Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-400	*Brand Name*	LEVITRA™
OCPB Division (I, II, III)	DPE II (HFD 870)	*Generic Name*	Vardenafil hydrochloride
Medical Division	DRUDP (HFD 580)	*Drug Class*	PDE 5 inhibitor
OCPB Reviewer	Dhruba J. Chatterjee, Ph.D.	*Indication(s)*	Male Erectile Dysfunction
OCPB Team Leader	Ameeta Parekh, Ph.D.	*Dosage Form*	5, 10, 20 mg tablets QD
Date of Submission	9/24/2001	*Dosing Regimen*	Once daily
Estimated Due Date of OCPB Review	5/30/2002	*Route of Administration*	Oral
PDUFA Due Date	9/24/2002	*Sponsor*	Bayer Corporation
Division Due Date	7/24/2002	*Priority Classification*	1S

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X	39		Complete (100%) electronic submission
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X			
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			
multiple dose:	X			
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X			
In-vivo effects of primary drug:				
In-vitro:	X			
Subpopulation studies -				
ethnicity:	X			
gender:	X			
pediatrics:				
geriatrics:				
body wt.				
renal impairment:	X			
hepatic impairment:	X			

PD:				
Phase 2:	X			
Phase 3:	X			
PK/PD:				
Phase 1 and/or 2, proof of concept:	X			
Phase 3 clinical trial:	X			
Population Analyses -				
Data rich:				
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability:	X			
Relative bioavailability -	X			
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X			
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class	X			
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies	39			

Filability and QBR comments

	"X" if yes	*Comments*
Application filable ?	X	
Comments sent to firm ?		
QBR questions (key issues to be considered)	• Effect of Vardenafil on QT Interval • Optimal Dose (lower, 2.5 mg dose) • DDI	
Other comments or information not included above	• This is a fully electronic NDA submission. All study reports and summaries are hyperlinked • Formal Pop-PK analysis report available – PM review attached	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

OCPB Briefing held on July 16, 2002 was attended by: G. Benson, S. Al-Habet, F. Houn, J. Hunt, F. De-Guia, J. Boal, H. Malinowski, M. Kim, V. Jarugula, S. Huang, J. Venitz, M. Hirsch, H. Sun, S. Haider, A. Dave, A. Parekh, DJ. Chatterjee.

Clinical Pharmacology & Biopharmaceutics Review

NDA:	21-400
Product Trade Name:	LEVITRA™
Active Ingredient/s:	Vardenafil hydrochloride (5, 10 and 20 mg)
Indication:	Male Erectile Dysfunction
Submission Dates:	9/24/2001 (original NDA)
Sponsor:	Bayer Corporation
Submission/Priority Type:	Original/1S
Reviewer:	Dhruba J. Chatterjee, Ph.D.
Team Leader:	Ameeta Parekh, Ph.D.
Pharmacometrics:	He Sun, Ph.D.

Table of Contents

Synopsis

The subject of this submission, LEVITRA (vardenafil hydrochloride), is an oral therapy for the treatment of male erectile dysfunction. This monohydrochloride salt of vardenafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase enzyme type 5 (PDE5). Proposed doses are 5, 10 and 20 mg (as oral tablets), not to exceed once per day.

RECOMMENDATION

From an OCPB perspective, the application is acceptable provided i) appropriate changes are incorporated in the label (as indicated in the review), ii) the cardiovascular (QT prolongation potential) safety of this drug is established from the high (10 – 15 fold) exposure scenarios possible with drug interaction with potent 3A4 inhibitors (eg. indinavir, ritonavir etc.) and iii) drug interaction of vardenafil with α-adrenergic blockers is addressed.

COMMENTS TO THE SPONSOR

The following need to be communicated to the sponsor:

- Sponsor should consider a lower (eg. 2.5 mg) dose to accommodate safer labeling instructions for concomitant administration with potent CYP 3A4 inhibitors
- Sponsor needs to address the issue of drug safety (mainly cardiovascular - QT prolongation) at elevated exposure levels of vardenafil as expected to be seen when used concomitantly with potent CYP 3A4 inhibitors (eg. indinavir, ritonavir etc.)
- Sponsor needs to address the issue of drug interaction of vardenafil with α-adrenergic blockers

Overall Summary of Clinical Pharmacology and Biopharmaceutics Findings

- **Pharmacokinetic Highlights:** Following administration of vardenafil, C_{max} is achieved within 1 hour. The drug eliminates from the body relatively quickly with a half-life ($t_{1/2}$) of around 4 hours. Vardenafil has 1 major metabolite (M1) and 2 minor metabolites (M4 and M5) all as a result of the degradation of the piperazine ring. M1 is the most active among the 3 metabolites against PDE-5, and has about 25% the activity of the parent. M1 levels are about 25 – 50 % of that of the parent. Vardenafil is almost entirely excreted in the feces (> 90% of dose, majority as metabolites). The drug shows linear pharmacokinetics between 5 – 20 mg (proposed dosing), but shows non-linear PK beyond 40 mg. Both vardenafil and the major metabolite are 93 – 95% bound to plasma proteins. Absolute bioavailability of vardenafil is about 15%.

- **Comparative Exposure-Response of 10 and 20 mg:** Based on two small phase 2 studies comparing 10 mg vs. 20 mg and 20 mg vs. 40 mg doses on penile rigidity and tumescence, there was no evidence showing further improvement in efficacy beyond the10 mg dose. All the 3 doses showed significantly higher rigidity/tumescence than the placebo. However, there was no evidence at least in these two (although small) Phase 2 studies that the incidence or severity of serious adverse events increased when the dose was increased from 10 to 20 mg.

- **Intrinsic Factors:** (i) There was >50 % increase in AUC and >30% increase in C_{max} in $\geq$ 65 year olds. A low starting dose is recommended. (ii) Based on results showing increase in drug exposure (2.5 folds), the starting dose of vardenafil in the moderately hepatic-impaired should be lower and the maximal dose should be carefully chosen. Patients with severe hepatic impairment were not studied. (iii) Renal impairment does not have a significant effect on the exposure, and dose adjustment might not be required in renal impairment.

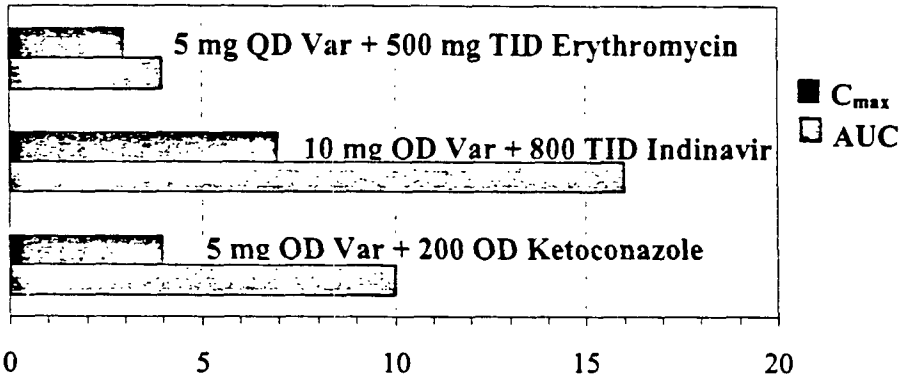
- **Extrinsic Factors:**

(i) **Pharmacodynamic Drug-Drug Interaction (DDI)**: The sponsor studied numerous scenarios by which vardenafil may pharmacodynamically interact with other agents (eg. alcohol, nitroglycerine and nefidipine) to potentiate the effects on blood pressure and heart rate.

Alcohol – Although there is a drop in blood pressure and increase in heart rate following concomitant administration of vardenafil and alcohol, the effects do not appear to be of a significant concern (please see detailed review of this study).
Nitroglycerine – Effects on blood pressure and heart rate within one hour of concomitant administration of the two drugs did not significantly differ between vardenafil and placebo. However, in this study, 10 mg (not the highest possible) dose of vardenafil was used.
Nifedipine – No significant potentiation in lowering of blood pressure was observed when the two drugs were co-administered. A final opinion on the PD-interaction studies with regards to the clinical relevance of the results is deferred to the Medical Officer's Review.

(ii) **Metabolic/Pharmacokinetic Drug-Drug Interactions:** Vardenafil is extensively metabolized by the CYP 3A4 enzyme system in the liver with minor contributions also from CYP 2C9. Based on the numerous metabolic drug interaction studies conducted by the sponsor, only the

following are of significant clinical relevance and warrants dosing adjustments (please see individual review sections ('Extrinsic Factors') for additional discussion on this subject).



Ratio (fold increase) of Vardenafil Exposure (Combination/Mono)

Note: For the ketoconazole DDI study, the lowest dose of vardenafil and a lower than maximum possible ketoconazole were evaluated for DDI potential. There is at least a theoretical concern that the highest ketoconazole dose (200 mg BID) and higher vardenafil doses may lead to even increased exposure scenarios than that observed currently (depicted in the above figure). There was a somewhat increasing trend towards side effects (eg. headaches) in the combination arm (5 mg vardenafil + ketoconazole) compared to 20 mg vardenafil.
For the indinavir study, there was clearly a significant increase in the incidences of dizziness, headache and rhinitis in the vardenafil + indinavir arm, as compared to vardenafil alone.

*Dosing Adjustments (**bold faced** recommendations are <u>not</u> in the currently proposed label):*

1. _____

2. _____

DRAFT

3. _____

Other drug interaction studies with warfarin, digoxin, antacid, cimetidine/ranitidine, glyburide did not show any significant potential for drug interactions requiring dosing recommendations.

- **QT Prolongation:** The sponsor has not addressed the potential of QT prolongation related safety of vardenafil from high elevated exposure scenarios (i.e 10 – 15 folds), such as those observed in the DDI studies with ketoconazole and indinavir (note that ritonavir is considered to be a more potent 3A4 inhibitor than indinavir). The formal QT analysis report that was submitted to the Clinical section of the NDA used 40 mg as the high dose, a two fold multiple of the highest dose sought after (20 mg) for marketing. In these studies (10010 and 10011), the first time point of ECG monitoring post drug administration was over a hour after the T_{max} of the drug (a design deficiency). Based on the review by the Division of Cardio Renal Drug Products (DCRDP) on the QT prolongation potential for vardenafil, there were no particularly significant concerns regarding the arrhythmogenic potential from *commonly anticipated levels/scenarios of vardenafil exposure.*

- Since this drug will be used in a population that frequently uses α-adrenergic blockers (for management of BPH), sponsor should address the issue of drug interaction between the two.

Background

Questions addressed in this section:

- ***What are the highlights of chemistry and formulation of the drug and drug product?***
- ***What is the mechanism of action, proposed indication and main goal of therapy?***
- ***What are the other drugs available in this class?***
- ***What are some highlights of claims for this product in the proposed label?***

The subject of this submission, LEVITRA (vardenafil hydrochloride), is an oral therapy for the improvement of erectile function in men with erectile dysfunction. This monohydrochloride salt of vardenafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). Proposed doses are 5, 10 and 20 mg (as oral tablets).

Vardenafil HCl is a nearly colorless, crystalline substance with molecular weight of 579.1 g/mol and a solubility of mg/mL in water. LEVITRA is formulated as orange, round, film coated tablets with "BAYER" cross embossed on one side and "5", "10" and "20" on the other side corresponding to 5 mg, 10 mg and 20 mg of vardenafil. The following is the composition of the tablets.

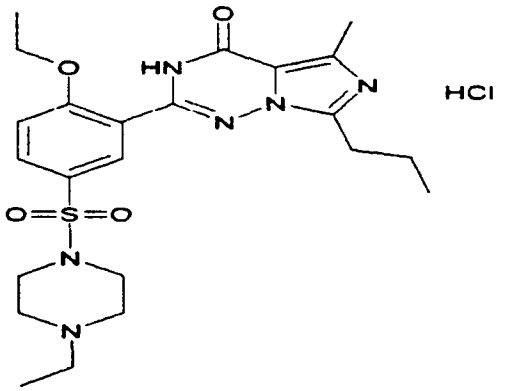


Fig. 1. Chemical Structure of Vardenafil HCl

Table 1. Vardenafil Tablet Formulations for Clinical Studies and for the Market
The formulation used in the Phase 3 studies is identical to the formulation proposed for marketing.

Vardenafil is indicated for the treatment of erectile dysfunction. Penile erection is a hemodynamic process initiated by the relaxation of smooth muscle in the corpus cavernosum and its associated arterioles. During sexual stimulation, nitric oxide is released from nerve endings and endothelial cells in the corpus cavernosum. Nitric oxide activates the enzyme soluble guanylate cylase resulting in increased synthesis of cyclic guanosine monophosphate (cGMP) in the corpus cavernosum smooth muscle cells. The cGMP in turn triggers smooth muscle relaxation, allowing increased blood flow into the penis resulting in erection. The tissue concentration of cGMP is regulated by both the rates of synthesis and degradation via phosphodiesterases (PDEs). The most prominent PDE in the human corpus cavernosum is the cGMP-specific phosphodiesterase type 5 (PDE5);

Bay 38-9456 Tablet Dev. No.⇒	2.5 mg	5 mg	10 mg	20 mg
Component	Weight (in mg)	Weight (in mg)	Weight (in mg)	Weight (in mg)
Bay 38-9456 (Vardenafil HCl),				
Crospovidone, NF				
Magnesium Stearate, NF				
Microcrystalline Cellulose, NF				
Colloidal Silicon Dioxide, Anhydrous, NF				
Total Weight of Core				
Polyethylene Glycol NF				
Hypromellose, USP				
Titanium Dioxide, USP				
Ferric Oxide, NF, yellow				
Ferric Oxide, NF, red				
Total Tablet Weight	74.292	89.773	128.985	182.648

therefore, the inhibition of PDE5 enhances erectile function by increasing the amount of cGMP. Because sexual stimulation is required to initiate the local release of nitric oxide, the inhibition of PDE5 has little effect in the absence of sexual stimulation. The following figure is a schematic (adapted from Pfizer's website on VIAGRA):

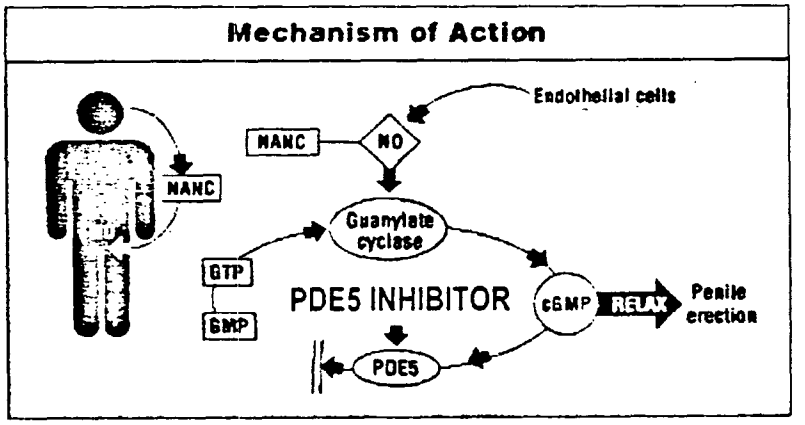


Figure 2. Mechanism of action of PDE5 inhibitors (adapted from WWW.VIAGARA.COM)

This application seeks approval of a PDE5 inhibitor for the treatment of male erectile dysfunction. VIAGRA (sildenafil) was the first to be approved in this class in 1999. In this application, sponsor claims high effectiveness of this product from all the three doses intended for marketing (5, 10, 20 mg). Contraindications and certain drug interaction information are included in the label.

