

Appendix D: “A randomized, double-blind, placebo-controlled, period-balanced, two-part, three period crossover drug interaction study of vardenafil (10 mg and 20 mg) and tamsulosin (0.4 mg) in healthy males aged 45 to 75 to evaluate changes in blood pressure” (Trial 100481). Trial start date: October 1, 2002. Trial end date: November 6, 2002. Principal investigators: Stephan Bart, M.D./ Royce Morrison, M.D. Study centers: Radiant Research (Gainesville, Florida), Northwest Kinetics (Tacoma, Washington).

Rationale for study: It is expected that many men who seek treatment for erectile dysfunction will require concomitant treatment for BPH. There is a potential for a drug-drug interaction between alpha-antagonists and vardenafil both of which may cause hypotension.

D.1 Objectives:

The primary objective was to compare *changes in blood pressure*, induced by vardenafil (10 mg and 20 mg) and placebo, in healthy male subjects when administered to subjects receiving the alpha-blocker tamsulosin 0.4 mg at steady state.

The secondary objectives were to:

- Measure *changes in heart rate* until 6 hours after administration of vardenafil or placebo concomitant to steady state levels of tamsulosin
- Evaluate safety and tolerability
- Evaluate the pharmacokinetics of tamsulosin and vardenafil

D.2 Design and conduct summary: This was a Phase I, two center, two part, randomized, period balanced, placebo-controlled, double-dummy, three way crossover study. Parts I and II of the study were double-blind with respect to placebo, 10 mg vardenafil and 20 mg vardenafil. Tamsulosin 0.4 mg was given in open-label fashion.

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

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

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

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

Treatment Phases

Days 1-5: One Days 1-5, subjects presented to the clinic in the morning after a 1 hour fast and had orthostatic blood pressure (supine and standing) and heart rate measurements. Subjects remained seated for 10 minutes before all measurements of vital signs. After all doses of tamsulosin in this study, subjects remained seated for approximately 1 hour, after which they were allowed to move about. After approximately 2 hours after dosing, vital signs were measured and subjects received breakfast. A urine drug screen was performed on Day 1.

Part I: In session 1, a pre-dose blood sample (approximately 26 mL) was collected for future safety analysis, and subjects were asked whether their partner was pregnant. Subjects were asked to fast at least hour prior. Fifteen minutes prior to tamsulosin dosing, orthostatic blood pressure (supine and standing) and heart rate were measured and a pharmacokinetic blood sample for tamsulosin was taken. Two hours after dosing with tamsulosin, orthostatic blood pressure (supine and standing) and heart rate were measured. Subjects were dosed with vardenafil 10 mg or vardenafil 20 mg or placebo in the afternoon of each study session (approximately 17:00 after a 1 hour fast). Three baseline orthostatic blood pressures (supine and standing) and heart rate were obtained, at least 15 minutes before dosing. After blood pressure measurements, a blood sample was taken for pharmacokinetic analysis. After dosing with vardenafil 10 mg or vardenafil 20 mg or placebo, one orthostatic blood pressure (supine and standing) measurement was taken at each of the following times post-dose: 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 15, and 24 hours. Orthostatic blood pressure measurements were always taken before blood samples were collected. Blood samples (3 mL) for the determination of plasma tamsulosin and vardenafil concentrations were collected pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours relative to tamsulosin and vardenafil dosing, respectively.

Part II: Two hours after dosing with tamsulosin, orthostatic blood pressure (supine and standing) and heart rate were measured. Three measurements of baseline orthostatic blood pressures (supine and standing) and heart rate were made approximately 15 minutes before vardenafil/placebo dosing and a blood sample was taken for tamsulosin pharmacokinetics (after 1 hour fast). At approximately 11:00 in each session subjects were dosed with either vardenafil 10 mg or vardenafil 20 mg or placebo. After dosing, one orthostatic blood pressure (supine and standing) measurement was taken at each of the following times: 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 15, and 24 hours. Blood samples (3 mL) were taken for the determination of plasma tamsulosin and vardenafil concentrations, pre dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours following tamsulosin and vardenafil dosing.

Dietary considerations: Subjects received breakfast 2 hours after tamsulosin dosing (9:00), a light lunch (12:00), snack (14:00), dinner (18:00) and a snack (20:00) during the study. During each dosing session, subjects abstained from ingesting caffeine- or xanthine-containing products for 24 hours prior to the start of dosing until collection of the final blood pressure in Part II. During each dosing session, subjects abstained from alcohol for 24 hours prior to the start of dosing. Subjects were not be allowed to drink grapefruit juice or eat grapefruit within 7 days prior to the first dose of study medication until the end of Part II. Subjects were allowed to consume water and other permitted beverages ad libitum throughout the study.

Screening: Screening occurred within 30 days prior to administration of study medication. Screening included:

- Medical history.
- Complete medication history of all drugs taken (including the use of vitamins and herbal supplements; including St. John's Wort) at least 30 days prior to screening procedures.
- A history of alcohol use.
- Complete tobacco history including the type (e.g., pipe, cigar, chewing tobacco, or cigarette), quantity, and duration of use.
- Physical examination including height and weight, sitting vital signs (blood pressure, and heart rate).
- Standard 12-lead electrocardiogram (ECG).
- Following at least a 4-hour fast, blood and urine specimens for clinical laboratory safety tests were collected and a urine drug screen was performed.

Activity considerations: Subjects were inpatients during Parts I and II of the study. Subjects abstained from strenuous exercise for 48 hours prior to each study session until the completion of the session. Written informed consent was obtained from each subject.

Follow-up: All subjects returned for a follow-up visit 7 days after the final dose of study medication in Part II. At this visit, subjects received a brief physical examination. Safety blood and urine tests and a 12-lead electrocardiogram (ECG) were also performed. AEs and partner pregnancy were also assessed at this time.

D.3 Study population: Healthy male subjects between 45 and 75 years of age, and with a body mass index between 19 - 34 kg/m² were eligible for the study. A total of 31 subjects were randomized to treatment and enrolled in the study.

Table D.2 Demographic Data

Parameter	Age (years)	Height (m)	Weight (kg)
n	30	30	30
Mean	57	1.80	89.8
SD	8.5	0.06	11.3
Range	46 -72	1.7 -1.91	73.9 - 124

100% male, 97% White, 3% Hispanic
Source: study report, page 56.

Reviewer's comment: The cohort was 97% White/3% Hispanic compared to 17% White/80% Hispanic in the terazosin study (100480).

D.4 Eligibility criteria

D.4.1 Inclusion criteria

1. Healthy male subjects between the ages of 45 and 75 years inclusive.
2. Body mass index (BMI) between 19 and 34 kg/m² inclusive where:
BMI = (weight in kg) / (height in meters)²
3. Must have provided written informed consent.

D.4.2 Exclusion criteria

1. Treatment with any prescription or non-prescription drugs (including St John's Wort, vitamins, herbal and dietary supplements, as well as grapefruit-containing products) within 7 days prior to first dose of study medication and until the last study visit. Excluded from this list was acetaminophen at doses of ≤ 2 g/day.
2. History of alcohol abuse/dependence within 6 months of the administration of the first dose of study medication. Alcohol abuse was defined as consumption exceeding, on average, 14 drinks/week for men (1 drink = 5 ounces of wine or 12 ounces of beer or 1.5 ounces of hard liquor).
3. History of illicit drug use as defined by a positive urine drug test at screening.
4. Treatment with an investigational drug within 30 days or five half-lives, whichever was longer, prior to the first dose of study medication (this included investigational formulations of marketed products).
5. Any clinically relevant abnormality identified on the screening history, physical or laboratory examination.
6. History of lightheadedness or syncope upon standing.
7. History of hypotension.
8. Systolic blood pressure greater than 160 mmHg or diastolic blood pressure greater than 100 mmHg.
9. Systolic blood pressure less than 100 mmHg or diastolic blood pressure less than 60 mmHg.
10. History of sickle cell anemia or disease.
11. History of retinitis pigmentosa.
12. Known history of allergy to PDE-5 inhibitors or tamsulosin.
13. Subjects not willing and able to follow the procedures outlined in the protocol or who are unable to provide written informed consent.
14. Blood collection of greater than 500 mL within 56 days prior to study start.

Reviewer's comments: 1) The inclusion and exclusion criteria are acceptable. 2) Subjects with hypertension or hypotension have been excluded.

D.5 Primary and secondary endpoints

Pharmacodynamic: Pharmacodynamic parameters comprised of standing and supine systolic and diastolic blood pressures and standing and supine heart rates. Additionally, orthostatic systolic and diastolic blood pressures were calculated as the standing minus the supine blood pressure.

The primary pharmacodynamic endpoint was the maximal change in standing systolic blood pressure from baseline within 6 hours of dosing with vardenafil 10 mg, 20 mg or placebo after p.m. dosing (Part I).

The secondary pharmacodynamic endpoints were:

- Maximal change in standing systolic blood pressure from baseline within 6 hours of dosing with vardenafil 10 mg or 20 mg or placebo for a.m. dosing.
- Maximal change in standing diastolic blood pressure from baseline within 6 hours of dosing with vardenafil 10 mg or 20 mg or placebo (a.m. and p.m. dosing)
- Maximal change in supine systolic and diastolic blood pressure from baseline within 6 hours of dosing with vardenafil 10 mg or 20 mg or placebo (a.m. and p.m. dosing)
- Maximal change in orthostatic (e.g. standing minus supine) systolic and diastolic blood pressure from baseline within 6 hours of dosing with vardenafil 10 mg or 20 mg or placebo (a.m. and p.m. dosing).
- Maximal change in standing and supine heart rate from baseline within 6 hours of dosing with vardenafil 10 mg or 20 mg or placebo (a.m. and p.m. dosing).

