0	124.0	-15.0
2014	Pla	128.3	124.0	-4.3	133.3	118.0	-15.3
	Var	131.3	121.0	-10.3	119.3	112.0	-7.3
2017	Pla	127.3	129.0	1.7	123.3	121.0	-2.3
	Var	129.7	118.0	-11.7	131.7	117.0	-0.2
2018	Pla	120.7	115.0	-5.7	120.0	116.0	-4.0
	Var	121.0	116.0	-5.0	127.3	120.0	-7.3
3003	Pla	127.0	125.0	-2.0	121.0	117.0	-4.0
	Var	125.7	116.0	-9.7	133.7	129.0	-4.7
3009	Pla	117.0	109.0	-8.0	110.7	107.0	-3.7
	Var	114.0	100.0	-14.0	106.0	103.0	-3.0
3012	Pla	164.0	127.0	-37.0	138.0	134.0	-4.0
	Var	153.7	103.0	-50.7	124.0	113.0	-11.0
3013	Pla	no data	no data	no data	no data	no data	no data
	Var						
3018	Pla	131.0	106.0	-25.0	134.3	123.0	-11.3
	Var	134.7	121.0	-13.7	118.7	106.0	-12.7
4004	Pla	136.0	131.0	-5.0	130.3	130.0	-0.3
	Var	136.7	118.0	-18.7	134.3	122.0	-12.3
4009	Pla	112.0	92.0	-22.0	115.0	85.0	-30.0
	Var	110.7	82.0	-28.7	115.3	80.0	-35.3
4010	Pla	117.3	98.0	-19.3	112.7	90.0	-22.7
	Var	112.7	82.0	-30.7	113.0	91.0	-22.0
4011	Pla	124.3	115.0	-9.3	133.3	107.0	-26.3
	Var	119.0	100.0	-19.0	121.7	110.0	-11.7
4013	Pla	115.0	106.0	-9.0	118.7	110.0	-8.7
	Var	131.0	110.0	-21.0	117.3	100.0	-17.3
4014	Pla	146.0	134.0	-12.0	138.3	124.0	-14.3
	Var	141.0	129.0	-12.0.	134.0	124.0	-10.0
4015	Pla	122.7	111.0	-11.7	122.3	101.0	-21.3
	Var	123.0	110.0	-13.0	118.7	95.0	-23.7
4016	Pla	115.3	99.0	-16.3	112.3	105.0	-7.3
	Var	114.0	88.0	-26.0	110.3	84.0	-26.3
5003	Pla	146.3	138.0	-8.3	120.0	117.0	-3.0
	Var	131.0	125.0	-6.0	138.7	127.0	-26.3

(5) This reviewer believes that vardenafil should be contraindicated in patients taking alpha-blockers.

Reviewer's comment: The European label does not recommend the use of alpha-blockers with vardenafil (Special Warnings and Special Precautions section).

4) Aspirin interaction: Aspirin can be used safely with vardenafil.

5) Ritonavir interaction: When dosed concurrently with ritonavir or other potent CYP3A4 inhibitors, vardenafil use should be restricted to the 2.5 mg dose in a 72-hour period.

6) Time to onset: There is no clinical or statistical evidence to support a time to onset of action shorter than 1 hour.

7) Back pain: Studies showed that there was a clear dose-response and dose-frequency-response. The tolerability at the 20 mg/qd and 40 mg/qod dose levels was similar. The back pain/myalgia incidence was lower at these dose levels than at the 40 mg/qd dose level and it was much lower than that at the 40 mg/bid dose level.

8) Ophthalmology effects: The pooled datasets show very little change in the total number of patients with reportable adverse events and no change in the total percents of patients affected. Color vision change was reported rarely (<0.1%) with vardenafil treatment in all clinical studies. The sponsor has agreed to a Phase IV commitment as recommended by the Ophthalmology consultant.

9.2 Recommendations

In the opinion of this reviewer, from a clinical standpoint, vardenafil at doses of 2.5, 5, 10 and 20 mg, should be approved for the indication "treatment of erectile dysfunction." The risks associated with the use of this drug are acceptable and can be managed adequately with labeling.

10. Appendices