Information from 38 clinical pharmacology studies and additional literature reports have been submitted in support of this NDA. This CPB review follows a 'Question-Based' GRP format, addressing questions only relevant to this application.

Clinical Pharmacology

Q. ***Were appropriate clinical endpoints, surrogate endpoints or pharmacodynamic (PD) biomarkers selected, adequately measured and used to assess efficacy and safety in clinical pharmacology studies?***

The efficacy of this drug has been determined in several phase 3 clinical trials based on measures of penetration, maintenance to successful intercourse, satisfaction with hardness of erection/rigidity, ejaculation, satisfaction with the sexual experience, reliable response, confidence in getting and maintaining an erection, orgasmic function and improvement in global efficacy. Efficacy end points were based on Global Assessment Question (GAQ) and Erectile Function Domain score of the validated International Index of Erectile Function (IIEF) Questionnaire. Additionally, satisfaction with hardness of erection/rigidity was also captured in patient diaries (supportive evidence for improved rigidity was also measured in RigiScan®). Relevant adverse effects (related to cardiovascular, body as a whole, vision and others) were monitored.

Q. ***Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?***

Yes. The parent, one major metabolite (4 times less active than the parent) and 3 other minor metabolites were monitored in the pharmacokinetic and PK-PD studies.

Q. ***What are the exposure (pharmacokinetic) characteristics of vardenafil?***

Is there a mass balance of the drug following administration?

In Study 10079, the sponsor conducted a mass balance, metabolism and excretion profiling of vardenafil following administration 40 mg of an oral solution of radiolabelled [^{14}C] vardenafil in 4 healthy male subjects. The following are the results:

Figure 1 Plasma concentrations (µg/L) after a single oral target dose of 40 mg [^{14}C] BAY 38-9456 x 3H$_2$O (geometric means, N=4), logarithmic scale (total radioactivity plasma concentrations in µg-eq-vardenafil/L)

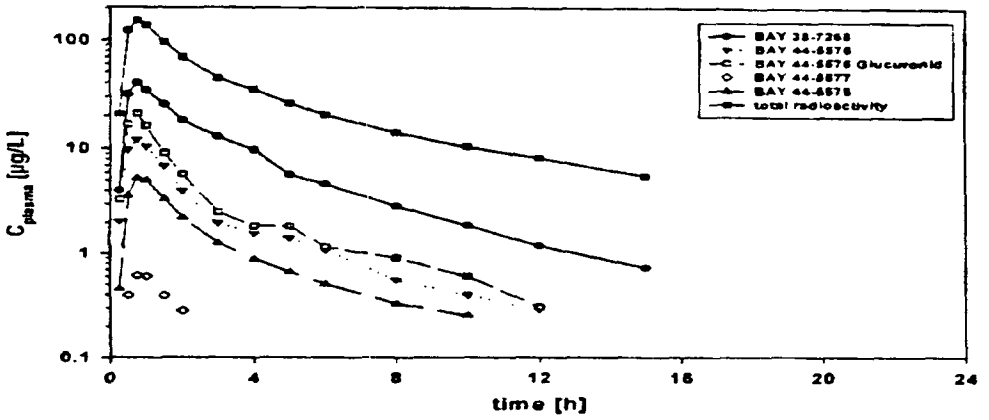


Table 2A. Cumulative excretion of total radioactivity

	Unit	Subject 1	Subject 2	Subject 3	Subject 4	arithm. mean	arithm. sd
Ae_{ur}	%					4.894	1.49
Ae_{feces}	%					92.526	1.63
$Ae_{ur+feces}$	%					97.420	0.73

Table 2B

Ratios of sum of AUCs [µg-eq-vardenafil*h/L] of all analytes relative to AUC of total radioactivity [µg-eq-vardenafil*h/L] in plasma

	VOL 01	VOL 02	VOL 03	VOL 04
total radioactivity [%]	1014 [100]	786 [100]	266 [100]	468 [100]
BAY 38-7268 [% of total radioact.]	112 [11]	139 [18]	49.4 [19]	201 [43]
BAY 44-5576 (M1) [% of total radioact.]	56.3 [5.6]	29.8 [3.8]	14.1 [5.3]	36.3 [7.8]
M1-Glucuronide* [% of total radioact.]	80.2 [7.9]	43.7 [5.6]	17.2 [6.5]	43.9 [9.4]
BAY 44-5577 (M5) [% of total radioact.]	2.62 [0.25]	1.76 [0.22]	0.55 [0.21]	1.37 [0.29]
BAY 44-5578 (M4) [% of total radioact.]	16.4 [1.5]	16.3 [2.1]	7.38 [2.8]	23.4 [5.0]
sum of active drug [% of total radioact.]	268 [26]	231 [29]	88.6 [33]	306 [65]

*BAY 44-5576 formed from corresponding glucuronide

Table 2C

Ratios of sum of C_{max} [µg-eq-vardenafil/L] of all analytes relative to C_{max} of total radioactivity [µg-eq-vardenafil/L] in plasma

	VOL 01	VOL 02	VOL 03	VOL 04
total radioactivity [%]	223 [100]	167 [100]	112 [100]	188 [100]
BAY 38-7268 [% of total radioact.]	39.2 [18]	53.7 [32]	22.5 [20]	64.0 [34]
BAY 44-5576 (M1) [% of total radioact.]	22.5 [10]	13.6 [8.1]	8.98 [8.0]	16.5 [8.8]
M1-Glucuronide* [% of total radioact.]	35.7 [16]	19.2 [12]	15.7 [14]	28.5 [15]
BAY 44-5577 (M5) [% of total radioact.]	1.09 [0.49]	0.66 [0.40]	0.60 [0.54]	0.83 [0.44]
BAY 44-5578 (M4) [% of total radioact.]	5.97 [2.7]	5.56 [3.3]	4.77 [4.3]	8.22 [4.4]
sum of active drug [% of total radioact.]	104 [47]	92.7 [56]	52.6 [47]	118 [63]

*BAY 44-5576 formed from corresponding glucuronide

Reviewer's comments:

- The % of total radioactivity in drug plasma accounted for by all the species (together) was 25 – 35% in 3 out of 4 subjects, and 65 % in the 4th subject (with high bioavailability). *Only* about 30% (mean) of the amount of radioactivity in plasma was accounted for as the drug molecule and metabolites in 3 out of 4 subjects (70 % of the radioactivity in plasma was unaccounted for)
- Fraction of total drug excreted in the feces is > 90% all patients, that in urine is 2 – 6 %
- Highest plasma levels among the 4 species followed was that of the parent, followed by the M1-glucuronide, M1, M4 and M5
- Major metabolite is M1, present in the plasma as M1 and M1-glucoronide – the total of these two species is more than the parent levels
- One of the subjects showed 2-3 fold higher bioavailability of the parent compared to the other three subjects

Study Deficiencies:

- The sponsor, in the study report, did not mention how or whether the urine/feces samples were analyzed for the proportion of parent and metabolites, nor did they report the results; from the study report it was not clear whether the above determinations were not performed
- In this study report, sponsor did not present any chromatogram that was typically obtained from patient samples showing all the peaks - only chromatograms presented were for standards.

However, in the Human PK Summary document, the sponsor presented a lot of additional data derived from the same study as above (Study 10079) as following:

- A complex metabolite profile was obtained in urine, indicated by more than 20 peaks with 14 metabolites and the unchanged drug being identified by chromatography
- In total, 83.3 % of the radioactivity in urine and 82.3 % of the radioactivity in feces could be assigned to known structures

Table 3: Percent of radioactivity in urine, feces and plasma present as unchanged drug (vardenafil) and metabolites (M1, M4 and M5)[a]

matrix	% vardenafil	% M1[b]	% M4	% M5
urine	22	23	9.6	2.8
feces	0.76	28	16	6.7
Plasma[c]	36	32	4.6	1.2

a) figures represent percent of radioactivity in a given matrix present as drug or metabolite
b) includes conjugate
c) 45 minutes after dosing

- In plasma, the fraction of total radioactivity present as unchanged drug was 36% at 45 minutes after dosing, and 33% at 90 minutes after dosing. At these same time points, metabolite M1 accounted for 32 % and 25 % of total radioactivity, while approximately 5 % of the radioactivity at both time points was present as metabolite M4. In total, 80 % and 72 % of the radioactivity present in plasma 45 and 90 minutes after dosing could be attributed to known structures (similar conclusion was not obtainable based on the report of the study submitted)
- Appears that the drug undergoes extensive first pass (liver and possibly GI) metabolism and majority of the products of metabolism is excreted in the feces

What is the metabolic pathway of the drug?

The following is the possible metabolic pathway of vardenafil, as postulated by the sponsor:

Figure 4A: Biotransformation processes of vardenafil

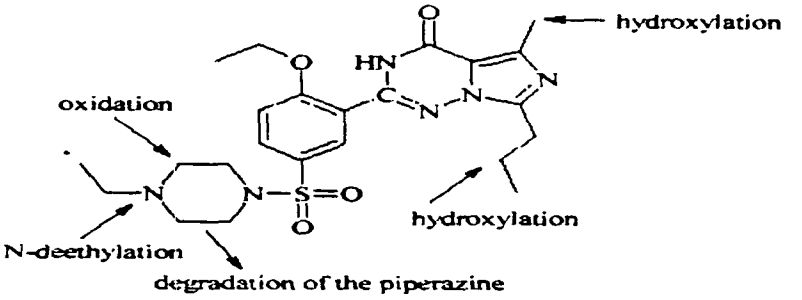
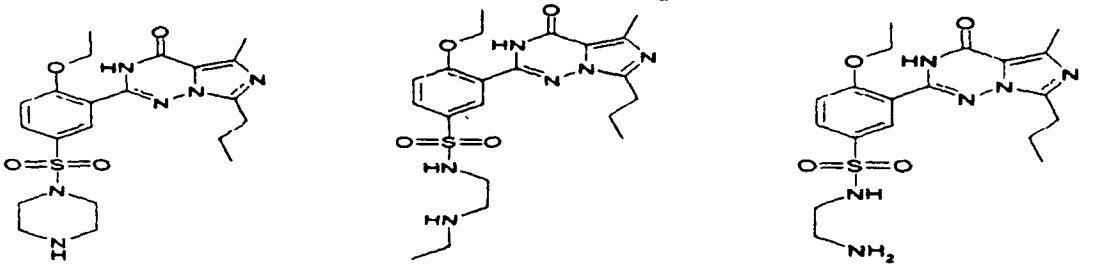


Figure 4B: Structures of BAY 44-5576 (M1), BAY 44-5577 (M5) and BAY 44-5578 (M4)



M1 M4 M5

Sponsor also reports that the metabolites M1, M4 and M5 were found to be potent inhibitors of PDE-5 with 28 %, 5.6 % and 4.9 % potency (IC_{50}-values) of the parent drug in vitro. Based on their exposure in man, only M1 may contribute to any meaningful extent (7 %) to the overall efficacy of vardenafil. Corroboration of the above is deferred to the Pharmacology review.

How much of the drug is bound to plasma proteins?

Based on *in vitro* investigations in human plasma, about 93 – 95% of the drug bound to plasma proteins (similar to that obtained *in vivo* in rats, but higher than dogs). About 80% of vardenafil is bound to albumin and about 11% to α_1-acid glycoprotein. The binding to plasma proteins was fully reversible in all the species. Major metabolite M1 had similar protein binding properties to parent.

Based on PK parameters, what is the degree of linearity or non-linearity in the dose-exposure relationship?