For blood pressure endpoints, the maximal change from baseline was calculated as the difference between the minimum post-dose value and the baseline value. For heart rate endpoints, the maximal change from baseline was calculated as the difference between the maximum post-dose value and the baseline value. For all endpoints in Part I and Part II of the study, baseline was defined as the average of the three measurements taken at pre-dose of the vardenafil/placebo dose. The post-dose value (minimum or maximum) occurred within 6 hours of vardenafil/placebo dosing.

Pharmacokinetic: Blood samples for pharmacokinetic analysis of tamsulosin and vardenafil were collected from each subject up to 24 hours post-dose following drug administration in Parts I and II of the study. Pharmacokinetic parameters (secondary endpoints C_{max}, T_{max} and AUC) were calculated using non-compartmental methods for each session in Parts I and II.

Safety: Safety (secondary endpoint) was assessed by blood pressure and heart rate measurements, adverse events, standard clinical laboratory safety tests and twelve-lead electrocardiograph (ECG). Clinical laboratory safety tests and 12-lead ECGs were performed during screening and follow-up only.

Orthostatic hypotension was defined as a reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg within 3 minutes of standing. If orthostatic hypotension occurred, it was to be treated at the discretion of the Investigator. If orthostatic hypotension occurred prior to any dosing (as per the definition above) the subject was not to have been dosed. If orthostatic hypotension occurred following any dosing (with either tamsulosin or vardenafil/placebo), the subject was observed carefully and/or discharged at the discretion of the Investigator. If at any time during the study, a subject's blood pressure was less than 100 mmHg systolic and less

than 60 mmHg diastolic or the subject was symptomatic for hypotension, the subject was to have been withdrawn from the study. If at anytime during the study a subject had a systolic pressure less than 100 mmHg and was symptomatic, the subject was to have been treated with 500 mL - 1,000 mL of intravenous normal saline at the discretion of the Investigator. Post hoc, the sponsor determined that any episode of standing systolic blood pressure less than or equal to 85 mmHg would be reported as a serious adverse event.

D.6 Withdrawals, Compliance and Protocol violations

D.6.1 Withdrawals

Subject 214 was withdrawn prior to dosing. Five (5) subjects (008, 015, 019, 204 and 213) were withdrawn during the run-in phase (subject 019 was hypertensive prior to the first dose of study medication and was dosed and withdrawn immediately after dosing); 8 subjects (201, 203, 206, 207, 211, 215, 1003 and 1010) withdrew during Part I and 5 subjects (205, 209, 212, 1001 and 1009) withdrew during Part II.

D.6.2 Compliance

Study medication was administered under the supervision of study personnel. The oral cavity of each subject was examined following dosing to assure that the study medication was taken.

D.6.3 Protocol violations

There were 26 protocol violations reported in 14 subjects. There were 17 episodes where subjects were not withdrawn when their blood pressure met the withdrawal criteria. Three subjects (204, 206 and 211) had their follow up visit occur greater than 7 days after discharge from the study. There were three episodes in subjects 1003, 1009 and 1011 where the PK sample was taken late. Two subjects were dosed late (205 and 209) and subject 215 received prohibited medication within 7 days of the first dose of study medication (Zicam nasal spray for nasal congestion). The sponsor felt that these violations were not considered sufficient to affect the conduct of the study nor did it represent a potential risk to the subject during participation in the study or affect interpretation of the data.

Reviewer's comments: 1) This reviewer agrees that the violations would not affect the study results substantially. 2) Other variations that were not counted as protocol violations by the sponsor were eight subjects (008, 201, 207, 1003, 1004, 1005, 1011, 1013) who received medications or nutritional supplements during the study consisting of aspirin, normal saline, Keflex, Motrin, and Tylenol (which was allowed).

D.7 Pharmacodynamic analysis

Run-in Phase:

Mean BP and HR values prior to tamsulosin treatment on Day 1 and Day 6 are shown in Table D.3.

Table D.3 Standing and supine mean (SE) blood pressure and heart rate prior to tamsulosin treatment on Day 1 and Day 6

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

Source: study report page 71 table 22.

Reviewer's comment: There were small tamsulosin effects on BP and HR during the run-in period (i.e. 5 mmHg decrease in standing SBP).

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

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

Table D.4 Maximal change from baseline in standing blood pressure and heart rate- Part I (n=20)

Parameter	Regimen	Means ¹ (SE)	Comparison	Point Estimate ²	95% CI
Primary PD Parameter					
Standing Sys BP (mm Hg) ³	A	-9 (2.1)			
	B	-13 (2.1)	B - A	-4	(-8, -1)
	C	-17 (2.1)	C - A	-8	(-11, -4)
Secondary PD Parameter					
Standing Diastolic BP (mm Hg) ³	A	-8 (1.4)			
	B	-11 (1.4)	B - A	-3	(-5, 0)
	C	-12 (1.4)	C - A	-4	(-7, 0)
Standing HR (bpm) ⁴	A	7 (2.1)			
	B	11(2.2)	B - A	4	(-2, 10)
	C	13 (2.2)	C - A	6	(0, 12)

1 represents adjusted arithmetic mean from ANCOVA model

2 represents difference between adjusted arithmetic means

3 maximal change from baseline (minimum minus baseline)

4 maximal change from baseline (maximum minus baseline)

Regimen Key: A Placebo; B 10 mg Vardenafil; C 20 mg Vardenafil

Source: study report, talbe 23, page 72.

Smaller effects on standing diastolic blood pressure were observed for the 20 mg of vardenafil relative to placebo, while similar effects were observed for 10 mg of vardenafil. There appeared to be little to no change in the maximal change in standing heart rate. Similar effects and trends were observed for supine blood pressures and heart rate. There also appeared to be no change in orthostatic blood pressures. See table D.5.

Table D.5 Summary of the comparisons of interest for maximal change from baseline for supine blood pressure and heart rate and orthostatic blood pressures (secondary endpoints)

Parameter	Regimen	Means ¹	Comparison	Point Estimate ²	95% CI
Secondary PD Parameter					
Supine Sys BP (mm Hg) ³	A	-8 (1.5)			
	B	-13 (1.5)	B - A	-4	(-9, 0)
	C	-15 (1.5)	C - A	-7	(-11, -3)
Supine Diastolic BP (mm Hg) ³	A	-6 (1.0)			
	B	-10 (1.0)	B - A	-5	(-7, -2)
	C	-12 (1.0)	C - A	-6	(-8, -3)
Supine HR (bpm) ⁴	A	8 (1.7)			
	B	11 (1.7)	B - A	3	(0, 6)
	C	10 (1.6)	C - A	2	(-1, 5)
Orthostatic Sys BP (mm Hg) ³	A	-10 (1.5)			
	B	-10 (1.5)	B - A	1	(-3, 4)
	C	-11 (1.5)	C - A	0	(-4, 3)
Orthostatic Diastolic BP (mm Hg) ³	A	-8(0.9)			
	B	-7 (0.9)	B - A	1	(-1, 3)
	C	-9 (0.9)	C - A	-1	(-3, 2)

1 represents adjusted arithmetic mean from ANCOVA model

2 represents difference between adjusted arithmetic means

3 maximal change from baseline (minimum minus baseline)

4 maximal change from baseline (maximum minus baseline)

Regimen Key: A Placebo; B 10 mg Vardenafil; C 20 mg Vardenafil Source: Study report, table 24 page 73.

Part II: Only 14 subjects were included in the formal statistical analysis.

Mean maximal reduction in standing systolic blood pressure was, on average, 8 mmHg greater following single doses of both 10 and 20 mg vardenafil relative to placebo. The average maximal reduction from baseline following placebo was 11 mmHg. See Table D.6.

Similar effects on standing diastolic blood pressure were observed for both 10 mg and 20 mg of vardenafil relative to placebo. There appeared to be little to no change in the maximal change in standing heart rate. While trends for supine blood pressures and heart rates were similar to that of standing, the magnitude of the effects on supine blood pressure appeared to be smaller. There also appeared to be no change in orthostatic blood pressures. See Table D.6 (above)

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Table D.6 Maximal Change from Baseline- Part II

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

1 represents adjusted arithmetic mean from ANCOVA model

2 represents difference between adjusted arithmetic means

3 maximal change from baseline (minimum minus baseline)

4 maximal change from baseline (maximum minus baseline)

Regimen Key: A Placebo; B 10 mg Vardenafil; C 20 mg Vardenafil Source: Study report, table 25 page 75.

D.8 Pharmacokinetic analysis – See Clinical Pharmacology review

A total of 30 subjects were randomized to receive treatment. Of these, 21 subjects were included in the formal statistical analysis of AUC and Cmax in Part I and 14 subjects were included in the formal statistical analysis of AUC and Cmax in Part II.

Part I: Following steady-state oral administration of tamsulosin, maximum tamsulosin plasma concentrations typically occurred between approximately 3 and 4 hours post-dose for each of the 3 regimens (see Table D.7)

Table D.7 Pharmacokinetic parameters for tamsulosin following 10 hours of separation (p.m. dosing) with single oral placebo, 10 mg and 20 mg vardenafil

p.m. vardenafil dosing Part I	N	AUC(0-t) (Ng.h/ml)	Cmax (Ng/ml)	Tmax (Hours)
Placebo	21	178	13.8	3.98
10 mg vardenafil	20	174	13.2	4.00
20 mg vardenafil	21	171	14.3	4.00

Source: Study report, Table 16 page 66.

Individual AUC(0-t), Cmax and Tmax values were similar across the three regimens. The study was not powered for bioequivalence.

Subject 203 was a potential statistical outlier for AUC. This is likely related to the fact that the subject withdrew at 10 hours post-dose during regimen C and, consequently, the AUC for this regimen was underestimated.

Reviewer's comment: Please see Clinical Pharmacology review.

Following single oral administration of 10 mg and 20 mg vardenafil 10 hours after repeat oral administration of tamsulosin, maximum vardenafil plasma concentrations generally occurred between 0.5 and 1.5 hours post dose. See Table D.8.

Table D.8 Pharmacokinetic parameters for 10 mg and 20 mg vardenafil administered 10 hours after 0.4 mg repeat oral tamsulosin dose

p.m. vardenafil dosing Part I	N	AUC(0-t) (Ng.h/ml)	Cmax (Ng/ml)	Tmax (Hours)
10 mg vardenafil	20	31.0	8.15	1.13
20 mg vardenafil	22	63.7	16.7	1.54

Source: Study report table 18, page 68.

Based on the mean data, AUC and Cmax values for vardenafil increased approximately dose-proportionately and the AUC and Cmax values observed following single oral 10 and 20 mg vardenafil administration were consistent with those observed in prior Phase I clinical trials (per the sponsor).

Part II: Following steady-state oral administration of tamsulosin, maximum tamsulosin plasma concentrations typically occurred between approximately 3 and 4 hours post dose for each of the 3 regimens. (see Table D.9)

Table D.9 Pharmacokinetic parameters for tamsulosin following 10 hours of separation (a.m. dosing) with single oral placebo, 10 mg and 20 mg vardenafil

a.m. vardenafil dosing Part II	N	AUC(0-t) (Ng.h/ml)	Cmax (Ng/ml)	Tmax (Hours)
Placebo	14	190	15.0	4.00
10 mg vardenafil	14	164	15.0	3.57
20 mg vardenafil	12	190	14.9	3.57

Source: Table 19 page 69 study report

Subject 205 was identified as a potential statistical outlier for AUC. Subject 205 was withdrawn during the session in which regimen E was administered, and the last pharmacokinetic sample was obtained at 4 hours as compared to 24 hours for all other subjects resulting in a low AUC value.

The study was not powered for bioequivalence.

Following single oral administration of 10 mg and 20 mg vardenafil 4 hours after repeat oral administration of tamsulosin, maximum vardenafil plasma concentrations generally occurred between 1 and 2 hours post dose. See Table D.10.

Table D.10 Pharmacokinetic parameters for 10 mg and 20 mg vardenafil administered 4 hours after 0.4 mg repeat oral tamsulosin dose

a.m. vardenafil dosing Part II	N	AUC(0-t) (Ng.h/ml)	Cmax (Ng/ml)	Tmax (Hours)
10 mg vardenafil	13	37.0	8.22	1.60
20 mg vardenafil	13	82.9	16.0	1.20

Source: Study report table 18, page 68.

Based on the mean data, AUC and Cmax values for vardenafil increased approximately dose-proportionately. Despite the pharmacokinetic variability and the smaller sample size, vardenafil pharmacokinetic parameters in Part II appeared to be consistent with results observed in Part I.

Reviewer's comment: Compared to Part I, the AUC for 20 mg vardenafil is 20 Ng.h/ml higher in Part II. Tmax and Cmax are consistent in both Part I and Part II.

D.9 Safety analysis

D.9.1 Extent of exposure:

Thirty subjects were exposed during the drug study.

Table D.11 Exposure

Description of Regimen	Number of Subjects
Regimen A placebo	21
Regimen B 10 mg vardenafil	21
Regimen C 20 mg vardenafil	24
Regimen D placebo	15
Regimen E 10 mg vardenafil	16
Regimen F 20 mg vardenafil	13
TOTAL SUBJECTS EXPOSED	30

Source: study report page 58.

Reviewer's comment: If 25 subjects were enrolled in Part I and 5 subjects were withdrawn during the tamsulosin run-in phase.

D.9.2 Deaths

There were no deaths reported during the study.

D.9.3 Adverse events:

A total of 175 adverse events (AEs) were reported during the study. The most common events were headache, rhinitis, dizziness, flushing and postural hypotension.

Table D.12 Adverse Event Listing

Adverse Events (Preferred Term)*	Regimen						
	Run In	A	B	C	D	E	F
Headache	4	4	5	7	1	5	3
Rhinitis	1	2	6	6		5	4
Dizziness	3		2	1	1	2	5
Flushing			1	2		4	4
Hypotension							1
Hypotension postural	1	1		3		3	
Diarrhea	1	2	2	2			
Sinusitis		2		1		2	2
Abdominal pain			1				
Anemia			1				
Arthralgia	1		1				
Arthritis						1	
Asthenia				1			1
Back pain	1			1			
Chest pain	1						
Dyspepsia						1	3
Dyspnea							1
Ear disorder nos	1		1				
Ejaculation disorder	1			1			
Emotional lability						1	
Epistaxis		2		1			
Fatigue	1						
Flatulence		1		1			
Gastroesophageal reflux		1		1			
Hyperglycemia	1					1	
Hypertension							1
Injection site inflammation				1			
Injection site pain		1					
Injection site reaction			1				
Injury			1				
Leukocytosis	2						
Mouth dry	2	1					
Myalgia		1		1			1
Nausea	2			1			1
Nervousness						1	
Palpitation	1						
Paresthesia				1			
Paronychia	1						
Pharyngitis		1					
Phlebitis		1					
Pruritus		1					
Psoriasis						1	
Pyuria	2						
Rash		1					
Somnolence			1			1	
Sweating increased					1		
Syncope				1		1	
Tendinitis							1
Tooth ache					1		
Urethral disorder				1			
Urinary casts	1						
Vision abnormal			1			1	
Xerophthalmia			1				
???		1	1	1			
Total Number of AE's	29	23	26	35	4	30	28
Total Number of Subjects Exposed	30	21	21	24	15	16	13
Number of Subjects with AE's	11	12	12	12	3	13	9

* Coded from verbatim term using Adverse Events Dictionary

A=Placebo; B=Vardenafil 10 mg; C=Vardenafil 20 mg; D=Placebo and Terazosin 10 mg; E=Vardenafil 10 mg and Terazosin 10 mg; F=Vardenafil 20 mg and Terazosin 10 mg

Source: Study report, table 12, page 60.

Reviewer's comment: Table D.12 is incomplete, the last listing is blank but has 3 adverse events.

Two subjects (1005, 1007) experienced back pain during the study. Subject 1005 experienced mild back pain during the run-in phase. Subject 1007 was a 61 year-old white male who experienced 2 episodes of moderate back pain during the study. The pain began approximately 10 minutes post 20 mg vardenafil dosing in session 3, part I and resolved following vardenafil dosing in session 3, part II. The subject completed dosing in all remaining study sessions. CPK levels were obtained and were within the normal range.

Reviewer's comments: (1) Subject 1005 data describes the onset of mild back pain during session 1 with a duration of 1 day. CK levels were 83 and 114 IU/l (normal < 200 IU/l). It is unclear from the referenced material which treatment period this occurred but the sponsor felt this related to "study drug". (2) Data on subject 1007 documents 2 episodes of moderate back pain occurring in session 4 (vardenafil 20 mg) lasting approximately 6 days. CK ranged between 58 and 74 IU/l (normal < 200 IU/l). There are some discrepancies but findings are not concerning.

Dizziness

Seven subjects experienced AEs related to dizziness. See Table D.13.

Table D.13 Subjects with Adverse Events of Dizziness

Subject	Relationship to dose	Comment
210	4 h after vardenafil 20 mg	Part II, St. SBP < 100 mmHg on placebo (Part I and II), and vardenafil 10 mg in Part II and 20 mg in Part I and II (nadir BP 90/62 HR 80)
212	3 h after vardenafil 10 mg	Part I, St. SBP <100 mmHg 1.5 hr after vardenafil 10 mg in Part II (BP 98/52 HR 104)
1001	13 h after tamsulosin 4 h after tamsulosin 47 min after vardenafil 20 mg 54 min after vardenafil 20 mg	Run-in Part II Part II Part II, withdrawn from study (BP 90/60 HR unknown)
1005	19 h after tamsulosin	Run-in (nadir BP 112/84 HR not listed)*
1006	1.5 h after placebo 50 min after vardenafil 10 mg 2 min before vardenafil 20 mg	Part II Part II Part II St. SBP < 100 mmHg 12 h after vardenafil 10 mg in part I (BP 96/80 HR 60)
1008	1-h after vardenafil 20 mg	Part II St. SBP <100 mmHg during run-in (BP 96/62 HR 84), and 15 h after vardenafil 20 mg (part II) (BP 92/70 HR 92)
1011	2.5 h after tamsulosin 1.25 h after vardenafil 10 mg 1 h after vardenafil 10 mg 60 h after vardenafil 10 mg 1 h after vardenafil 20 mg	Run-in Part I Part II Part II Part II St. SBP < 100 mmHg 15 hours after placebo (BP 92/68 HR 76) and vardenafil 10 mg in Part II (BP 92/60 HR 88)

*Taken from Table F1 page 872

Source: Study report, Table 13, page 61. BP measurements taken from Table J1, page 1044.