(i) A randomized, double blind placebo controlled dose-escalation Study 300020 was conducted in Japan to determine the tolerability and single dose PK of 10, 20 & 40 mg of vardenafil (BAY 38-7286 as free base and BAY 44-5576, the primary metabolite M1) in healthy subjects. The following are the results:

Table 4A Pharmacokinetic parameters of BAY 38-7268 after single oral dosing of 10, 20 and 40mg under fasting condition

Parameter [unit]		10 mg	20 mg	40 mg
AUC	[µg·h/L]	20.94 (1.72)	44.14 (1.39)	137.73 (1.72)
AUC_{inf}	[µg·h/L]	20.19 (1.77)	43.41 (1.39)	136.39 (1.73)
AUC_{norm}	[kg·h/L]·10^{-3}	127.78 (1.67)	136.67 (1.43)	215.05 (1.72)
AUC_{inf_norm}	[kg·h/L]·10^{-3}	123.24 (1.71)	134.41 (1.43)	212.97 (1.72)
C_{max}	[µg/L]	10.05 (1.86)	18.35 (1.29)	51.71 (1.86)
C_{max_norm}	[kg/L]·10^{-3}	61.30 (1.84)	56.82 (1.39)	80.74 (1.80)
t_{max}	[h]	0.75 (0.50 - 1.00)	0.75 (0.50 - 1.00)	0.75 (0.75 - 3.00)
$t_{1/2}$	[h]	3.19 (1.08)	3.98 (1.46)	5.33 (1.20)

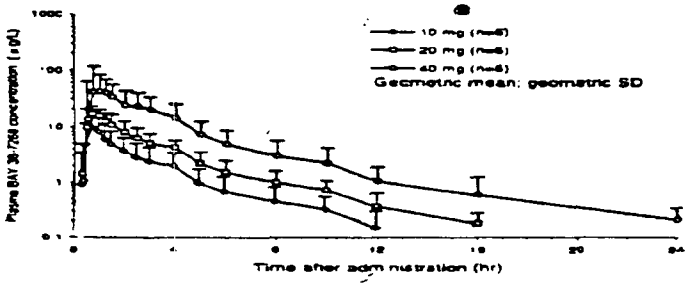


Figure 5 Plasma concentration profiles of BAY 38-7268 after single oral dosing of 10, 20 and 40mg under fasting condition

Table4B Pharmacokinetic parameters of BAY 44-5576 after single oral dosing of 40mg under fasting condition

Parameter [unit]		40 mg
AUC	[µg·h/L]	37.67 (1.59)
AUC_{∞}	[µg·h/L]	34.63 (1.65)
$AUC_{\infty,norm}$	[kg·h/L]·10^{-3}	62.40 (1.46)
$AUC_{\infty,norm}$	[kg·h/L]·10^{-3}	57.37 (1.52)
C_{max}	[µg/L]	16.12 (2.16)
$C_{max,norm}$	[kg/L]·10^{-3}	26.69 (1.99)
t_{max}	[h]	1.00
$t_{1/2}$	[h]	2.65 (1.72)
CL/f	[L/h]	1000.88 (1.59)
MRT	[h]	3.43 (1.45)
Vz/f	[L/kg]	61.32 (1.76)
A_{eur}	[%]	1.06 ± 0.41

Geometric mean (geometric SD), n=6, t_{max} give as median (range) and Ae_{∞} as arithmetic mean±arithmetic SD

Reviewer's comments:

- The exposure (based on AUC and C_{max}) are generally proportional between the 10 to 20 mg dose, but is clearly over-proportional beyond 20 mg
- The half life of the parent drug is higher from the 40 mg dose as compared to the 10 and 20 mg doses
- Half life of the parent as well as the primary metabolite is between 2 – 5 hours

(ii) Sponsor conducted another randomized, double blind placebo controlled single oral dose-escalation study (Study 94) with oral solution dosing to compare PK and tolerability of 5 – 80 mg vardenafil doses. A total of 45 healthy volunteers took part in the study. Other than PK of the drug and 3 metabolites, the adverse events were monitored for safety.

Following are the results of the study (PK of the parent and the 3 metabolites – major M1 and minor M4 and M5):

Table 5A: Geometric means/SD of PK parameters for vardenafil (free base)

Parameter	Units	5 mg,	10 mg,	20 mg,	40 mg,	80 mg,
Parameter	Units	5 mg N = 5	10 mg N = 4 1)	20 mg N = 6	40 mg N = 6	80 mg N = 5
AUC	µg*h/L	-	6.60 / 1.66	14.9 / 1.50	30.6 / 1.71	94.0 / 1.24
AUC_{norm}	10^{-3}*kg*h/L	-	55.2 / 1.62	65.8 / 1.54	60.3 / 1.62	89.4 / 1.28
C_{max}	µg/L	1.47 / 1.38	3.87 / 1.38	5.51 / 1.84	12.1 / 1.53	25.7 / 1.23
$C_{max,norm}$	10^{-3}*kg/L	23.1 / 1.37	30.5 / 1.38	24.4 / 1.98	23.9 / 1.48	24.4 / 1.29
MRT	h	-	1.65 / 1.51	6.22 / 1.83	4.59 / 1.53	5.36 / 1.27
$t_{1/2}$	h	-	0.874 / 2.00	5.36 / 1.80	4.49 / 1.93	4.74 / 1.62
t_{max} +	h	0.75	0.75	0.63	0.88	0.75
CL/f	L/h	-	1429 / 1.66	1265 / 1.50	1232 / 1.71	804 / 1.24
V_z/f	L/kg	-	22.9 / 1.25	117 / 1.79	107 / 1.58	76.5 / 1.61

*) C_{max}; $C_{max,norm}$; t_{max}: N = 6 + median (range) - not applicable

Table 5B: Geometric means/SD of PK parameters for M1

Table 5C: Geometric means/SD of PK parameters for metabolites BAY 44-5577 (M4) and BAY 445578 (M5) following a 80 mg dose

Parameter	Units	BAY 44-5577, N=5	BAY 44-5578, N=5
AUC	µg*h/L	9.41 / 1.15	65.3 / 1.15
AUC_{norm}	10^{-3}*kg*h/L	9.51 / 1.11	62.0 / 1.20
C_{max}	µg/L	2.14 / 1.33	13.5 / 1.25
$C_{max,norm}$	10^{-3}*kg/L	2.16 / 1.28	12.8 / 1.23
MRT	h	5.13 / 1.35	8.16 / 1.17
$t_{1/2}$	h	3.38 / 1.41	8.50 / 1.19
t_{max} +	h	1.0	1.25
CL/f	L/h	7552 / 1.16	1158 / 1.15
V_z/f	L/kg	513 / 1.50	198 / 1.36

+ median (range)

Reviewer's comments:

- This study confirms that the exposure of the parent and the major metabolite (M1) clearly over-proportional between 40 – 80 mg
- The exposure of the drug is generally linear to the dose administered between 5 – 40 mg
- Clearance (Cl/f) values for the vardenafil and M1 noticeably decrease when the dose increases from 40 to 80 mg
- $t_{1/2}$ of the parent drug is marginally higher at the higher doses

- The $t_{1/2}$ and t_{max} of M1 is almost exactly similar to the parent. The maximum $t_{1/2}$ for one minor metabolite is about 8 hours.
- Comparing levels from the 40 mg dose, metabolite M1 levels are approximately 25% of the parent levels (based on AUC/exposure)

How do PK parameters change with time following chronic dosing?

Study 100204 was a randomized, double blind, placebo-controlled, parallel group trial in 42 healthy postmenopausal women to determine the safety and PK of multiple doses of vardenafil (10 and 20 mg) for one month. PK of vardenafil and M1 were determined (as below).

Table 6.

Pharmacokinetics of BAY 38-9456 and its Metabolite, BAY 44-5576					
			Geometric Least Square Means		
Day	Parameters, units	n	10 mg	n	20 mg
1	BAY 38-9456				
	AUC_{0-24}, µg-h/l	14	45.5	14	85.3
	$AUC_{0-24,\ norm}$ g-h/l	14	323.9	14	292.5
	C_{max}, µg/l	14	14.6	14	23.0
	$C_{max,\ norm}$, g/l	14	103.9	14	79.0
	t½, h	14	4 4	14	5.5
1	BAY 44-5576				
	AUC_{0-24}, µg-h/l	14	25 0	14	48.6
	$AUC_{0-24,\ norm}$, g-h/l	14	177.9	14	166.7
	C_{max} µg/l	14	12 0	14	19.2
	$C_{max\ norm}$ g/l	14	85.7	14	65.9
	t½, h	14	3 9	14	5.2
31	BAY 38-9456				
	$AUC_{0\ 24}$, µg-h/l	13	50.3	14	95.1
	$AUC_{0-24,\ norm}$, g-h/l	13	356.1	14	325.9
	C_{max} µg/l	13	14.5	14	25.8
	$C_{max\ norm}$ g/l	13	102.8	14	88.5
	t½, h	13	5.7	14	5.6
	AUC Accumulation Ratio, (%)	13	121.0	14	112.2
	C_{max} Accumulation Ratio, (%)	13	107.2	14	112.7
31	BAY 44-5576				
	AUC_{0-24}, µg-h/l	13	19.0	14	36.1
	$AUC_{0-24,\ norm}$, g-h/l	13	134.1	14	123.7
	C_{max} µg/l	13	8.1	14	13.9
	$C_{max\ norm}$ g/l	13	57.2	14	47.7
	t½, h	13	4 8	14	5.5
	AUC Accumulation Ratio, (%)	13	78 0	14	74 4
	C_{max} Accumulation Ratio, (%)	13	67.6	14	72.4

Reviewer's comments:

- There is no evidence of any significant accumulation of the drug (or its primary metabolite) even after one month of daily dosing

- Although not presented above in Table 4, the data was highly variable on AUC and C_{max} parameters (% CVs were as high as 100%). The maximum variability was observed with the parent drug on Day 1
- Levels of M1 were generally lower on Day 31 as compared to Day 1
- The $t_{1/2}$ values were no longer than the parent drug (and in fact are shorter than the parent)

Q. ***What are the exposure-response (PK-PD) characteristics of vardenafil?***

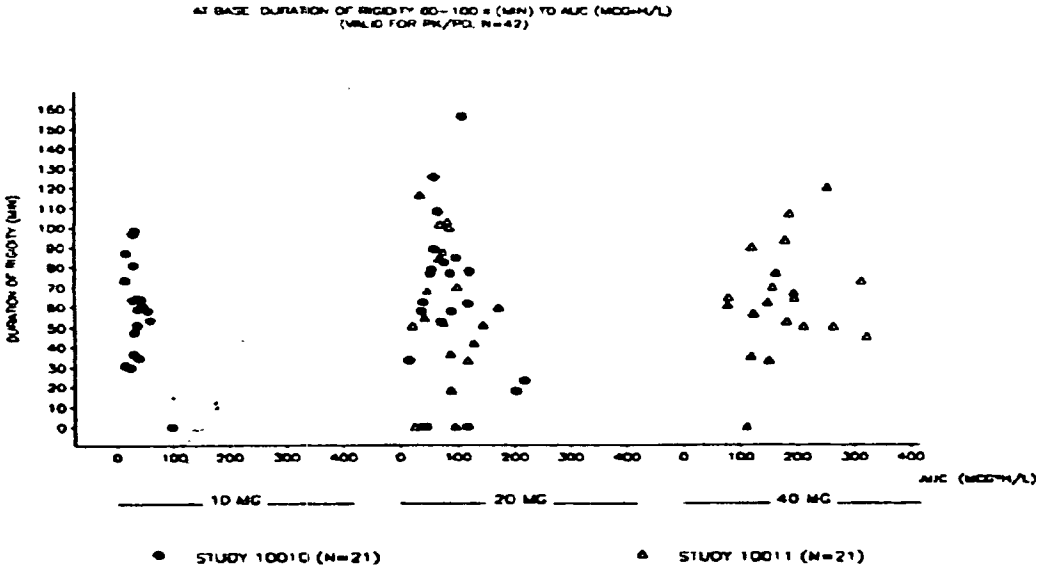
Is the dose and dosing regimen consistent with the known relationship between dose-concentration-response?

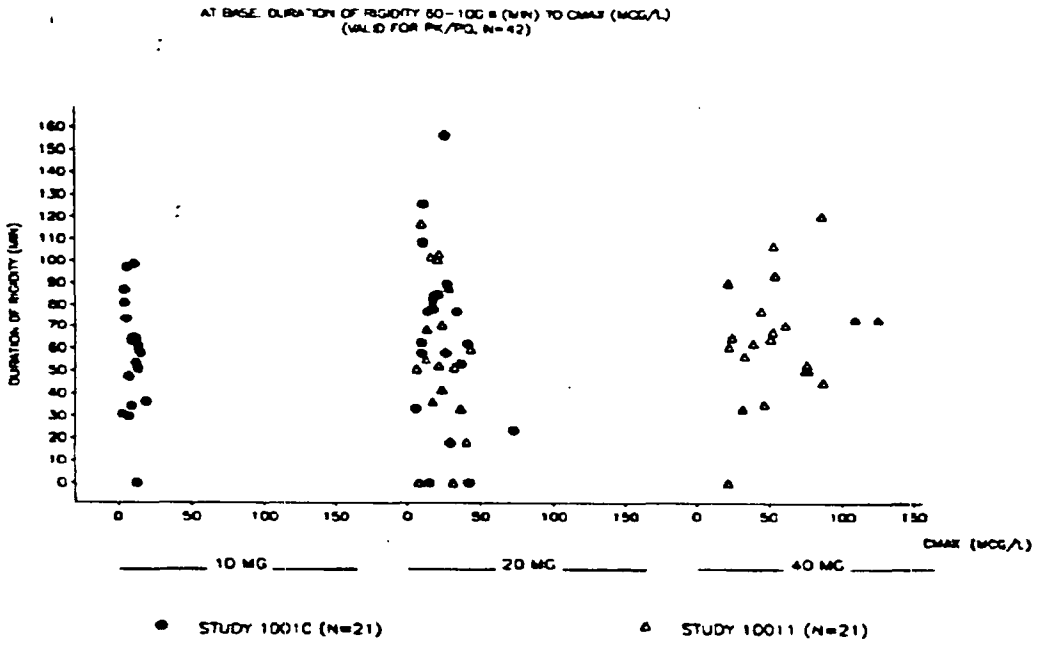
In this application, the sponsor is seeking approval for 5, 10 and 20 mg doses. Sponsor conducted two 'proof-of-principle' Phase II studies (double blind, randomized, placebo controlled and crossover) to determine the dose-response relationship of vardenafil from (i) single 10 and 20 mg oral doses (Study 10010) and (ii) single 20 and 40 mg oral doses (Study 10011) in patients with mild to moderate erectile dysfunction. All PK parameters obtained to correlate with several critical PD parameters involving penile rigidity and tumescence (at tip and base). The primary end point of the study was duration of > 60% rigidity at the tip and base of the penis. The following are the results:

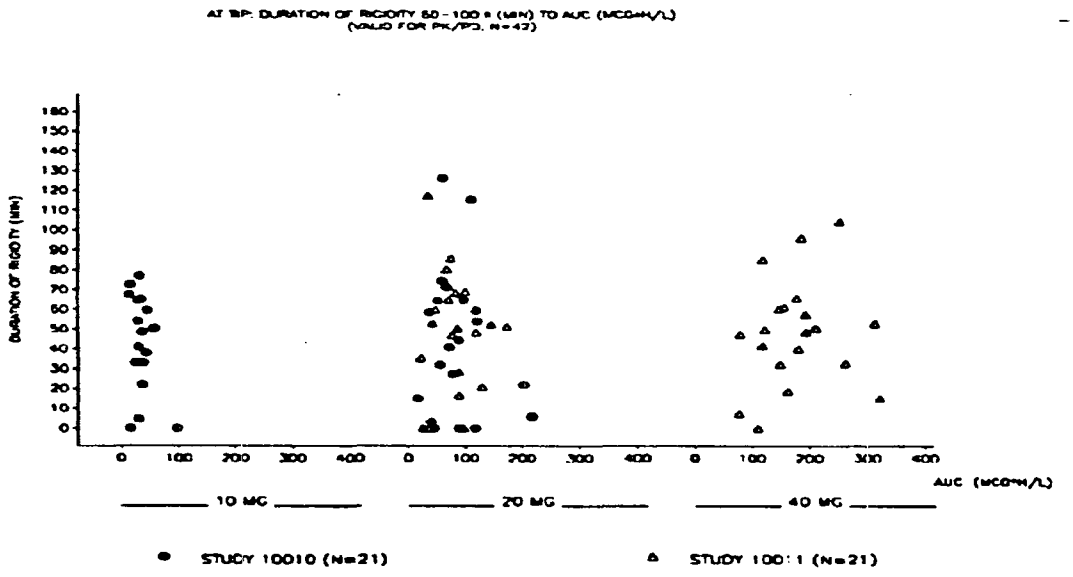
Efficacy

PD parameters were correlated with Dose/AUC/C_{max}, (pooled data from 2 studies) as follows:

Figure 8.