D.9.4 Serious adverse events

There were no SAEs reported by the principal investigator during the study, however post hoc, the sponsor considered any episode of standing systolic blood pressure less than or equal to 85 mmHg, symptomatic hypotension and hypotension requiring treatment to be a serious adverse event. Three subjects qualified the post hoc definition and are shown in Table D.14

Table D.14 Subjects with Standing Systolic Blood Pressures < 85 mmHg

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

C: 20 mg Vardenafil (Part I)

E: 10 mg Vardenafil (Part II)

* In relation to dosing of study medication (vardenafil/placebo) in hours

Narratives:

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

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

Subject 209: 47 year-old Caucasian male who experienced asymptomatic orthostatic hypotension 1.5 hours following vardenafil 10 mg and 5.5 hours following tamsulosin. His supine BP was 118/58 (HR 88) and supine BP was 80/58 (HR 120). The duration of event was 30 minutes.

Reviewer's comments: Outliers: (1) During Part I, there was one occurrence of standing SBP < 85 mmHg following vardenafil 20 mg (subject 201, described above). There were 37 subjects with a standing SBP < 100 mmHg, 8 in the run-in period, 4 following placebo, 15 following vardenafil 10 mg, and 10 following vardenafil 20 mg (2) During Part II, there were three occurrences (2 subjects- 205 and 209 described above) of standing SBP < 85 mmHg all following vardenafil 10 mg. There were 38 subjects with a standing SBP < 100 mmHg, 7 following placebo, 16 following vardenafil

10 mg, 15 following vardenafil 20 mg. (3) Events were more common in Part II following study drug administration

Nine subjects were withdrawn due to AEs with 3 of these due to SAEs. An additional six subjects were withdrawn due to postural hypotension or related symptoms, which were not considered as SAEs.

Table D.14 Withdrawals due to adverse events

Subject	Adverse Event	Comment
008	postural hypotension in tamsulosin run- in	related to tamsulosin run-in (BP not listed)
1010	-“mild” postural hypotension BP after VAR 20 mg (Part I) - moderate urethral discharge 12 hours post VAR 20 mg	142/80 supine → 120/94 standing
203	“moderate” postural hypotension for 1 minute after VAR 20 mg (Part I)	117/68 supine → 100/64 standing
1003	“moderate” postural hypotension after placebo (sequence VAR 10, 20, placebo (Part I)	154/94 supine → 130/90 standing
1001	-dizziness, feeling faint, lightheaded 45 min after VAR 20 mg (Part II) -weakness 1 hour after VAR 20 mg	120/76 supine → 90/60 standing
212	“moderate” postural hypotension 50 min after VAR 10 mg (Part II)	115/70 supine → 98/52 standing
1009	“mild” postural hypotension 3 hours after VAR 10 (Part II)	120/70 supine → 100/68 standing

Source: Created from study report text, pages 62-63.

Reviewer’s comment: The study report lists 9 withdrawals due to adverse events. Three of these (201, 205, 209) were SAEs and are discussed above. There are actually 7, not 6, remaining subjects with adverse events.

ECG data: There were no values considered to be of potential clinical concern.

Laboratory data: Five subjects had laboratory values that exceeded values of potential concern. They included 3 subjects (008, 205, 1007) with mild to moderate elevations in blood glucose (127-160), one subject (1002) with a fall in hematocrit from 42.3 to 35.6%, and one subject (1008) with an elevated ALT of 135 from baseline of 15.

Reviewer’s comment: Subject 008 had an elevated blood sugar (BS) at screening of 133. Subject 205 had a normal screening BS of 92. During the study BS reached 160 and follow-up BS was 104. Subject 1007 had a screening BS of 127. The final BS was 101. Subject 1002 had a corresponding hemoglobin dropped from 14.3 to 12.1 g/dl. Serum sodium, creatinine and urine specific gravity remained constant. There were no evidence of fluid changes. Subject 1008 had normal AST, total bilirubin, ALK Phos levels. These values do not cause concern.

D.10 Statistical analysis: Statistical analysis was conducted by or under the direct auspices of _____

Target Sample Size: It was planned to enroll 30 subjects to ensure 24 subjects completed the study. The sample size was based on feasibility. In a previous study, within-subject variability of maximal change from baseline in standing systolic blood pressure ranged from 11 mmHg to 15 mmHg. Based on these estimates and the sample size of 24, the half width of 95% confidence interval for the difference between regimens would be 6.2 mmHg and 8.8 mmHg for the smaller and higher variabilities. Sample size re-estimation was not planned in this study.

No formal statistical analysis of safety data was planned. Post hoc, the sponsor defined serious adverse events as standing systolic blood pressure less than or equal to 85 mmHg, symptomatic hypotension or hypotension requiring treatment. These were listed and summarized by time of occurrence (pre-dose tamsulosin, post-dose tamsulosin, pre-dose vardenafil 10 mg or 20 mg or placebo and post-dose vardenafil 10 mg or 20 mg or placebo). Occurrences of standing systolic blood pressure less than 100 mmHg were summarized in a similar manner. All other adverse experiences were to be summarized by treatment.

The primary endpoint, maximal change from baseline within 6 hours of dosing for standing systolic blood pressure from Part I of the study, was analyzed by mixed effects analysis of covariance (ANCOVA), fitting fixed terms for sequence, period and regimen, a random term for subject-within-sequence and baseline standing systolic blood pressure as a covariate. Using the residual variance, point estimates and 95% confidence intervals for comparisons C-A and B-A were obtained. Additionally, point estimates and 95% confidence intervals for means for each regimen were also calculated. Secondary endpoints from Part I and Part II of the study were analyzed in a similar fashion. For Part II, point estimates and 95% confidence intervals were constructed for differences, E-D and F-D.

For all endpoints, baseline covariates were statistically significant ($p < 0.05$). There were no statistically significant sequence effects ($p > 0.05$). However, there were significant period effects ($p < 0.05$) in the analysis of maximal change from baseline in orthostatic systolic blood pressure and standing heart rate for Part II.

The impact of withdrawn subjects not included in the statistical analyses of both Part I and II was evaluated. For Part I, the individual values for subjects not included in the analyses were well within the range of the data for subjects included in the analysis. This suggests that exclusion of these subjects from the analyses does not bias the results from Part I. However, for Part II, while individual values for subjects not included in the analyses were within the range of the data included in the analyses, the maximal changes were in the upper half of the data. This suggests that the exclusion of these subjects from the analysis may have resulted in an underestimate of the true effect of vardenafil.

Pharmacokinetic:

The secondary endpoints (AUC and Cmax of tamsulosin) were analyzed by analysis of variance (ANOVA) fitting terms for sequence, period, subject (sequence) and regimen within each part (a.m. and p.m. dosing) separately. Point estimates and corresponding

90% confidence intervals were constructed for the difference between regimens B/C and regimen A and regimens E/F and regimen D using residual variance.

D.11 Sponsor's conclusions

- (1) Vardenafil resulted in an additional decrease in mean standing and supine systolic blood pressure (range 4 mmHg – 8 mmHg for systolic, 3 mmHg – 7 mmHg for diastolic), with no further orthostatic changes in blood pressure in the period 0.5 to 6 hours after vardenafil 10 or 20 mg on a background of tamsulosin.
- (2) Repeat oral administration of tamsulosin 0.4 mg with vardenafil 10 or 20 mg did not affect the steady state pharmacokinetics of tamsulosin.
- (3) There is no evidence for greater risk of hypotension associated with vardenafil when maximal concentrations of both drugs coincide.

D.12 Reviewer's assessment/comments

Summary of Tamsulosin results

	Part I			Part II			
	Mean Max Δ	Point Est	95% CI	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)

- 1) The combination of tamsulosin 0.4 mg and vardenafil 10 or 20 mg given with simultaneous C_{max} produced decreases in SBP/DBP and HR increases.
- 2) When C_{max} was separated by 6 hours, the changes were not as dramatic but were still significant.
- 3) The separation of the doses did not negate the effect of concomitant treatment.
- 4) The sponsor has proposed using vardenafil 5 mg in combination with alpha-blockers without dose/time modification. No data was initially submitted to justify this combination. See "Conclusion" section in Clinical Summary for a brief review of study 100535 which was submitted by the sponsor during labeling negotiations.
- 5) Based on the current data, the vardenafil 10 mg or 20 mg should not be used concurrently with tamsulosin 0.4 mg.

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this page is the manifestation of the electronic signature.**

/s/

Marcea Whitaker
8/19/03 06:03:06 PM
MEDICAL OFFICER

George Benson
8/19/03 06:12:19 PM
MEDICAL OFFICER

NDA 21400

Date submitted: September 24, 2001

Draft review completed: June 18, 2002

Review completed: July 22, 2002

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: 5, 10, and 20 mg

Proposed indication: treatment of erectile dysfunction

Related IND's:

George S. Benson, MD – Medical Officer, DRUDP
Mark S. Hirsch, MD – Medical Team Leader, DRUDP

Executive summary:

1) Recommendations

In the opinion of this reviewer, from a clinical perspective, vardenafil in doses of 5, 10, and 20 mg should receive an approvable action for the indication "treatment of erectile dysfunction." The major reason for this decision is the fact that this reviewer is unable to exclude an effect of vardenafil on the QT interval. A consultation concerning the QT issue was obtained from the CardioRenal Division. The consultant concluded that "although the available data raise no concern regarding arrhythmogenic potential, the data are not particularly compelling that such a risk has been ruled out." High drug exposures are expected to occur, particularly in patients taking CYP 3A4 inhibitors. In addition, for the 20 mg dose, the nitrate interaction study evaluated 10, but not 20 mg, of vardenafil. Finally, the sponsor should attempt to elucidate the etiology of back pain associated with vardenafil use. In the opinion of this reviewer, this is not an approvability issue and could be resolved with a Phase 4 commitment.

2) Summary of Clinical Findings

2.1 Brief overview of the clinical program

NDA 21400 is a submission for vardenafil hydrochloride (a Type V phosphodiesterase inhibitor) for the indication "treatment of erectile dysfunction." Proposed doses for this oral medication are 5, 10, and 20 mg.

Penile erection is primarily the result of relaxation of the smooth muscle of the penile corpora cavernosa. Nitric oxide released from non-adrenergic/non-cholinergic nerves activates guanylate cyclase which, in turn, increases the synthesis of cyclic GMP. Cyclic GMP mediates relaxation of the corporal smooth muscle which causes increased expansion and filling with blood of the corpora cavernosa and penile erection. Cyclic GMP is metabolized by the enzyme phosphodiesterase. The most prominent phosphodiesterase in the penis is phosphodiesterase Type V (PDE5). Inhibition of PDE5 prevents the breakdown of cyclic GMP and thereby enhances penile erection. The only currently approved PDE5 inhibitor for the indication "treatment of erectile dysfunction" is sildenafil (Viagra) available in oral doses of 25, 50, and 100 mg.

In support of NDA 21400, the sponsor submitted 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 patients. In addition to the 4 primary efficacy studies, the sponsor submitted Trial 100199 (a Phase 2b study). Additional safety studies include Trial

100312 (an extension of Trial 100250), Trial 10125 (a one year safety trial of 10 and 20 mg vardenafil), Trial 10152 (a 6 month extension of Trial 100199), and Trial 10232 (a trial using doses of 2.5 and 5 mg vardenafil). Multiple studies dealing with specific safety issues (nitroglycerin interaction, cardiovascular response to stress, QT interval, alcohol interaction, ophthalmologic effects, drug-drug interactions, etc) are included in the submission. These studies are further described and discussed in Sections 4.1 and 7. of the Clinical Review Section. Overall, vardenafil was administered to 3750 patients during the clinical trials. Approximately 1630 patients have been treated for 6 months or longer and 730 patients have been treated for at least one year. In Trials 100199 (Phase IIB trial), 100249, 10128, 100250, 100285, 10232, 10125, and 10152 combined, 667 patients received 5 mg, 1304 received 10 mg, and 1540 received 20 mg vardenafil. In the 4 primary efficacy studies and Trials 10232, 10125, and 10152, 520 patients received 5 mg, 1214 received 10 mg, and 1345 received 20 mg. With regard to the 20 mg dose, 995 patients received 20 mg for 6 months (Trials 10125, 10152, and 100249) and 392 patients received 20 mg for one year in Trial 10125).

2.2 Efficacy

Four primary pivotal studies were submitted to support the efficacy of vardenafil for the treatment of erectile dysfunction. All 4 of these studies were randomized, double-blind, placebo-controlled, parallel-group multicenter studies. All 4 study designs were similar and the 4 major efficacy trials are summarized in Table 1.

Table 1. 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	177/91	General (excluded radical prostatect omy)	77	57 (26-76)
		Vard 5 mg	190/128		77	58 (29-82)
		Vard 10	196/151		80	57 (27-83)
		Vard 20	186/138		82	58 (20-79)
10128 (Europe)	12 weeks	Placebo	160/140	General (excluded radical prostatect omy)	68	56 (23-78)
		Vard 5 mg	156/146		66	57 (21-78)
		Vard 10	157/148		68	55 (26-75)
		Vard 20	163/137		67	56 (25-74)
		Sildenafil 50 mg	162/147		68	56 (22-81)
100250 (North America)	12 weeks	Placebo	140/121	Diabetics (Excluded radical prostatect omy)	79	57 (35-74)
		Vard 10	149/131		82	58 (33-81)
		Vard 20	141/127		78	57 (34-78)
100285 (North America)	12 weeks	Placebo	137/97	Post- radical prostatect omy	93	60 (47-72)
		Vard 10	139/114		99	61 (44-77)
		Vard 20	147/119		87	60 (45-74)

There were 3 primary efficacy endpoints for all of the 4 major efficacy studies: 1) the Erectile Function Domain score of the International Index of Erectile Function (IIEF) at week 12 compared with baseline 2) Sexual Encounter Profile Question (SEP) #2 “Were you able to insert your penis into your partner’s vagina?” from randomization to Week 12 using the per-patient overall success rate and 3) SEP Question #3 “Did your erection last long enough for you to have successful intercourse?” from randomization to Week 12 using the per-patient overall success rate.

The 12-week efficacy results for Trials 100249 and 10128 (general ED population trials) are shown in Tables 2 and 3.

Table 2. Trial 100249

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

Variable	Placebo	Vardenafil		
		5 mg	10 mg	20 mg
IIEF domain: EF at Week 12 LOCF				
N	170	188	195	183
LS mean baseline	13.6	12.5	13.4	12.8
LS mean value (SE)	15.0 (0.7)	18.4 (0.6) 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

^aThe P value is for the comparison of the vardenafil groups with placebo

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

Variable	Placebo	5 mg	Vardenafil		Sildenafil 50 mg
			10 mg	20 mg	
IIEF domain: EF at Week 12 LOCF					
N	158	150	155	158	158
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) P<0.0001	20.91 (0.62) P<0.0001	21.49 (0.62) P<0.0001	21.27 (0.62) P<0.0001
Week 12 overall per-patient diary: success in penetration (%)					
N	152	152	151	156	158
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) P<0.0001	76.43 (2.56) P<0.0001	79.48 (2.54) P<0.0001	78.74 (2.54)
Week 12 overall per-patient diary: maintenance of erection for successful intercourse (%)					
N	151	152	151	156	158
LS mean baseline	15.91	14.60	15.95	15.31	18.59
LS mean value (SE)	24.95 (2.92)	54.88 (2.89) P<0.0001	61.58 (2.90) P<0.0001	63.92 (2.87) P<0.0001	64.93 (2.87) P<0.0001

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

The primary efficacy analyses in the other two major efficacy trials (#'s 100250 and 100285) also demonstrate that the two doses of vardenafil studied (10 mg and 20 mg) are clinically and statistically superior to placebo.

Reviewer's comments:

- 1) *Vardenafil doses of 5, 10, and 20 mg are clinically and statistically superior to placebo.*
- 2) *In 3 of the 4 major trials, the dose of 20 mg is not clinically or statistically superior to 10 mg. In Trial 100250 (diabetic patients with erectile dysfunction), the difference between 20 and 10 mg for the EF domain of the IIEF was statistically different in favor of the 20 mg dose. 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 "pivotal" studies was designed to specifically compare the 10 and 20 mg doses of vardenafil. From an efficacy standpoint, this reviewer believes that the proposed 5, 10, and 20 mg doses are acceptable.*
- 3) *All 4 studies enrolled large numbers of patients (70%, 59%, 60%, and 80%) who had previously taken sildenafil. Erections had been improved by sildenafil in nearly all of these patients. A "history of unresponsiveness to sildenafil" was an exclusion criterion in Trials 100249, 100250, and 100285. A history of significant side effects with sildenafil use was an exclusion criterion in Trials 100250 and 100285. It is difficult to enroll large numbers of patients in erectile dysfunction trials who are naïve to sildenafil. This reviewer believes that the data presented in this NDA provides sufficient evidence to approve vardenafil at doses of 5, 10, and 20 mg from an efficacy standpoint. Despite the exclusion of patients with a history of "significant side effects with sildenafil use in Trials 100250 and 100285," this reviewer believes that there remains a safety data base which is adequate for evaluation.*

There is insufficient data directly comparing vardenafil to other drugs indicated for the treatment of erectile dysfunction to make meaningful efficacy and safety comparisons.

2.3 Safety

At the time of NDA submission, the pooled safety data base of patients treated with vardenafil 5 mg, 10 mg, and 20 mg included in the Integrated Summary of Safety included 3872 patients of whom 793 were treated with placebo and 3079 were treated with vardenafil. By the time of the 7 month safety update, vardenafil had been administered to 3750 patients. Over 1630 patients have been treated for 6 months or longer and over 730 patients have been treated for at least one year. In Trials 100199 (Phase IIB trial), 100249, 10128, 100250, 100285, 10232, 10125, and 10152 combined, 667 patients received 5 mg, 1304 received 10 mg, and 1540 received 20 mg vardenafil. In the 4 primary efficacy studies and Trials 10232, 10125, and 10152, 520 patients received 5 mg, 1214 received 10 mg, and 1345

received 20 mg. With regard to the 20 mg dose, 995 patients received 20 mg for 6 months (Trials 10125, 10152, and 100249) and 392 patients received 20 mg for one year in Trial 10125).

Significant adverse events:

Deaths: Seven patients enrolled in clinical trials died. In placebo-controlled trials, one death occurred in a placebo group, one in a drug comparator (sildenafil) group, and one in a 2.5 mg vardenafil group. The patient in the 2.5 mg vardenafil group (Patient #10232-013-004) was a 55-year-old man with diabetes and hypercholesterolemia who experienced a myocardial infarction 6 days after taking his last dose of study drug. He underwent coronary artery bypass surgery, developed pneumonia, experienced acalculous cholangitis, and died 51 days after the myocardial infarction. The investigator did not consider the event to be related to vardenafil. Three deaths occurred in uncontrolled and ongoing studies. One 67-year-old man (Patient #100312-905-004) with a history of coronary artery disease and hypertension died suddenly 1 month after entering an extension study and 21 days after his last dose of 10 mg vardenafil. (His wife returned the diary and unused medication to the site). He had been taking nitroglycerin more frequently in the weeks before his death due to worsening chest pain. This fact was never revealed to the study site by the patient. One patient committed suicide and one died of lung cancer prior to taking any study drug. The last death was a 69-year-old man (Patient # 10125-110-342) who died in his sleep and was found unresponsive at home. An autopsy determined the cause of death to be "cardiovascular disease secondary to diabetes and hypertension." No other information concerning this patient is available.