AT BASE: DURATION OF RIGIDITY 60 - 100 s (MIN) TO CMAX (MCG/L)
(VALID FOR PK/PD, N=42)
DURATION OF RIGIDITY (MIN)
CMAX (MCG/L)
10 MG
20 MG
40 MG
STUDY 10010 (N=21)
STUDY 10011 (N=21)


AT TRP: DURATION OF RIGIDITY 60 - 100 s (MIN) TO AUC (MCG*H/L)
(VALID FOR PK/PD, N=42)
DURATION OF RIGIDITY (MIN)
AUC (MCG*H/L)
10 MG
20 MG
40 MG
STUDY 10010 (N=21)
STUDY 10011 (N=21)

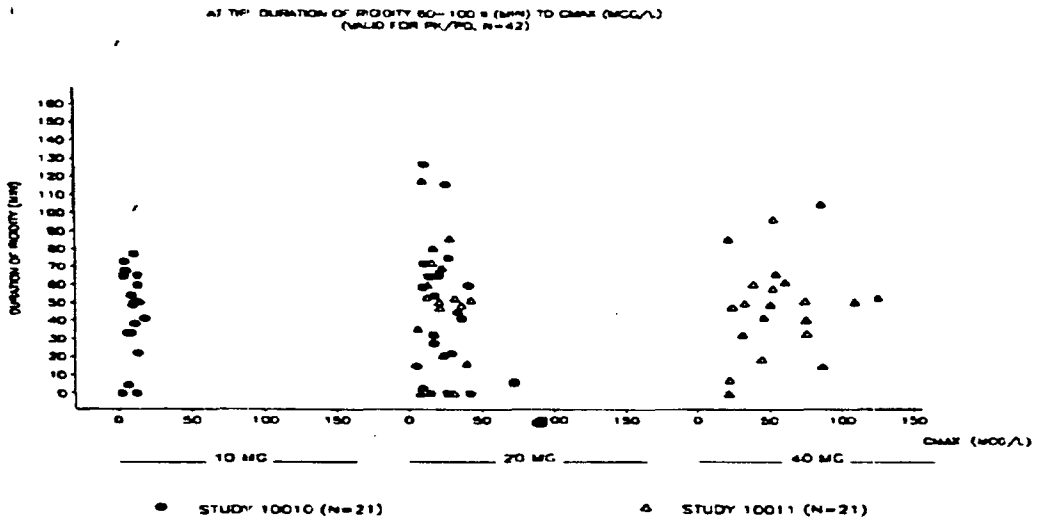


Table 10A. Statistical comparison for duration (mins) of > 60% rigidity:

	Comparison	Estimate	p-value	95% C.I.	90% C.I.
Base	10 mg - Placebo	24.38	0.006	(7.42, 41.33)	(10.26, 38.50)
	20 mg – Placebo	37.19	<0.001	(20.23, 54.14)	(23.07, 51.31)
	20 mg – 10 mg	12.81	0.127	(-3.82, 29.44)	(-1.04, 26.65)
Tip	10 mg – Placebo	24.81	0.004	(8.53, 41.08)	(11.27, 38.34)
	20 mg – Placebo	28.68	<0.001	(12.71, 44.66)	(15.39, 41.97)
	20 mg – 10 mg	3.88	0.601	(-11.07, 18.82)	(-8.56, 16.31)

Safety

There is no clear indication that adverse events in this small study significantly increased when dose was increased from 10 to 20 mg. Phase 3 safety information is summarized in the table below:

Table 10B. Summary of Adverse Events (in > 2% of patients) in 2 pivotal clinical trials is shown below:

Adverse Event	Placebo n = 342	Vardenafil 5 mg n = 350	Vardenafil 10 mg n = 358	Vardenafil 20 mg n = 351	Total Vardenafil n = 1059
Headache	2.0	8.0	11.7	17.4	12.4
Vasodilatation	0.9	5.7	10.9	12.8	9.8
Rhinitis	0.9	1.1	6.7	7.7	5.2
Dyspepsia	0.3	2.0	2.8	6.0	3.6
Nausea	0.3	0.6	0.8	2.8	1.4
Dizziness	0.3	0.6	2.5	2.8	2.0

Reviewer's comments:

- Based on the primary end point for these two studies (duration for > 60% rigidity), no obvious improvement of rigidity was observed (as proven by statistical tests) when the exposure (AUC or C_{max}) was increased from doses 10 mg to 20 mg (even upto 40 mg).

- Based on seçondary PD parameters (duration for > 80% rigidity, tumescence, rigidity activity and tumescence activity), an increase in response was *not* observed when exposure was increased between 10 – 20 mg (upto 40 mg) doses
- It appears, at least in these two studies, that the effect may have maximized at a dose of 10 mg
- The effect of all the doses were significantly different from placebo

Sponsor conducted another Study 10342 to determine the 'time to onset' of action following 10 and 20 mg oral vardenafil doses as compared to placebo in 44 patients with erectile dysfunction. The results of this study are not presented in details here. The following may be concluded:

- Because of a strong placebo effect, there was no detectable difference in the time to onset between the placebo, 10 and 20 mg groups
- A dose dependent increase in rigidity and tumescence
- A dose dependent increase in adverse events (between 10 and 20 mg groups) was not clearly evident, but the number of incidents were significantly more than the placebo arm

Based on the results of these 3 PK-PD 'proof-of-principle' Phase II studies, there is no clear trend/evidence that the 20 mg dose is any different (either efficacy or safety) than the 10 mg.

In the Phase III clinical trials, according to the Medical Officer, similar results were obtained. While all the 3 doses were statistically significantly different (more effective) than the placebo arm, there was no clear evidence that the 20 mg dose was superior in efficacy. However, in one study in diabetics (Study 100250), there was a marginal higher efficacy with the 20 mg dose compared to the 10 mg (this statistically significant difference, according to the Medical Officer, was only with the ED domain of the IIEF). In almost all the phase 3 studies, the adverse event profile worsened in the 20 mg arm as compared to the 10 mg dose and there is a dose-related trend for adverse events (Table 10B above).

Sponsor's proposed dosing recommendation is starting at 10 mg with a possibility of adjustment to 5 mg or 20 mg based on efficacy/tolerability. Increasing dose to 20 mg either only in diabetic patients or to all the patients will be based on the Clinical Team's final review decision on this.

Q. What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

All PK parameters were variable (CV values were as high as 50 – 60 %) generally in all studies involving normal volunteers and patients. This inter patient variability may not be attributable to any specific factor. A reliable estimation of intra-subject variability could not be easily made from the data provided.

NOTE: All PK parameters in almost all studies are reported as geometric means and geometric standard deviations (numerically small with respect to the means giving an unreal impression of a small %CV).

Intrinsic Factors

Q. How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Patients with erectile dysfunction are considered healthy otherwise, unless age and other disease conditions are prevalent. Hence, a significant difference in the PK parameters of the drug and metabolites are not expected between the patients and normal volunteers.

If one compares the results obtained in Study 94 (oral solutions 5 – 80 mg in normal volunteers) and Study 10010 (10 & 20 mg oral doses in erectile dysfunction patients aged 18 – 60), the PK parameters are generally comparable.

Q. What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

Age and Gender:

Sponsor conducted Study 100195 to study the effect of age and gender on PK parameters in the 4 groups (as below) with a single 40 mg oral dose of vardenafil. Results follow:

- Group 1: 12 young males, aged 18-45 years
- Group 2: 12 young females, aged 18-45 years*
- Group 3: 12 elderly males, aged ³65 years
- Group 4: 12 elderly females, aged ³65 years

Table 11A: Pharmacokinetics of BAY 38-9456 Following a Single 40 mg Vardenafil Dose

parameter	unit	young male (n = 8)	elderly male (n = 9)	young female (n = 9)	elderly female (n = 9)
		Linear Scale		Semi-log Scale	
					15/1.3
					89/1.3
					3.3/1.3
					15/1.3
					(0.3-2.0)
					.5/1.3

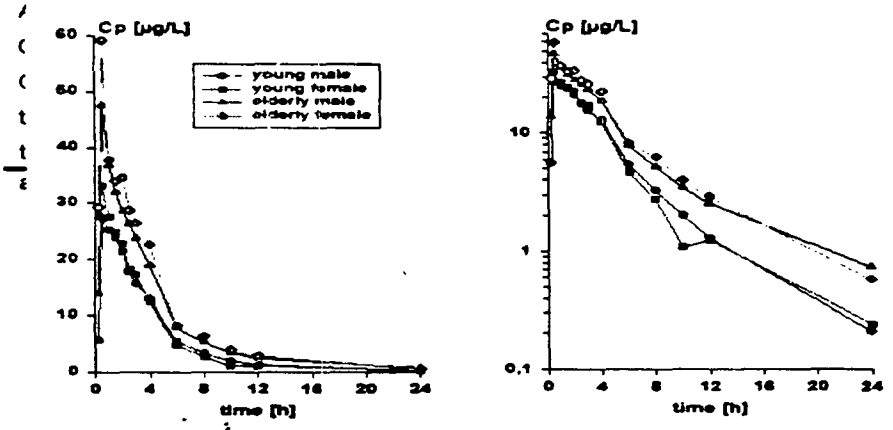


Figure 9. Vardenafil - plasma concentration/time data (geo. means) following a single dose of 40 mg vardenafil solution in young and elderly male and females (n = 8/9; Study 100195)

Table 11B: Pharmacokinetics of BAY 44-5576 (M1) Following a Single 40 mg Vardenafil Dose

parameter	unit	young male (n = 8)	elderly male (n = 9)	young female (n = 9)	elderly female (n = 9)
AUC_{0-tn}	µg*h/L	57.2/1.8	76.4/1.4	54.4/1.8	106/1.5
C_{max}	µg/L	25.8/1.9	31.1/1.5	18.9/1.8	40.1/1.3
t_{max} [b]	h	0.8	0.5	0.5	0.5
$t_{½}$	h	6.4/1.3	9.6[a]/1.3	9.1/1.5	7.8/1.2

a) n = 8
b) median (range)

Reviewer's comments:

- Based on the proposed indication, gender effect may not be relevant
- On average, elderly males had a 52 % higher AUC and 34 % higher C_{max} than young males
- In elderly females, both AUC and C_{max} increased about 65 % compared to young females
- Slightly higher half-life of the drug was observed in the elderly males as compared to the young
- PK parameters were generally similar between young males and females
- There was a slight trend of higher drug exposure in the elderly females as compared to the elderly males
- Similar trend was observed for the active major metabolite (M1) – higher exposure in the elderly than the young, with older females showing higher exposure to M1 than the older males
- There was a statistically significant increase in half-life of the M1 when compared between young vs. old males as well as young vs. old females
- Sponsor conducted serial ECG analysis on all patient groups with active drug and placebo

The above information on the effect of age on PK parameters will be incorporated in the label to help practitioners prescribe the drug appropriately in the elderly.

Ethnicity:

Following 3 Phase III studies, the sponsor did a Population PK analysis to estimate the interethnic differences (if any) for the PK parameters as follows:

Figure 10A. Box-whisker-plot of vardenafil AUC/Dose in healthy subjects and patients of different ethnic groups

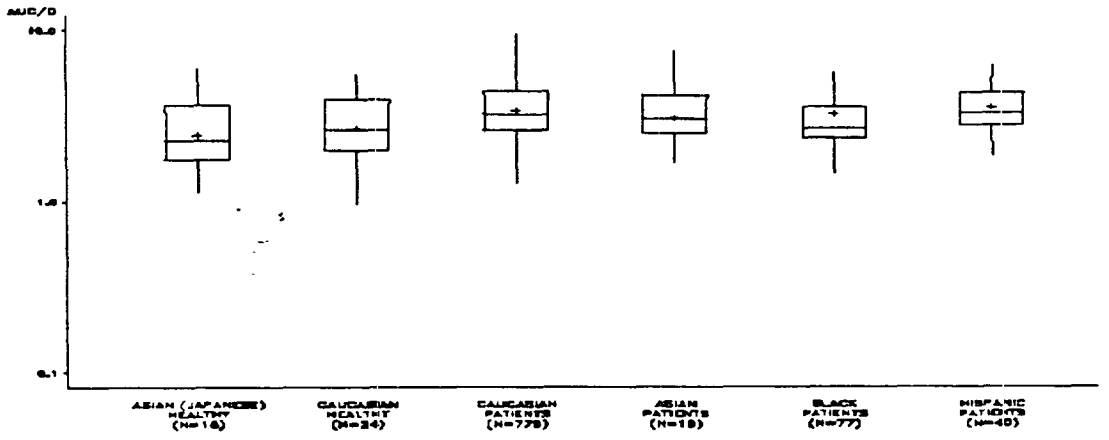
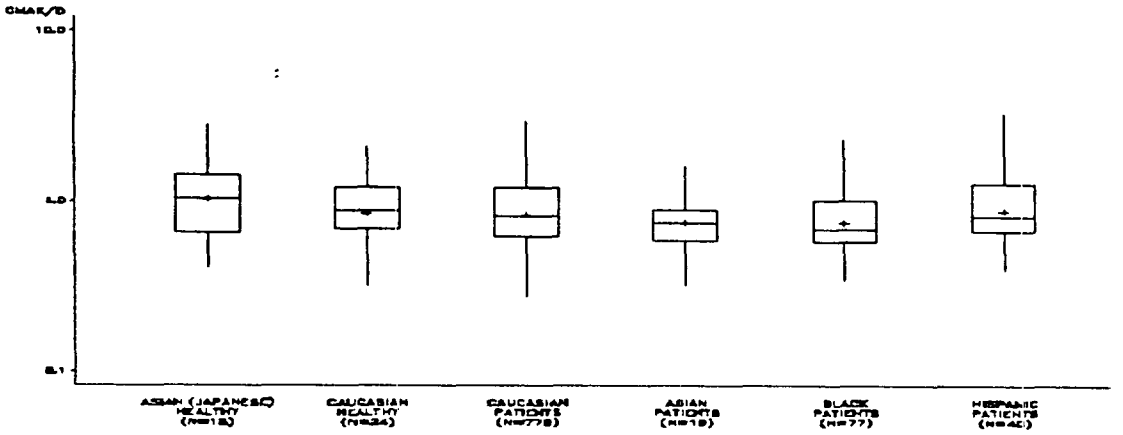


Figure 10B. Box-whisker-plot of vardenafil C_{max}/Dose in healthy subjects and patients of different ethnic groups



Reviewer's comments:

- In general, no significant interethnic differences for the key PK parameters could be observed in the above plots following the Phase 3 analysis
- If one compares the results obtained in Study 94 (oral solutions 5 – 80 mg in normal young Caucasian volunteers) with those obtained in Study 3000200 (10 – 40 mg single oral doses in young Japanese normal volunteers), the normalized AUC and C_{max} values were about 100% and 50 % ***lower*** in the Japanese group compared to the Caucasian group from the 10 and 20 mg oral doses; half lives of the parent drug and M1 levels were comparable in both group

Disease Conditions:

a) Renal Impairment

From the mass balance study that the sponsor conducted, majority of the drug (> 90%) was excreted in the feces, hence renal impairment is not expected to alter vardenafil PK significantly.