The incidence of serious adverse events was similar in the vardenafil and placebo groups and no single event deemed "serious" was associated with drug significantly more often than with placebo.

Frequent adverse events:

The most frequent adverse events were those which are known to be associated with PDE5 inhibitors. The incidence of these adverse effects (in the 2 pivotal trials which evaluated the 5, 10, and 20 mg doses of vardenafil) is shown in Table 4.

Table 4. Incidence rates (%) by dose of drug-related treatment emergent adverse events (judged by the investigator as “possibly” or “probably” related to study drug”) reported by >2% of patients treated with vardenafil and more frequent on vardenafil than on placebo

Adverse event	Placebo N=342	Vard. 5mg N=350	Vard. 10 mg N=358	Vard. 20 mg N=351
Headache	2.0	8.0	11.7	17.4
Vasodilation	0.9	5.7	10.9	12.8
Rhinitis	0.9	1.1	6.7	7.7
Dyspepsia	0.3	2.0	2.8	6.0
Nausea	0.3	0.6	0.8	2.8
Dizziness	0.3	0.6	2.5	2.8

Reviewer’s comment: These frequent adverse events demonstrate a relationship to vardenafil dose.

Relationship of safety to other drugs approved for the indication “treatment of erectile dysfunction”:

There are no adequate trials which directly compare the safety of vardenafil to other drugs indicated for the treatment of erectile dysfunction.

Other Significant Safety Issues:

1) Effect of vardenafil on the QT interval:

The increase in heart rate produced by vardenafil complicates the analysis of the QT interval data. The sponsor retrospectively evaluated 8 Phase 1 and 2 studies in which EKG’s had been performed and included manual (computer assisted) readings of the EKG’s in the ISS. This information included QT, QTc Bazett, and QTc Fridericia data. Two of the studies did not include a placebo control group and in two the first EKG’s were obtained at 2 1/2 hours post-vardenafil dosing (well past the T_{max}). Only 5 patients were studied at the maximum dose of 80 mg. All of these trials were reviewed (see Section 7 of the Clinical Review and Appendix M). This reviewer is unable to exclude a vardenafil effect on the QT interval. A CardioRenal consultation was obtained. The conclusion of the consultant was that “although the available data raise no concern regarding arrhythmogenic potential, the data are not particularly compelling that such a risk has been ruled out.”

2) Vardenafil nitrate interaction:

Although nitrates are a contraindication to vardenafil use, some men with cardiovascular disease using vardenafil will experience emergency situations where use of nitrates is indicated. Information is needed to label the effects of nitrates on blood pressure in patients taking vardenafil. The effect of 0.4 mg nitroglycerin on vital signs was determined in 18 healthy men (mean age 48

years; range 40 to 65 years) at 24, 8, 4, and 1 hour after dosing with study drug (varденаfil 10 mg or placebo). This trial (#100304) is reviewed in Appendix I. The effect of nitroglycerin on systolic and diastolic blood pressure in patients taking 10 mg vardenafil was not clinically significant (1 to 2 mm range). The sponsor did not submit data for 20 mg vardenafil.

3) Alcohol interaction:

Trial 10348, an alcohol interaction study, is reviewed in Appendix K. A 20 mg dose of vardenafil was given with an alcohol dose of 0.5g/kg. This dose of alcohol produced blood alcohol levels which were just below the legal limit for intoxication. The addition of vardenafil to alcohol consumption produced no clinically significant changes in vital signs over alcohol alone.

4) Back Pain:

As with other PDE5 inhibitors, back pain and myalgia are observed, primarily with high and frequent dosing of vardenafil (most notably at 40 mg bid). In Trial 10006, 5 of 7 patients in the 40 mg/day dose (given for 14 days) group experienced back pain. The back pain was described as “mild” in all cases. In the 40 mg bid dose group, all 8 patients taking vardenafil experienced back pain (moderate intensity in 7 of 8 patients) versus no back pain in the placebo group and the dosing of vardenafil was discontinued on Day 4 of the trial. In clinical pharmacology Trial 100196, back pain was reported in 0/12 placebo patients, 3/12 20 mg/day patients, 3/13 40 mg every other day patients, and 7/13 40 mg vardenafil/day patients. In the 20 mg group, in 2 of the 3 patients the back pain was rated as “mild” and in the third patient the back pain was rated as “moderate.” In the Phase 3 clinical trials, back pain was not observed more commonly with vardenafil at doses up to 20 mg than with placebo. The incidence of myalgia/back pain at doses of 5 to 20 mg (Safety Pool 3 – all placebo controlled studies) was placebo 2.4% and vardenafil 2.2% for back pain and placebo 0.3% and vardenafil 0.7% for myalgia.

In the 2 Phase 3 placebo-controlled studies which evaluated the 5, 10, and 20 mg doses of vardenafil, the incidence of back pain is shown in Table 5:

Table 5. Incidence and severity of back pain in Trials 100249 and 10128.

Trial	Placebo	Vard. 5 mg	Vard. 10 mg	Vard. 20 mg
10249	6 (3%) (2 mild, 3 moderate, 1 severe)	6 (3%) (3 mild, 3 moderate)	9 (5%) (8 mild, 1 moderate)	5 (3%) (2 mild, 3 moderate)
10128	5 (3%) (3 mild, 2 moderate)	5 (3%) (2 mild, 1 moderate, 2 severe)	2 (1%) (2 mild)	1 (<1%) (1 severe)

The etiology of back pain seen with vardenafil exposure is unknown. This adverse event appears to a "drug class effect" of PDE5 inhibitors. The back pain subsides within 48 hours of discontinuing the drug. There is no associated significant CK increase. In the Phase 3 clinical trials, the incidence of back pain was not different from placebo. In the opinion of this reviewer, the etiology of back pain seen with vardenafil should be further evaluated (by Phase 4 commitment) but is not an approvability issue.

5) Ophthalmology adverse events:

Visual adverse events occur with PDE5 inhibitors. These adverse events and other data concerning eye findings were reviewed by a consultant ophthalmologist. The recommendations of the consultant were: 1) "From an ophthalmologic perspective, there is no objection to the approval of this NDA provided that the labeling is consistent with other phosphodiesterase inhibitors" and 2) "It is recommended that repeated dose studies evaluating the effect of vardenafil on retinal function be conducted and submitted for review."

6) Effect of vardenafil on patients with coronary artery disease:

Trials 100408 (vardenafil 20 mg) and 100302 (vardenafil 10 mg) evaluated the effect of vardenafil on the cardiovascular response to exercise in patients with coronary artery disease. These studies are reviewed in Appendix K. These trials did not demonstrate any adverse effect of vardenafil on total treadmill exercise time, time to angina pectoris, or time to ST-segment depression during treadmill testing in patients with stable coronary artery disease.

7) Effect of vardenafil on liver function tests:

One patient in Clinical Pharmacology Trial 10006 experienced an elevation in liver function tests which was considered by the investigator to not be related to study drug. This patient (#10) had normal ALT and AST values at baseline prior to beginning 14 days of study drug (40 mg/day). On treatment day 7, the enzymes were "slightly elevated." After a further increase on Day 8 (AST 24 U/L; normal value <19 and ALT 45.8 U/L; normal value <23) drug was discontinued. Three days after the drug was stopped, ALT was 114.6 and AST was 54.9. He was hospitalized for 24 hours for "further control and diagnostics." Maximum AST was 66 U/L on Day 12 and ALT was 142 U/L also on Day 12. On follow-up, all values returned to the normal range. The patient's bilirubin was never elevated. Ultrasound of the liver was normal. No etiology for the increased transaminases was determined. Although the sponsor considers that it is "very unlikely" that this adverse event was related to study drug, this reviewer believes that a relationship to vardenafil can not be excluded.

The incidence of high AST, ALT, and CK values which occurred in Safety Pool 3 (all placebo-controlled studies using vardenafil 5, 10, or 20 mg (Trials 100249, 10128, 100250, 100285, and 10232) is shown in Table 6.

Table 6. Incidence of elevated AST, ALT, and CK values in Pool 3.

Laboratory study	Placebo N=793 (%)	Vardenafil 1812 (%)
Creatine kinase (CK,CPK)	122/598 (20.4%)	313/1402 (22.3%)
SGOT/AST	57/698 (8.20%)	139/1630 (8.5%)
SGPT/ALT	66/664 (9.9%)	159/1565 (10.2%)

“Potentially clinically significant chemistry laboratory abnormalities” for patients in Safety Pool 3 are shown in Table 7.

Table 7. Potentially Clinically Significant Chemistry Laboratory Abnormalities in Safety Pool 3.

Table 8-10 Pool 3: Incidence Rates of Treatment-Emergent Potentially Clinically Significant Chemistry Laboratory Abnormalities

Lab Variable		Placebo	Vardenafil
CK	>3xULN	16/746 (2.1%)	50/1745 (2.9%)
	>5xULN	8/752 (1.1%)	18/1762 (1.0%)
	>10xULN	2/753 (0.3%)	5/1764 (0.3%)
SGOT/AST	>3xULN	2/753 (0.3%)	4/1760 (0.2%)
	>5xULN	1/753 (0.1%)	3/1764 (0.2%)
	>10xULN	0/754 (0%)	2/1765 (0.1%)
SGPT/ALT	>3xULN	8/752 (1.1%)	4/1760 (0.2%)
	>5xULN	2/753 (0.3%)	2/1764 (0.1%)
	>10xULN	0/754 (0%)	0/1765 (0%)

Pool 3, Table 3/3

Two patients experienced serious adverse events of abnormal liver function tests. Both patients had a history of alcohol consumption relating temporally to the abnormal liver function tests. (See Appendix N).