Sponsor conducted Study 10230 - Non-randomized, non-blinded, stratified group-comparison study to investigate the pharmacokinetics, safety and tolerability of a single oral dose of a 20 mg BAY 38-9456 tablet in male subjects with different degrees of renal impairment in comparison to healthy male subjects. There were 32 subjects in the following 4 groups:

Group 1: CL_{cr} > 80 ml/min (normal renal function)
Group 2: CL_{cr} > 50-80 ml/min (mild renal impairment)

Group 3: CL_{cr} > 30-50 ml/min (moderate renal impairment)
Group 4: $CL_{cr} \leq 30$ ml/min (severe renal impairment but not yet on dialysis)

Results: Figure 11A.

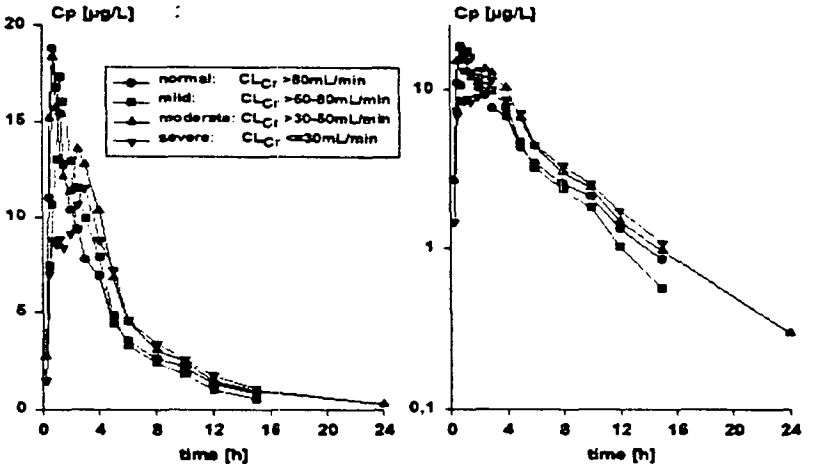


Table 12A: Vardenafil – PK parameters/results in plasma following a single oral dose of 20 mg vardenafil tablet in subjects with varying degrees of renal impairment (geo. mean/SD; n = 32; Study 10230)

parameter	unit	CL_{cr} >80 ml/min n = 8	CL_{cr} >50-80 ml/min n = 8	CL_{cr} >30-50 ml/min n = 8	CL_{cr} ≤30 ml/min n = 8
AUC	µg*h/L	78.2 / 2.08	77.9 / 1.68	102 / 1.37	94.3 / 1.50
AUC_{norm}	g*h/L	302 / 2.03	296 / 1.84	428 / 1.42	374 / 1.51
C_{max}	µg/L	22.4 / 2.67	22.7 / 1.46	31.0 / 1.79	17.2 / 1.51
$C_{max,norm}$	g/L	86.4 / 2.56	86.4 / 1.58	130 / 1.70	68.2 / 1.57
$t_{½}$	h	4.60 / 1.27	5.00 / 1.44	5.61 / 1.32	5.81 / 1.44
t_{max}[a]	h	0.75	0.75	0.63	1.38
CL/f	L/h	256 / 2.08	257 / 1.68	196 / 1.37	212 / 1.50
CL_R	L/h	2.15 / 1.44	1.18 / 1.60	1.00 / 1.19	0.684 / 1.72
$Ae_{u(0-48)}$[b]	%	1.01 ± 0.68	0.537 ± 0.30	0.553 ± 0.23	0.415 ± 0.33
f_u	%	7.82 / 1.91	6.22 / 1.37	6.83 / 1.38	9.03 / 1.36

a) median (range)
b) arithmetic mean ± SD

Table 12B: Vardenafil - ratios (X 100%) of geometric LS mean of pharmacokinetic parameters between subject groups and corresponding 90 % confidence limits (Study 10230)

	CL_{cr} >50-80 ml/min / CL_{cr} >80 ml/min	CL_{cr} >30-50 ml/min / CL_{cr} >80 ml/min	CL_{cr} ≤30 ml/min / CL_{cr} > 80 ml/min
AUC	99.59	130.56	120.66
	(64.14 - 154.64)	(84.08 - 202.72)	(77.71 - 187.36)
C_{max}	101.51	138.55	76.78
	(59.12 - 174.27)	(80.70 - 237.87)	(44.72 - 131.82)

Figure 11B: Metabolite (M1 and M4) - plasma concentration/time data (geo. means) in subjects with different degrees of renal impairment following a single dose of 20 mg vardenafil tablet (n = 8 per group; Study 10230)

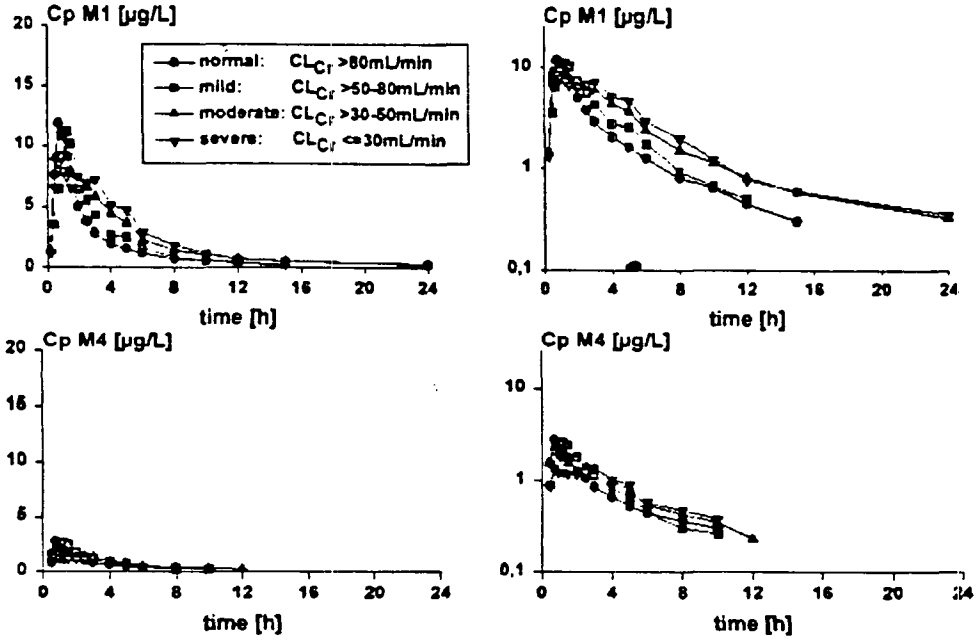
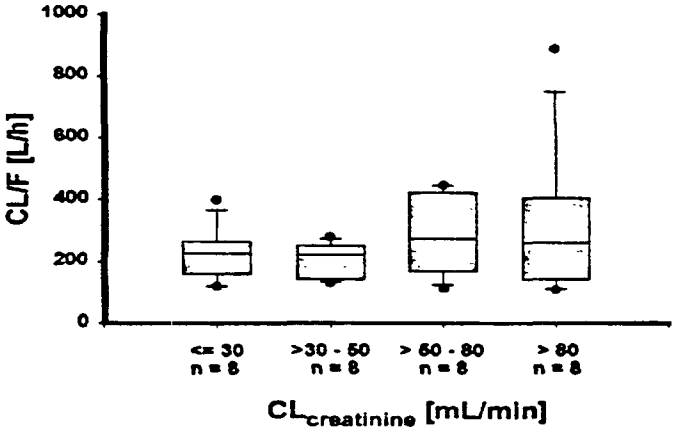


Figure 11C: Box-Whisker plot of BAY 38-7268 apparent oral clearances (CL/F) as a function of creatinine clearance



Reviewer's comments:

- As expected from the results of the mass balance study, there was no significant effect of renal impairment on the PK parameters
- There was a 25 – 40 % increase in vardenafil AUC in the moderate to severe group, however the highest exposure was in the moderate group
- There was an increase in C_{max} by almost 50% in the moderate group, but a lowering of the C_{max} in the severe group

- There was no evident correlation between the severity of the impairment and the exposure of vardenafil
- There was a trend in marginal increase in the half life of vardenafil with increase in severity of the disease – this increase in half life was very significant for metabolite M1 (about a 50% increase in the half life in all the 3 disease groups compared to the normal)
- Similar trend in partial increased exposure for M1 was also observed, but levels of M4 were practically similar in the 4 groups

Based on the above, there might not be a necessity to suggest dose adjustment in renal impairment.

b) Hepatic Impairment

Vardenafil is extensively metabolized in the human body (primarily the liver) as was evidenced in the mass balance study. Hence, a significant increase in drug exposure is expected with hepatic impairment.

Sponsor conducted Study 100305 to compare the pharmacokinetics of 10 mg single dose vardenafil in 3 subject groups with different degrees of hepatic function, each consisting of 6 subjects:

Group 1: normal hepatic function (healthy)
Group 2: mild hepatic impairment (Child-Pugh Class A or CP-A)
Group 3: moderate hepatic impairment (Child-Pugh Class B or CP-B)

Results:

Figure 12A. Vardenafil - plasma concentration/time data (geo. means) in subjects with different degrees of hepatic impairment following a single dose of 10 mg vardenafil tablet (n = 6 per group; Study 100305)

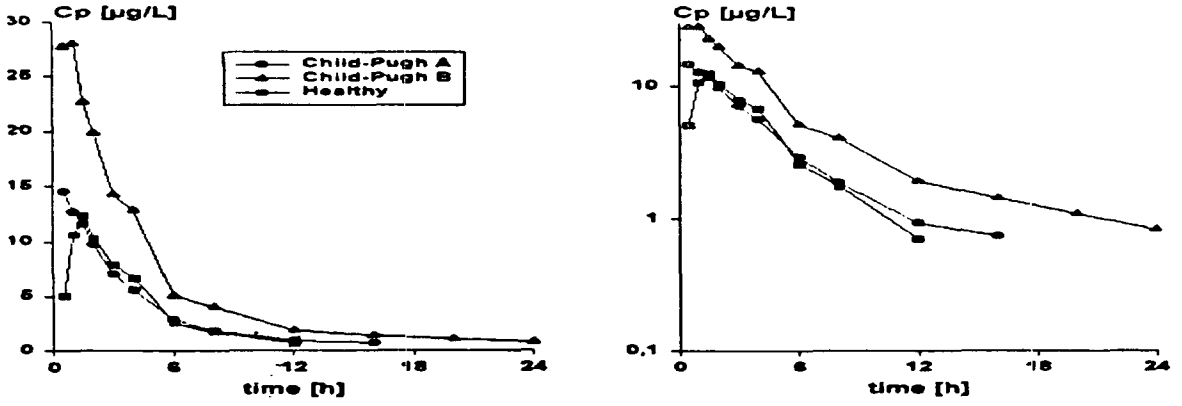


Figure 12B: Metabolite (M1 and M4) - plasma concentration/time data (geo. means) in subjects with different degrees of hepatic impairment following a single dose of 10 mg vardenafil tablet (n = 6 per group; Study 100305)

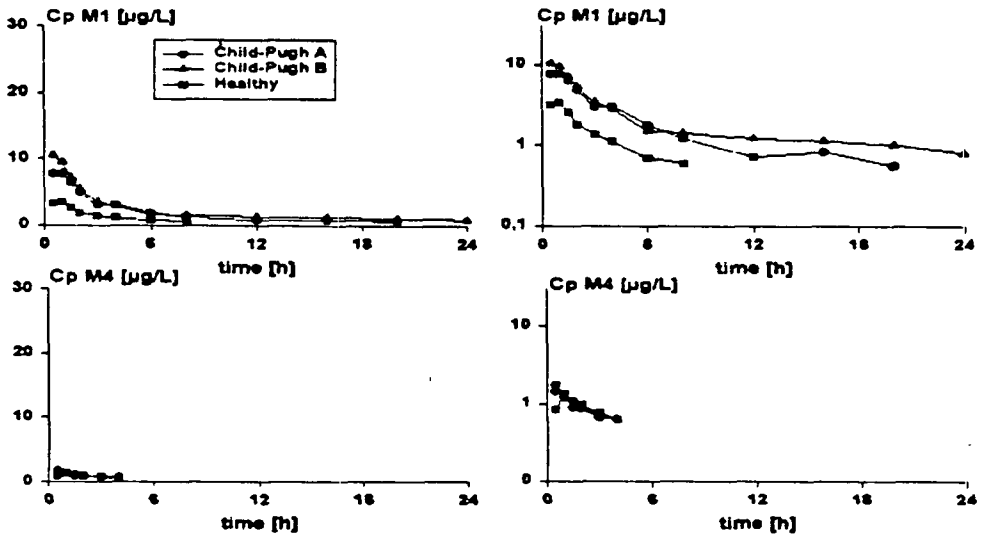


Table 13A: Vardenafil – PK parameters/results in plasma in patients with varying degrees of hepatic function following a single dose of 10 mg vardenafil tablet (geo. Means/SD; n = 6 per group, (Study 100305)

parameter	Unit	Healthy	Child-Pugh A	Child-Pugh B
AUC	µg*h/l	54.4 / 1.73	63.5 / 2.06	141.4 / 1.46
	CP-A vs. healthy	CP-B vs. healthy	CP-A vs. CP-B	
AUC	1.17 (0.66 – 2.07)	2.60 (1.47 – 4.61)	0.45 (0.25 – 0.80)	
C_{max}	1.22 (0.76 – 1.97)	2.33 (1.45 – 3.77)	0.52 (0.32 – 0.84)	
t_{max}[a]	h	1.5 (1.0 – 1.5)	0.5 (0.5 – 1.0)	1.0 (0.5 – 1.5)

a) median (range)

Table 13B: Vardenafil - ratios of geometric LS mean of PK parameters between subject groups and corresponding 90 % confidence limits (Study 100305).