This reviewer believes that the incidence of clinically significant elevations in liver function tests is low and, in the vast majority of patients, additional factors which could have contributed to the increases are present. There does not appear to be a relationship of dose of vardenafil administered and clinically significant elevations of LFT's. In the opinion of this reviewer, increased transaminases may occur at a low incidence in the broad population and information concerning transaminases should be included in the label.

8) CK elevations

The incidence of CK elevation in Safety Pool 3 and the incidence “potentially clinically significant” CK elevations are shown in Tables 5 and 6 above.

One patient experienced an elevation of CK to 18690 U/L and another patient had an elevation to 29940 U/L during the clinical trials. Both patients had recently participated in recent strenuous physical exertion and are discussed in Appendix N.

2.4. Dosing

In addition to the 4 major efficacy trials, two major dose-ranging studies are submitted to support the proposed doses of vardenafil (5, 10, and 20 mg). Trial 100199 was a Phase 2b study which enrolled healthier patients (no significant cardiovascular co-morbidities) than were enrolled in the subsequent Phase 3 trials. Vardenafil doses evaluated were 5, 10, and 20 mg. Primary endpoints were questions 3 and 4 of the IIEF. The treatment differences between vardenafil 5 mg and 10 mg and between vardenafil 10 and 20 mg were not statistically significant. The 20 mg vardenafil dose showed a trend toward improvement over the 5 mg dose for penetration ($p=0.087$) and maintenance of erection ($p=0.082$). Since Trial 100199 showed that vardenafil 5 mg was significantly more effective than placebo and not significantly less effective than vardenafil 10 mg, another study (Trial 10232) was performed to explore the lower end of the vardenafil dose range (2.5 and 5 mg). This study used the same patient population and the same primary efficacy measures as the major Phase 3 efficacy trials. “Because the 2.5 mg vardenafil dose showed relatively small treatment differences of questionable clinical value over placebo and because it conveyed no obvious safety advantage over the 5 mg dose, the development of the 2.5 mg dose was not pursued further.”

With respect to the high end of the proposed doses, in 3 of the 4 major trials, the dose of 20 mg is not clinically or statistically superior to 10 mg. In Trial 100250 (diabetic patients with erectile dysfunction), the difference between 20 and 10 mg for the EF domain of the IIEF was statistically different in favor of the 20 mg dose. 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 “pivotal” 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. Dosing is further discussed in the Clinical Review.

Dose modification recommendations for special populations:

Renal impairment: Renal impairment does not have a significant effect on vardenafil exposure and no dose adjustment is necessary. Vardenafil has not been studied in patients on dialysis.

Hepatic impairment: For patients with mild hepatic impairment, no dose adjustment is necessary. Based on results showing an increase in drug exposure (approximately 2 ½ -fold increase in both C_{max} and AUC of vardenafil), the starting dose of vardenafil in moderately hepatic-impaired patients should be 5 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.) Patients with severe hepatic impairment have not been evaluated.

When evaluated in the morning, food intake decreased the C_{max} of vardenafil by approximately 50%. No effect of food intake on the PK of vardenafil was seen in studies performed in the PM.

2.5 Drug-Drug Interactions:

There were no clinically significant changes in vital signs with co-administration of 20 mg vardenafil and alcohol or 10 mg vardenafil and 0.4 mg nitroglycerin.

The primary drug-drug interaction concern involves CYP 3A4 inhibitors. When 200 mg of ketoconazole was given for 4 days prior to administering 5 mg of vardenafil, the normalized AUC and C_{max} were increased 10-fold and 4-fold, respectively. When erythromycin 500 mg tid was given for 4 days prior to administering 5 mg of vardenafil, the normalized AUC and C_{max} of vardenafil were increased by 4-fold and 3-fold, respectively. When indinavir 800 mg tid was given for 7 days prior to administering 10 mg vardenafil, the AUC and C_{max} of vardenafil were increased by 16-fold and 7-fold, respectively.

The recommendation that the clinical pharmacology reviewer finds most preferable is to contraindicate the use of vardenafil with ketoconazole and indinavir (and other potent CYP 3A4 inhibitors). Alternatively, the reviewer believes that, if vardenafil and a potent CYP 3A4 inhibitor are used together, that a 5 mg dose of vardenafil should not be exceeded in a 48 hour time period. The proposed label states that "a maximum dose of 5 mg of vardenafil should not be exceeded when used in combination with these medications."

Reviewer's comment: The dose of ketoconazole used in the drug-drug interaction Trial 10229 was 200 mg (not 400 mg)/day. Doses of 400 mg may increase the C_{max} and AUC of vardenafil even further.

For erythromycin, the clinical pharmacology reviewer believes that the starting dose of vardenafil should be 5 mg and a maximal dose of 10 mg should not be exceeded. The proposed label recommends that "a maximum dose of 10 mg vardenafil should not be exceeded when used in combination with the cytochrome P450 3A4 inhibitor, erythromycin."

Reviewer's comment: This reviewer agrees with the clinical pharmacology reviewer with respect to dosing of vardenafil when given with potent CYP 3A4 inhibitors. Because the maximum dose of ketoconazole administered in the drug-drug interaction study was a dose of 200 mg/day and this dose produced an increase in AUC and C_{max} of 10-fold and 4-fold, this reviewer believes that ketoconazole should be contraindicated. The primary reason for this decision is that, in the opinion of this reviewer, QT safety data is insufficient to justify these high exposures.

Drug interaction studies conducted at appropriate doses including warfarin, digoxin, antacid, cimetidine/ranitidine, glyburide, and nifedipine did not show any potential for drug interaction which would require dosing recommendations.

2.6 Special populations

Gender differences: vardenafil is indicated only for men

Pediatric studies: vardenafil is indicated only for men with erectile dysfunction. The sponsor has requested a pediatric waiver and this reviewer believes that it should be granted.

Pregnant women: the drug is indicated only for men

Ethnic/racial studies: 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.

Elderly patients: There was >50% increase in AUC and >30% increase in C_{max} in patients greater than 65 years of age. The clinical pharmacology reviewer recommends that a dose recommendation should be added to the label that "men over 65 years of age should not receive doses higher than 10 mg of vardenafil." Safety data from the clinical studies does not show any increased incidence of adverse events in men >65 years of age compared to those < 65 years of age. Because the safety data do not indicate any

significant concern for the 20 mg dose in patients >65 years of age, this reviewer does not believe that any dose adjustment is required in these patients.

Renal and hepatic impairment: Patients with renal and hepatic impairment are discussed in Section 2.4 above.

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Clinical Review:

1. Introduction and Background

1.1. Established and Proposed Trade Name of Drug, Drug Class, Sponsors Proposed Indication, Dose, Regimens, and Age Group

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 3 doses (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 sponsor has requested a pediatric waiver.

1.2 State of Armamentarium for Indication

The only currently approved oral medication for the "treatment of erectile dysfunction is sildenafil (Viagra). Sildenafil is also a PDE5 inhibitor and is approved in doses of 25, 50, and 100 mg. PDE5 inhibitors produce erection by relaxing penile corporal smooth muscle by inhibiting the breakdown of cyclic GMP.

The only other medication approved for the treatment of erectile dysfunction is alprostadil (prostaglandin E₁). Alprostadil is a vasodilator which relaxes corporal smooth muscle by stimulating the production of intracellular cyclic AMP and is the only drug approved for the local therapy of erectile dysfunction. This drug is currently approved for use by either needle injection into the penis (Caverject^R and Edex^R) or use of a urethral suppository (MUSE^R).

1.3 Important Milestones in Product Development

A face-to-face end of phase 2 meeting was held on March 17, 2000. The Division believed that the results of Phase 2b Trial 100199 would likely not qualify as an adequate and well-controlled study to demonstrate the safety and efficacy of vardenafil for the treatment of erectile dysfunction because of the generally healthy population enrolled. In addition to the proposed 10 and 20 mg doses, DRUDP recommended that 5 mg dose be evaluated.

Following review of the protocol for Trial 100304 (nitrate interaction study), a letter dated August 29, 2000, informed the sponsor that "hemodynamic effects of higher or repeat doses of vardenafil (or higher or repeat doses of nitroglycerin) cannot be imputed from the results of this study."

A face-to-face pre-NDA meeting was held on May 21, 2001.

1.4 Other Relevant Information

Vardenafil is not approved for marketing in any other countries.

1.5 Important Issues with Pharmacologically Related Products

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.

2. Significant Findings from Chemistry, Animal Pharmacology and Toxicology, and Microbiology

There are no major chemistry issues which affect the approvability of vardenafil.

Pharmacology/toxicology:

- 1) Testicular atrophy/degeneration was seen in rats and dogs. The NOAEL, however, was at least 11 times the maximal recommended human dose and the toxicity was seen at exposures of approximately 85-fold the human exposure of 20 mg.
- 2) Arteritis was seen in rats and dogs. There was a NOAEL observed that was approximately 11 times the human dose of 20 mg.

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 PK beyond 40 mg. Both vardenafil and the major metabolite are 93-95% bound to plasma proteins.

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 C_{max} in patients older than 65 years. The clinical pharmacology reviewer recommends an adjustment of the dose in the proposed product label to state that “men older than 65 years of age should not receive doses higher than 10 mg of vardenafil.” In the clinical trials, men >65 years of age did not experience an increased incidence of adverse events compared to patients <65 years of age. Because the safety data do not indicate any significant concern for the 20 mg dose in patients >65 years of age, this reviewer does not believe that any dose adjustment is required in these patients.

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 are discussed in the safety section of this review (Section 7) and in attached appendices.

Alcohol interaction Trial 10348 (Appendix K)

Nitroglycerine interaction Trial 100304 (Appendix I)

CYP 3A4 interaction Trials 10229 (ketoconazole), 10104 (erythromycin), and 100306 (indinavir) (Appendix J)

Effect of vardenafil on the QT interval Trials 94, 10006, 10104, 10229, 10010, 10011, 100195, and 10096 (Appendix M)

Effect of vardenafil on the cardiovascular response to exercise in patients with coronary artery disease Trials 100408 and 100302 (Appendix L)

4. Description of Clinical Data and Sources

4.1 Sources of Clinical Data

The sources of data included in the review consisted primarily of data submitted with the NDA, the 4 month safety update, and the 7 month safety update. Selected material from previously published literature was also reviewed.

4.2 Overview of Clinical Trials

In support of NDA 21400, the sponsor submitted 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 1.

Table 1. 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	177/91	General (excluded radical prostatect omy)	77	57 (26-76)
		Vard 5 mg	190/128		77	58 (29-82)
		Vard 10	196/151		80	57 (27-83)
		Vard 20	186/138		82	58 (20-79)
10128 (Europe)	12 weeks	Placebo	160/140	General (excluded radical prostatect omy)	68	56 (23-78)
		Vard 5 mg	156/146		66	57 (21-78)
		Vard 10	157/148		68	55 (26-75)
		Vard 20	163/137		67	56 (25-74)
		Sildenafil 50 mg	162/147		68	56 (22-81)
100250 (North America)	12 weeks	Placebo	140/121	Diabetics (Excluded radical prostatect omy)	79	57 (35-74)
		Vard 10	149/131		82	58 (33-81)
		Vard 20	141/127		78	57 (34-78)
100285 (North America)	12 weeks	Placebo	137/97	Post- radical prostatect omy	93	60 (47-72)
		Vard 10	139/114		99	61 (44-77)
		Vard 20	147/119		87	60 (45-74)

In addition to the 4 primary efficacy studies, 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).

Additional safety studies included in the NDA submission on September 24, 2001 were:

- Trial 100312 (an extension of Trial 100250 – diabetic patients)
- Trial 10125 (a one year safety trial of 10 and 20 mg vardenafil)
- Trial 10152 (a 6 month extension of Trial 100199 (Phase 2B trial))

The final study reports for Trials 100285, 10125, and 10152 were submitted on January 23, 2002 with the 4 month safety update.

An interim study report for Trial 100408 and safety data from Trial 10194 (an extension of Trial 10128) were submitted on April 23, 2002. Safety data from ongoing US and foreign Trials 10454 (foreign), 10503 (foreign), 10566, 10573 (foreign), 10769 (foreign), 10775 (foreign), and 10786 were also submitted.

Overall, vardenafil was administered to 3750 patients during the clinical trials. Approximately 1630 patients have been treated for 6 months or longer and 730 patients have been treated for at least one year.

Other trials of particular clinical importance included:

Cardiovascular response in patients with coronary artery disease Trials 100302 and 100408

QT interval Trials 94, 10006, 10104, 10229, 10010, 10011, 10195, and 10196.

Nitroglycerin interaction Trial 100304

CYP 3A4 interaction Trials 10229, 10104, and 10336.

Alcohol interaction Trial 10348.

Sperm motility Trial 10373.

Effect of vardenafil on ophthalmologic parameters Trial 10197 (a consultation from Ophthalmology was requested and received for review of this trial).

4.3 Post-marketing Experience

Vardenafil has not been approved in other countries.

5. Clinical Review Methods

5.1 Conduct of Review

NDA 21400 was entirely electronically submitted. The following trials/submissions were reviewed in detail:

Four primary efficacy trials:

100249 (general erectile dysfunction population) (see Appendix A)

10128 (general erectile dysfunction population) (see Appendix B)

100250 (erectile dysfunction in diabetics) (see Appendix C)

100285 (erectile dysfunction following radical prostatectomy (See Appendix D)

Integrated Summary of Safety (see Appendix E)

Integrated Summary of Efficacy

10125 (12 month safety study) (see Appendix F)

10152 (6 month safety extension of Phase 2b study 100199) (see Appendix G)

10373 (sperm motility study) (see Appendix H)

10304 (nitroglycerin interaction study) (see Appendix I)

10229, 10104, and 10336 (ketoconazole, erythromycin, and indinavir interaction studies) (see Appendix J)

10348 (alcohol interaction study) (see Appendix K)

94, 10006, 10104, 10229, 10010, 10011, 100195, and 100196 (QT studies) (see Appendix M)

100408 and 100302 (cardiovascular response to exercise) (see Appendix L)

Other trials were reviewed in less depth and not included in the appendices:

10194 (extension of Trial 10194)

10197 (visual safety trial)

10047 (PK study at 40 mg dose)

10232 (Phase 3 trial of 2.5 and 5 mg doses)

Published literature was not relied upon to support efficacy or safety.

5.2 Overview of Methods Used to Evaluate Data Quality and Integrity

DSI audited 3 clinical investigation sites and the data appeared to be acceptable.

5.3 Financial Disclosure

Adequate documentation was submitted to comply with financial disclosure. It is unlikely that the data is biased.

6. Integrated Review of Efficacy

6.1 Brief Statement of 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 General Approach to Review of the Efficacy of the Drug

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

The 4 major efficacy trials are summarized in Table 2.

Table 2. 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	177/91	General (excluded radical prostatectomy)	77	57 (26-76)
		Vard 5 mg	190/128		77	58 (29-82)
		Vard 10	196/151		80	57 (27-83)
		Vard 20	186/138		82	58 (20-79)
10128 (Europe)	12 weeks	Placebo	160/140	General (excluded radical prostatectomy)	68	56 (23-78)
		Vard 5 mg	156/146		66	57 (21-78)
		Vard 10	157/148		68	55 (26-75)
		Vard 20	163/137		67	56 (25-74)
		Sildenafil 50 mg	162/147		68	56 (22-81)
100250 (North America)	12 weeks	Placebo	140/121	Diabetics (Excluded radical prostatectomy)	79	57 (35-74)
		Vard 10	149/131		82	58 (33-81)
		Vard 20	141/127		78	57 (34-78)
100285 (North America)	12 weeks	Placebo	137/97	Post-radical prostatectomy	93	60 (47-72)
		Vard 10	139/114		99	61 (44-77)
		Vard 20	147/119		87	60 (45-74)

The four major efficacy trials (100249, 10128, 100250, and 100285) were reviewed in detail (see Appendices A, B, C, and D). Trials 100199 and 10232 were also reviewed.

6.3 Detailed Review of Trials

6.3.1 Protocols:

6.3.1.1 Objective/Rationale

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.

6.3.1.2 Overall Design

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

6.3.1.3 Population and Procedures

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

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

Patients with the following cardiovascular risk factors were excluded from the efficacy trials (because PDE5 inhibitors should “be used with caution in these patients (class labeling) or “because in these patients sexual activity is inadvisable”): unstable angina pectoris, history of recent myocardial infarction, stroke, electrocardiographic ischemia (except stable angina), life-threatening arrhythmia within the previous six months, atrial tachyarrhythmia with a heart rate of >100 bpm at screening, resting or orthostatic hypotension (in all 4 major Phase 3 trials, patients were excluded if they had a resting systolic blood pressure of <90 mmHg or symptomatic postural hypotension within 6 months of screening), uncontrolled hypertension, and patients taking nitrates or nitric oxide donors, and patients with retinitis pigmentosa. Diabetics with hemoglobin A_{1c} <12% were allowed in all studies except 100199 and 100285.

Reviewer's comment: In all 4 major efficacy studies, patients were excluded if the resting systolic blood pressure were <90 mmHg or the patient had a history of symptomatic postural hypotension within 6 months of screening.

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

6.3.1.4 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.

6.3.1.5 Statistical Plan and Results

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

6.3.2 Results

The results of the primary efficacy analyses of the 4 major efficacy trials are shown in Tables 3, 4, 5, and 6 below.

Table 3. Trial 100249

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

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

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

^aThe P value is for the comparison of the vardenafil groups with placebo

Table 4. Trial 10128

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

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

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

^aThe P value is for the comparison of the vardenafil groups with placebo

Table 5. Trial 100250

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

	Placebo	Vardenafil 10 mg	Vardenafil 20 mg
IIEF domain: erectile function at LOCF			
LS mean baseline	11.2	11.0	12.4
LS mean value (SE)	12.8 (0.7)	17.1 (0.7) P = 0.0001	19.0 (0.7) P = 0.0001
Overall per-patient diary: success in penetration (% yes)			
LS mean baseline	33.2	30.9	41.1
LS mean value (SE)	38.4 (2.8)	61.2 (2.8) P = 0.0001	63.8 (2.8) 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) P = 0.0001	54.2 (3.1) P = 0.0001

Source: Tables 14.2/1.1 and 14.2/1.2, Study 100250

^aP value is for comparison of the vardenafil groups with placebo

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Table 6. Trial 100285

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

	Placebo	Vardenafil 10 mg	Vardenafil 20 mg
IIEF domain: EF at LOCF			
N	135	135	143
LS mean baseline	9.1	9.3	9.2
LS mean value (SE)	9.2 (0.7)	15.3 (0.7) P = 0.0001	15.3 (0.7) 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) P = 0.0001	47.5 (3.4) 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) P = 0.0001	34.2 (3.3) P = 0.0001

Source: Tables 14.2/1.1 and 14.2/1.2, Study 100285

^aThe P value is for the comparison of the vardenafil groups with placebo