Reviewer's comments:

- There was almost a 2.5 fold increase in AUC and C_{max} of vardenafil in the moderately impaired group as compared to the normal group, and a marginal increase in drug exposure in the mild
- There was about a 50% increase in half life of vardenafil in the two impairment groups as compared to the healthy
- Effect on M1 was more pronounced than on vardenafil (4 fold increase in AUC and about 3 fold increase in C_{max})
- Half life of M1 was more than doubled in the two impaired groups as compared to the healthy
- No effect was observed in the minor metabolite M4
- Severe hepatic impaired group was not studied

Based on the above facts, this reviewer agrees with the sponsor that the **starting dose of vardenafil in the moderately hepatic-impaired should be 5 mg.**

Extrinsic Factors

Q. What extrinsic factors (drugs, herbals, diet, smoking, alcohol use etc.) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

Metabolic Drug-Drug Interactions:

Is there an in vitro basis to suspect in vivo drug-drug interactions?

There is a strong *in vitro* evidence (based on studies conducted by the sponsor) to conclude that vardenafil is extensively and decisively metabolized by CYP 3A4/5 with CYP 2C9 contributing a minor extent towards drug metabolism. The results were clearly verified by studies involving incubations with microsomes from cells transfected with human cDNA for several CYP isozymes, as well as incubations with human liver microsomes in the presence of isozyme-selective inhibitors.

Sponsor also conducted a specific *in vitro* study to determine the inhibitory potential of the parent and the metabolites on the CYP isozymes. The results indicate that major metabolite M1 has the highest inhibitory potential (K_i = 1.4 µM). Clinically, the range of the C_{max} obtained from the high doses (20 – 80 mg vardenafil) was approximately 0.01 – 0.06 µM, resulting in I/K_i ratios of 0.007 – 0.04. The sponsor rationalized that based on this there was a low potential of clinically significant inhibition of CYP enzymes by M1, hence no formal *in vivo* drug interaction study was conducted to determine the inhibitory potential of vardenafil and its metabolites. This conclusion/approach was acceptable to this reviewer.

Is there a potential for in vivo metabolic/pharmacokinetic drug-drug interactions?

With the above *in vitro* information, the sponsor conducted several *in vivo* metabolic pharmacokinetic drug-drug interaction studies with vardenafil, as follows:

Studies Showing Significant Interaction Potential:

DDI: Ketoconazole

Sponsor conducted Study 10229 to determine the effect of concomitant administration of 5 mg vardenafil and 200 mg qd ketoconazole (potent CYP 3A4 inhibitor) as compared to a 20 mg vardenafil tablet given alone. Results are as follows:

Figure 13: Vardenafil - plasma concentration/time data (geo. means) following administration of 5 mg vardenafil tablet + 200 mg ketoconazole and 20 mg vardenafil tablet alone (n = 12; Study 10229)

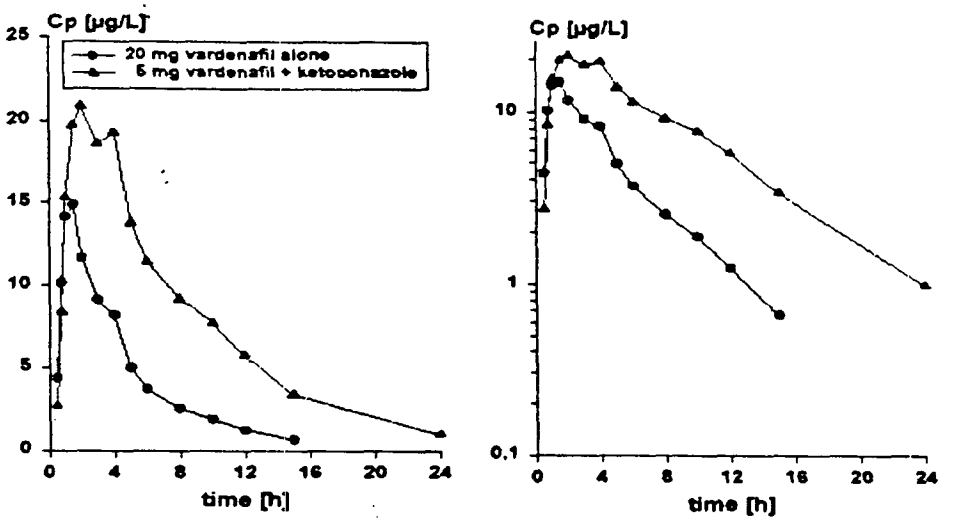


Table 14: Vardenafil and M1- pharmacokinetic parameters/results in plasma following a single oral dose of 5 mg vardenafil tablet with 200 mg ketoconazole and 20 mg vardenafil tablet alone (geo. means/SD; n = 12; Study 10229)

Vardenafil

Parameter	unit	vardenafil (5 mg) + 200 mg ketoconazole	vardenafil (20 mg) alone
AUC	µg*h/L	190 / 1.46	76.3 / 1.71
AUC_{norm}	g*h/L	3171 / 1.44	319 / 1.74
C_{max}	µg/L	25.0 / 1.32	24.6 / 1.76
$C_{max\ norm}$	g/L	418 / 1.26	103 / 1.77
t_{max}[a]	h	1.75	0.75
$t_{½}$	h	4.82 / 1.22	3.89 / 1.20

a) median (range)

M1

parameter	unit	vardenafil (5 mg) + 200 mg ketoconazole	vardenafil (20 mg) alone
AUC	µg*h/L	20.2 / 1.73	48.1 / 1.72
C_{max}	µg/L	1.97 / 1.84	22.6 / 1.93
t_{max}[a]	h	1.50	0.75
$t_{½}$	h	7.48 / 2.11	4.27 / 1.46

a) median (range)

Reviewer's comments:

- There was 10 and 4 fold increases in mean AUC_{norm} and $C_{max,norm}$ of vardenafil respectively following concomitant administration arm as compared to the single 20 mg dose of vardenafil (with ranges of 6 – 20 fold for AUC and 2 – 9 fold for C_{max})

- A trend towards an increase in the half lives of both the parent and the metabolite was observed
- There were higher number of adverse events (eg. headaches) reported for the concomitant drug (with 5 mg vardenafil) arm than the vardenafil (20 mg) alone arm
- The maximal dose of ketoconazole (200 mg BID) was not administered in this study
- Cardio-renal division was notified to assess the QT prolongation results of this study

The sponsor recommends not to exceed the 5 mg (lowest) dose of vardenafil when ketoconazole is administered concomitantly. A 10 fold increased exposure implies that a 5 mg dose being equivalent to a 50 mg vardenafil dose. The highest vardenafil dose studied in this NDA is 80 mg. There is a concern (at least theoretical) that the highest approved ketoconazole dose (200 mg BID) and higher vardenafil doses may lead to even increased exposure scenarios than that observed currently. Based on all the above, this reviewer recommends **not to exceed a ng vardenafil dose in any hour-period when used in conjunction with ketoconazole.**

DDI: Erythromycin

The influence of a pre- and co-treatment of erythromycin (a model CYP 3A4 substrate) on the pharmacokinetics of vardenafil was investigated in 12 healthy male volunteers (age 27 – 48 years) in a randomized, non-blinded, 2-way crossover study (Study 10104). The two treatments were as follows:

- a 20 mg vardenafil tablet given alone on the test day;
- 500 mg of erythromycin (tid given for three days, on day 4 (= test day) 500 mg erythromycin qd together with a 5 mg vardenafil encapsulated tablet

Results:

Table 15. Vardenafil and M1 - pharmacokinetic parameters/results in plasma following a single dose of 20 mg vardenafil tablet alone and 5 mg vardenafil encapsulated tablet with 500 mg tid erythromycin (geo. means/SD; n = 12; Study 10104)

Vardenafil

parameter	unit	vardenafil (20 mg) alone	vardenafil (5 mg) + erythromycin
AUC	µg*h/L	53.0 / 1.65	53.3 / 1.57
AUC_{norm}	g*h/L	204 / 1.74	821 / 1.63
C_{max}	µg/L	16.6 / 1.62	12.9 / 1.58
$C_{max,norm}$	g/L	63.9 / 1.70	199 / 1.63
$t_{½}$	h	3.83 / 1.36	4.62 / 1.29
t_{max}[a]	h	1.0	1.0

a) median (range)

M1

parameter	unit	vardenafil (20 mg) alone	vardenafil (5 mg) + erythromycin
AUC	µg*h/L	31.7 / 1.51	n.c.
C_{max}	µg/L	16.3 / 1.47	17.9 / 2.05
$t_{½}$	h	3.11 / 1.50	nc
t_{max}[a]	h	0.75 (—	1.0 —

a) median (range)
nc = not calculated

Reviewer's comments:

- There was 4 and 3 fold increases in mean AUC_{norm} and $C_{max,norm}$ of vardenafil respectively following concomitant administration as compared to the single 20 mg dose of vardenafil with ranges of 2 – 8 fold for AUC and 1.5 – 6 fold for C_{max}
- AUC and C_{max} values for all metabolites also increased in the range of 2 – 4 folds
- A trend towards an increase in the half life of the parent was observed
- Other than higher incidences of eye-related adverse events, the adverse events reported for the concomitant drug arm was almost similar vardenafil alone arm
- Cardio-renal division was notified to assess the QT prolongation results of this study

Based on the above facts, the sponsor recommends that the 10 mg dose should not be exceeded when administered concomitantly with erythromycin. This reviewer concurs with the sponsor but adds that **the starting dose of vardenafil should be the lowest approved dose.**

DDI: Indinavir

The influence of a pre- and co-treatment of indinavir (a potent CYP 3A4, as representative for the class of protease inhibitors, on the pharmacokinetics of vardenafil was investigated in 18 healthy male volunteers (age 22 - 43 years) in a randomized, non-blinded, 2-way crossover study. Additionally, the influence of vardenafil on the pharmacokinetics of indinavir was investigated (Study 100336). The schedule for the two treatments were as follows:

- 10 mg vardenafil tablet given alone on Day 1;
- 800 mg (2 x 400 mg) indinavir (tid given for six days (day 4 to day 9) alone,
- 800 mg indinavir given together with a 10 mg vardenafil tablet on Day 10

Results: Table 16. Vardenafil and M1 - pharmacokinetic parameters/results in plasma following a single dose of 10 mg vardenafil tablet alone or with 800 mg indinavir (geo. means/SD, ratios of LS means; n = 18; Study 100336

Vardenafil

parameter	unit	vardenafil alone (Day 1)	vardenafil + indinavir (Day 10)	Ratio (Day 10/Day 1) (90 % CI)
AUC	µg*h/L	23.2 / 1.70	377 / 1.46	16.3 —
C_{max}	µg/L	10.2 / 1.85	70.8 / 1.37	6.92 —
$t_{½}$	h	3.03 / 1.25	5.96 / 1.53	1.97 —
t_{max}[a]	h	1.0 —	1.0 —	Not assessed

a) median (range)

M1

Figure 14. Vardenafil - plasma concentration/time data (geo. means) following administration of 10 mg vardenafil tablet + 800 mg indinavir and 10 mg vardenafil tablet alone (n = 18; Study 100336)

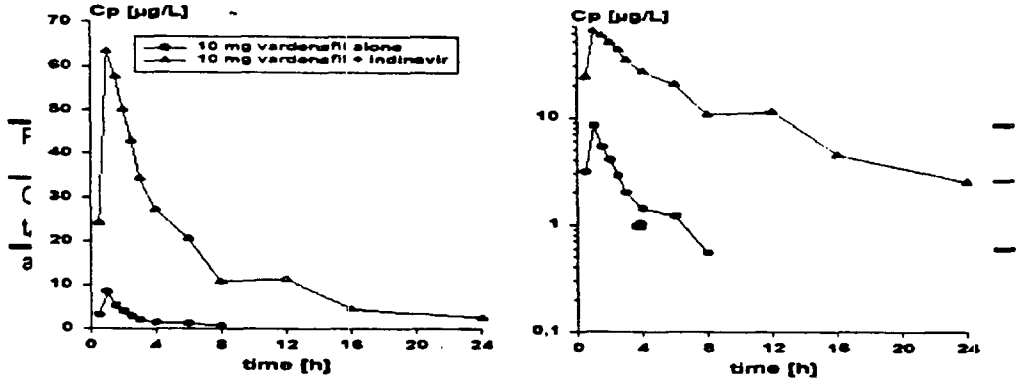


Table 17: Indinavir - pharmacokinetic parameters/results in plasma following a dose of 800 mg indinavir before (Day 9) and during (Day 10) concomitant dosing with 10 mg vardenafil tablet (geo. means/SD, ratios of LS means; n = 18; Study 100336)

parameter	unit	indinavir alone (i)	indinavir + vardenafil (i+v)	ratio, (90% CI) (i + v)/i
AUC_{0-8h}	mg*h/L	16.4 / 1.61	10.9 / 2.34	0.66 (0.45 – 0.99)
C_{max}	mg/L	8.8 / 1.5	5.1 / 2.34	0.58 (0.39 – 0.85)
t_{max} [a]	h	1.0 (	1.0	Not assessed

a) median (range)

Reviewer's comments:

- There was 16 and 7 fold increases in mean AUC and C_{max} of vardenafil respectively following concomitant administration as compared to the single 10 mg dose of vardenafil with ranges of 12 – 21 fold for AUC and 5 – 9 fold for C_{max}
- There was almost a doubling of vardenafil half-life for the combination arm as compared to vardenafil alone
- Due to almost complete metabolic inhibition of vardenafil, the major metabolite levels for M1 was significantly lower following the combination
- Literature suggests a much lower DDI potential between indinavir & viagra (↑4-5 fold in AUC)
- There was a clear and significant increase in the number of adverse events such as headaches, rhitinis and dizziness (0% in Var. arm vs. 29% in Var. + Ind. Arm for dizziness) in the combination arm as compared to vardenafil only
- There was a noticeable reduction in the mean AUC (↓ 30%) and C_{max} (↓ 40%) of indinavir following administration of vardenafil concomitantly – will update vardenafil label on this
- Reduction of indinavir exposure could not be explained by any mechanism known for vardenafil (eg. CYP inducer or affect on indinavir absorption) but probably might be explained by auto-induction of CYP enzymes by indinavir – however this study was not designed to conclusively prove that

- Sponsor does not comment on the QT prolongation potential following this study -- a formal analysis summary on this issue was not found

A 16 fold exposure implies that a 5 mg dose may appear as a 90 mg dose when administered concomitantly with indinavir, a level of exposure *not* covered in this NDA. The sponsor recommends not to exceed the 5 mg (lowest) dose of vardenafil when ketoconazole is administered concomitantly. Based on the above findings this reviewer recommends **a use of a lower (2.5 mg) dose of vardenafil during concomitant administration with indinavir (and similar protease inhibitors which are potent CYP3A4 inhibitors, eg. ritonavir).** Hence, sponsor is urged/encouraged to pursue marketing of the 2.5 mg dosage form (for which clinical safety/efficacy information is currently available).

Studies Showing Minimal Interaction Potential:

Sponsor conducted other metabolic/pharmacokinetic DDI studies showing less concerning results:

Table 18:

Study Number (N)	Interacting (I) Drug & Dose	Vardenafil (V) Dose	Avg. AUC, C_{max}, $t_{1/2}$ ratios for (V+I)/V	Metabolite Interaction	Adverse Events
10050 (N = 12)	Maalox 70 (antacid)	20 mg (single)	0.96, 0.82, 0.93	Not significant	≈ Similar in 2 groups
10052 (N = 12)	Cimetidine (H_2 antagonist) 400 mg BIDx4D	20 mg (single)	1.14, 1.02, 1.08	Not significant	≈ Similar in 2 groups
10052 (N = 12)	Ranitidine (H_2 antagonist) 150 mg BIDx4D	20 mg (single)	0.97, 0.94, 1.10	Not significant	1 severe cases of syncope in V+I arm*

* The Medical Reviewer for this NDA was notified about this case

DDI: Digoxin

Sponsor conducted Study 10105 to study the effect of vardenafil on Digoxin, a narrow therapeutic index cardiac glycoside commonly used drug for heart failure in 20 young healthy male subjects. This was a placebo controlled, 2-way crossover study with the following treatments:

- 0.375 mg of digoxin (-) qd for a total of 28 days, 2 x 14 days per treatment period with no washout period in between
- 20 mg of vardenafil or placebo were taken once daily every other day for a total of 7 days (days 2, 4, 6, 8, 10, 12 and 14)

Results are as follows:

Figure 15. Digoxin - serum concentration/time data (geo. means) on Day 14 (steady state) following a single dose treatment with 0.375 mg digoxin over 14 days alone and coadministered with 20 mg vardenafil tablet qod over 14 days (n = 18, Study 10105)

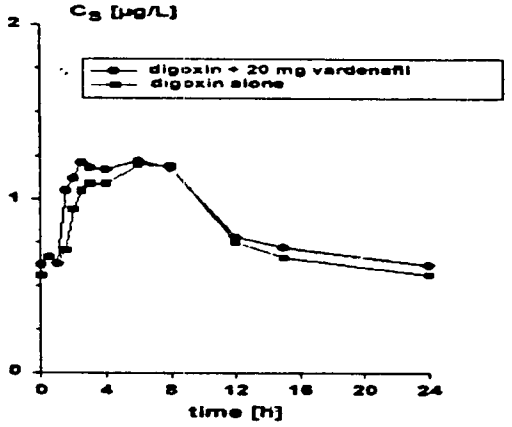


Table 19A: Digoxin - pharmacokinetic parameters/results in serum in steady state after 14 days following multiple doses of 0.375 mg digoxin over 14 days with 20 mg vardenafil tablet or vardenafil placebo every other day (geo. means/SD; n = 18; Study 10105)

parameter	unit	vardenafil + digoxin	vardenafil placebo + digoxin
$AUC_{\tau,ss}$	µg*h/L	17.9 / 1.28	16.5 / 1.31
$C_{trough,ss}$ [c]	µg/L	0.635 / 1.33	0.613 / 1.32
$C_{max,\tau,ss}$	µg/L	1.72 / 1.47	1.45 / 1.37
$t_{max,ss}$ [a]	h	2.0	3.0
CL_R	L/h	10.9 / 1.54	12.0 / 1.40
$Ae_{urt,ss}$ [b]	%	54.3 ± 14.3	54.3 ± 11.4
$Ae_{urt,ss}$ [b]	mg	0.204 ± 0.054	0.204 ± 0.043

a) median (range)
b) arithmetic mean ± SD
c) geometric mean trough level of day 12, 13, and 14

Table 19B: Digoxin - ratio of treatments for $AUC_{\tau,ss}$ and $C_{trough,ss}$ of digoxin (point estimate; 90 % CI)

pharmacokinetic parameter for digoxin	ratio of treatments*100 % vardenafil + digoxin / placebo + digoxin
$AUC_{\tau,ss}$	108.21 % (103.23 % - 113.44 %)
$C_{trough,ss}$	103.50 % (99.63 % - 107.53 %)

Reviewer's comments:

- No change in digoxin PK was observed when administered in combination with vardenafil

- Sponsor assessed the effect of digoxin on vardenafil PK (combination arm) by comparing the parameters with that obtained from another study (under similar conditions) where vardenafil was administered alone– no appreciable differences were observed
- There were significantly more adverse events reported in the vardenafil + digoxin arm than the placebo + digoxin arm of the study

Based on the above information, this reviewer agrees with the sponsor and recommends no dosage adjustments in patients with concomitant administration of digoxin and vardenafil.

DDI: Warfarin

Sponsor conducted Study 10233 to determine the influence of vardenafil on the pharmacokinetics and pharmacodynamics of the oral coumarin anticoagulant warfarin sodium was investigated in 24 healthy male volunteers (age 18 - 45 years) in a randomized, double-blind, 2-way crossover study (Study 10233). The study consisted of three periods: a single warfarin "priming" dose on day –21 and two 6-day treatment phases (Days 0 to 5), separated by a drug-free washout period of 17 days (period of 21 days between consecutive warfarin sodium administrations).

According to randomization, the subjects received either 20 mg of vardenafil or placebo qd for five days (Days 1 until Day 5); 25 mg of warfarin sodium was given once on Day 2 of each period. Pharmacokinetic profiles of R- and S-warfarin, as well as clotting profile (prothrombin time and clotting Factors II, VII and X), were taken for 96 hours after the administration of warfarin sodium (Days 2 to 6); 24-hour pharmacokinetic profiles of vardenafil and its main metabolite M1 were taken after the first intake of vardenafil on Days 1 and 2. Additionally, it was of interest to assess if concomitant intake of vardenafil had any pharmacodynamic effects on the clotting profile (prothrombin time and clotting Factors II, VII and X), taken for 96 hours after administration of warfarin sodium.

Results follow:

Table 20. Summary of pharmacodynamic data during treatment with warfarin sodium and a single dose of 20 mg of vardenafil or matching placebo ($AUC_{0\text{-}96h}$)

Parameter	Warfarin (W) + vardenafil (V)	Warfarin	mean ratio (%) [(W+V)/W alone]
PT (sec*h)	1588.10 ± 1.12	1597.61 ± 1.13	99.6 (97.8 – 101.5)
range			
Factor II (%*h)	5895.58 ± 1.15	5956.03 ± 1.14	98.99 (97.0 – 100.0)
range			
Factor VII (%*h)	4494.29 ± 1.29	4470.68 ± 1.32	99.7 (96.8 – 102.7)
Range			
Factor X (%*h)	5793.57 ± 1.18	5867.47 ± 1.19	98.8 (96.7 – 101.0)
(range)			

Figure 16: Vardenafil - plasma concentration/time data (geo. means) following administration of 20 mg vardenafil tablet alone and together with 25 mg warfarin sodium (n = 23; Study 10233)

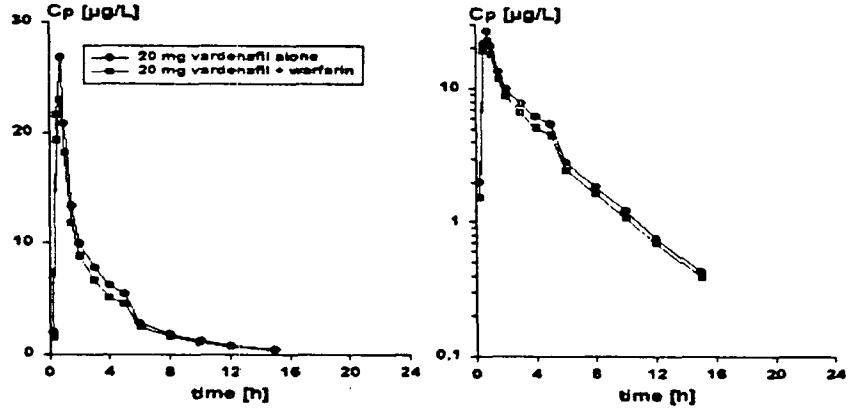


Table 20. Vardenafil & M1 - pharmacokinetic parameters/results in plasma following a single dose of 20 mg vardenafil tablet alone and with 25 mg warfarin sodium (geo. means/SD; n = 23; Study 10233)

Vardenafil

parameter	unit	Vardenafil (day 0)	Vardenafil + warfarin sodium (day 1)
AUC	µg*h/L	73.8 / 1.65	62.7/1.59
C_{max}	µg/L	32.7 / 1.81	26.8/1.59
$t_{½}$	h	4.09 / 1.39	4.17/1.37
t_{max} [a]	h	0.50	0.75

a) median (range)

M1

parameter	unit	Vardenafil (day 0)	Vardenafil + warfarin (day 1)
AUC	µg*h/L	67.0 / 1.53	63.2/1.50
C_{max}	µg/L	38.3 / 1.68	35.2/1.58
$t_{½}$	h	3.19 / 1.56	2.91/1.43
t_{max} [a]	h	0.50	0.75

a) median (range)

Table 21: R– and S– warfarin – pharmacokinetic parameters/results in plasma following a single dose of 25 mg warfarin sodium alone and with 20 mg vardenafil tablet (geo. Means/SD; n = 22; Study 10233)

parameter	unit	placebo + warfarin R-warfarin	vardenafil + warfarin R-warfarin	placebo + warfarin S-warfarin	vardenafil + warfarin S-warfarin
AUC	µg*h/mL	71.5 / 1.23	71.7 / 1.25	44.1 / 1.21	44.2 / 1.21
C_{max}	µg/mL	1.46 / 1.13	1.42 / 1.16	1.49 / 1.15	1.44 / 1.18
$t_{½}$	h	40.1 / 1.22	40.9 / 1.22	28.1 / 1.17	28.8 / 1.16
t_{max} [a]	h	1.50	1.75	1.50	1.75

a) median (range)

Reviewer's comments:

- Results suggest that there is no detectable interaction of vardenafil with warfarin

Based on the above results, there is no requirement of dose adjustment of either drug when used concomitantly.

DDI: Glyburide (glibenclamide)

Since a proportion of the users of this drug will be diabetics on oral hypoglycemic agents (glyburide being a common one), sponsor conducted Study 10112 to address the influence of vardenafil on the pharmacokinetics and pharmacodynamics of concomitantly administered glyburide ——— was investigated in 11 healthy male volunteers (age 24 - 50 years) in a randomized, double-blind (with regard to vardenafil), 2-way crossover study. The two treatments were as follows (Study 10112):

- 3.5 mg of glyburide (glibenclamide) ——— qd together with 20 mg of vardenafil tablet (together with a standardized high-fat breakfast)
- 3.5 mg of glibenclamide ——— qd together with vardenafil placebo (together with a standardized high-fat breakfast)

Based on the PK results in tables and figures (not presented here), it may be concluded that there were no detectable changes in PK parameters of either drug when used in combination. Hence no dose adjustments are necessary.

Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Yes. Due to the mode of action of PDE-5 inhibitors having vasodilating properties (lowering blood pressure with a compensatory increase in heart rate), there is a significant potential of pharmacodynamic drug interactions, which the sponsor evaluated with the following studies:

DDI: Nifedipine

Study 10289 was a randomized, double-blind (with regard to vardenafil), placebo-controlled, 2-way crossover study in 22 male hypertensive patients (age 27 – 65) to determine if there is any additive

effect on the lowering of blood pressure and increasing of heart rate produced by a calcium-channel blocker. The following were the 2 treatment arms in the study:

- Continuous once daily dosing of 30 mg or 60 mg of nifedipine SR (
- Single dose 20 mg of vardenafil or placebo treatment in a random crossover sequence

Following the treatments, the systolic and diastolic blood pressures and heart rates were monitored for each treatment group. The PK of nifedipine with or without concomitant use of vardenafil was also compared. The PK of vardenafil in combination with nifedipine was compared to the parameters obtained from another study when administered alone. Following are the results:

Table 22: Mean maximum changes from baseline in blood pressure and heart rate recorded from 0 up to 4 hours after treatment with 20 mg vardenafil or placebo in men with hypertension taking nifedipine SR (30 or 60 mg / day); (maximal mean ± SD)

Variable	Nifedipine placebo (reference) (Baseline: 0D 00H 00MIN)	Nifedipine BAY 38-9456 (test) (Baseline: 0D 00H 00MIN)	Maximal decrease from baseline (mmHg) [a]	90% CI (mmHg) [b]
Supine DBP (mmHg) Range	79.1 (8.95)	80.5 (9.16)	-5.18	-7.67– -2.69
Supine SBP Range	131 (15.1)	132 (14.2)	-5.87	-8.79 – -2.96
Standing DBP Range	84.0 (10.0)	84.6 (9.73)	-2.68	-5.43 – 0.07
Standing SBP Range	129 (20.7)	130 (14.5)	-5.10	-8.01 – -2.20
Supine HR [c] (/min) Range	67.3 (9.32)	69.1 (8.96)	3.66	0.04 – 7.28
Standing HR [c] (/min) Range	79.6 (10.0)	79.9 (7.75)	3.67	0.64 – 6.69

[a] Point estimate of "test – reference" mean difference from analysis of covariance for the maximal changes
[b] 90% Confidence interval for "test – reference" mean difference from analysis of covariance
[c] For heart rate, maximal increases were calculated

Reviewer's Comments

- Based on the above results, sponsor concludes that the further drop in blood pressure and increase in heart rate from the vardenafil + nifedipine arm as compared to the placebo + nifedipine arm is an additive effect that is expected of the vasodilator vardenafil from previous information, and that there was no synergistic effect
- There does not appear to be significant differences in the ranges of the blood pressures and heart rates when compared between the placebo vs. vardenafil groups in combination with nifedipine – this was also verified following visualizations of individual subject PD-time profiles
- A final decision on the clinical relevance of the above PD findings is deferred to the Medical Officers judgement and review of the above information

- Based on the PK data presented by the sponsor following this study (not included here), there is minimal effect of vardenafil on nifedipine PK (a 7% drop in nifedipine AUC and C_{max})
- Since Nifedipine is a substrate of CYP3A4, sponsor mentions that the inhibitory effects of metabolite M1 on CYP enzymes would have led to increased levels of nifedipine, which was not observed due to a lower concentration of M1 than what is expected from Ki values for observable inhibition – hence, inhibition of M1 is not clinically relevant. However, sponsor may be reminded that this study was *not* designed to typically determine inhibitory effects of M1 on CYP enzymes (this study used a single dose of vardenafil)
- Comparing the PK parameters of vardenafil from the combination arm of this study to that of Study 10119 ('fasted' arm of a food-effect study), there was a slight higher AUC (25%) and C_{max} (16%) of vardenafil seen in this study as compared to Study 10119.
- Although sponsor dose not make the comparison or comment of the reasons, the levels of major metabolite M1 significantly higher from this study as compared to Study 10119 (about 4 fold higher in AUC and 3 fold higher in C_{max}) – no obvious reasons could explain this results from the cross-study comparison

DDI: Alcohol

As above, since vasodilators may enhance/potentiate the PD effects of alcohol, generally all PDE5 inhibitors are studied for the potential of drug-alcohol interaction. Sponsor conducted study 10348 in 12 healthy male subjects (age 26 – 42 years) to study the effect on PD parameters with a randomized, double-blind, placebo-controlled, 3-way crossover study. Subjects received the following treatments:

- 20 mg of vardenafil together with alcohol (0.5 g of absolute alcohol per kg body weight, diluted to 200 ml with orange juice)
- vardenafil placebo together with alcohol (0.5 g of absolute alcohol per kg body weight, diluted to 200 ml with orange juice)
- 20 mg of vardenafil together with alcohol placebo (200 ml of orange juice and 2 drops of absolute alcohol)

Results:

PK of Ethanol

Following the administration of ethanol in either of the two arms of the study, then PK profiles of ethanol were identical with **mean** C_{max} of ethanol reaching above 700 mg/L (0.07 g/dL). The legal limit of alcohol for driving in many US states are 0.08 g/dL. Some of the **individual** plasma levels of ethanol ranged between 0.08 - 0.1 g/dL during 0.5 – 1.0 hour post administration of alcohol (on or above the legal alcohol limit for driving. Hence, there was an adequate exposure of alcohol in the subjects for results of this alcohol-drug interaction study to be deemed valid.

Table 23: Ethanol - pharmacokinetic parameters/results in serum following a single oral dose of 20 mg vardenafil tablet + 0.5 g ethanol/kg body weight and vardenafil placebo + 0.5 g ethanol/kg body weight (geo. means/SD; n = 12; Study 10348)

parameter	unit	0.5 g ethanol/kg bw + 20 mg vardenafil	0.5 g ethanol/kg bw + vardenafil placebo
$AUC_{(0-tn)}$	mg*h/L	1965 / 1.19	1948 / 1.18
C_{max}	mg/L	728 / 1.17	734 / 1.20
t_{max}[a]	h	1.00	0.50
Zero order rate constant	1/h	115 / 1.27	117 / 1.22
f_{rel}	%	100.9	-

a) median (range)

PK of Vardenafil

There were almost no discernable differences in vardenafil or M1 PK parameters when compared between the vardenafil + alcohol active and the vardenafil + placebo alcohol arms (results not presented here).

PD effects

The primary objective of the study was to determine the extent of changes in blood pressure and heart rate when the drug in administered in combination. The following are the findings:

Table 24: Maximum systolic & diastolic blood pressure decrease between baseline and 4 hours after drug administration (mm Hg)

Systolic

Time point	20 mg vardenafil + 0.5g ethanol/kg BW N = 12	vardenafil placebo + 0.5 g ethanol/kg BW N = 12	20 mg vardenafil + ethanol placebo N = 12
Baseline			
Mean ± SD	111.8 ± 6.1	114.2 ± 9.4	114.8 ± 9.8
Median	112	111	115
Max. change from baseline within 4 h			
Mean ± SD	-9.4 ± 6.2	-12.1 ± 7.5	-10.4 ± 6.3
Median	-10.5	-13.0	-8.5
Range			

Diastolic

Time point	20 mg vardenafil + 0.5g ethanol/kg BW N = 12	vardenafil placebo + 0.5 g ethanol/kg BW N = 12	20 mg vardenafil + ethanol placebo N = 12
Baseline			
Mean ± SD	60.8 ± 6.1	59.8 ± 6.4	60.0 ± 9.9
Median	60	59	59
Max. change from baseline within 4 h			
Mean ± SD	-15.3 ± 5.0	-11.5 ± 5.6	-11.3 ± 10.2
Median	-15	-11	-10
Range			

Reviewer's Comments

- Both for systolic and diastolic, there was a clear drop in blood pressure with either the drug or alcohol by itself and both in combination
- For systolic, the drop in pressure was generally similar in all the three groups, and remained almost the same between the vardenafil + placebo alcohol vs. the vardenafil + active alcohol groups
- For diastolic, it appears that either the drug or the alcohol by itself has the same effect on the drop in pressure – both in combination adds to the drop (mean drop of 15 mm of Hg as compared to a 11 mm of Hg drop due to each by itself)
- Looking at the mean ± sd plots on the blood pressure – time plots (below), there does not seem to be much of a trend pointing towards a more significant effect with any group

Table 25. Maximum heart rate increase between baseline and 4 hours after drug administration (bpm)

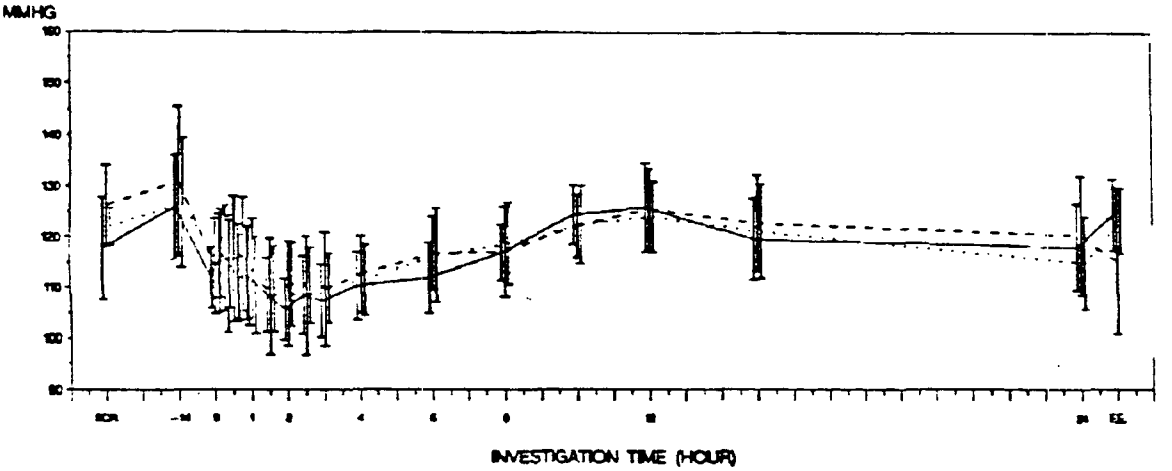
Time point	20 mg vardenafil + 0.5g ethanol/kg BW N = 12	vardenafil placebo + 0.5 g ethanol/kg BW N = 12	20 mg vardenafil + ethanol placebo N = 12
Baseline			
Mean ± SD	55.3 ± 8.8	55.6 ± 8.6	58.0 ± 12.4
Median	53	54	54
Max. change from baseline within 4 h			
Mean ± SD	23.2 ± 9.5	19.8 ± 8.5	11.7 ± 8.0
Median	26	22	13
Range			

Figure 17.

Vital signs – Systolic blood pressure (mmHg)

Subjects valid for safety, N=12

Mean and standard deviation



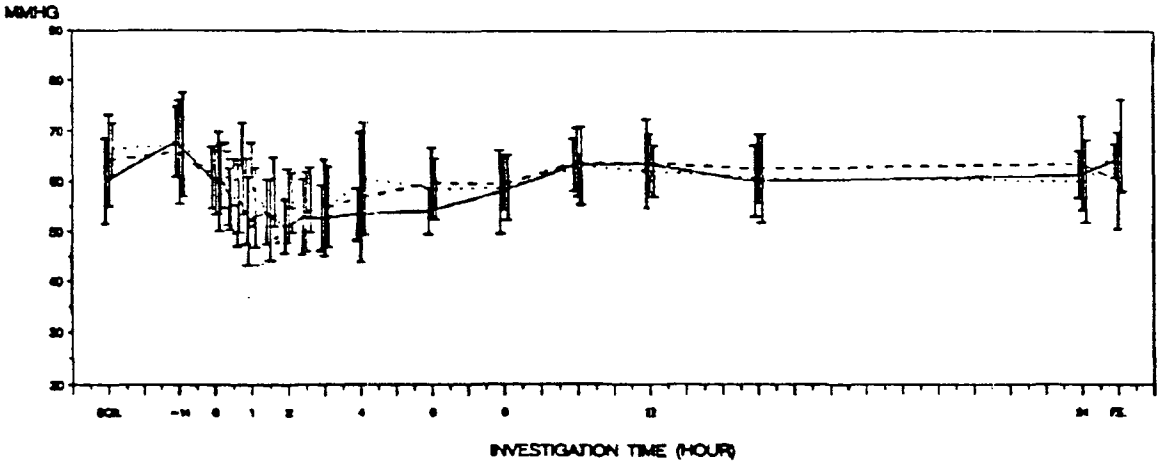
TREATMENT: —— 20MG BAY 38-9456+ALCOHOL-VERUM - - - 20MG BAY 38-9456 PLACEBO+ALCOHOL VERUM
····· 20MG BAY 38-9456+ALCOHOL-PLACEBO

SCR = SCREENING, FE. = FINAL EXAM.

Vital signs – Diastolic blood pressure (mmHg)

Subjects valid for safety, N=12

Mean and standard deviation



TREATMENT: —— 20MG BAY 38-9456+ALCOHOL-VERUM - - - 20MG BAY 38-9456 PLACEBO+ALCOHOL VERUM
····· 20MG BAY 38-9456+ALCOHOL-PLACEBO

SCR = SCREENING, FE. = FINAL EXAM.

Figure 18.

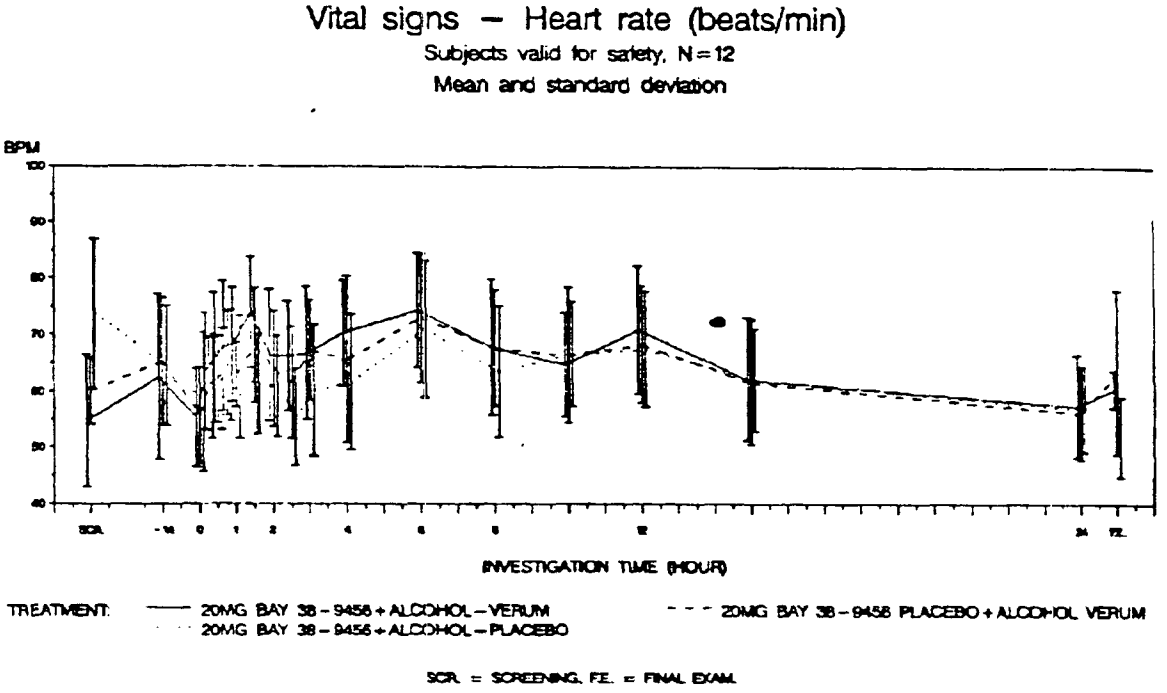


Table 26: Bleeding time (sec) at baseline and changes from baseline at 1 and 4 hours after drug administration

Time point	20 mg vardenafil + ethanol (n = 12)	Vardenafil placebo + ethanol (n = 12)	20 mg vardenafil + ethanol placebo (n = 12)
Baseline			
Mean ± SD	73 ± 26	93 ± 54	74 ± 20
Median	66	78	71
Range		[redacted]	
Change from Baseline after 1 h			
Mean ± SD	15 ± 28	0 ± 36	9 ± 22
Median	10	12	6
Range		[redacted]	
Change from baseline after 4 h			
Mean ± SD	7 ± 25	-24 ± 52	-4 ± 24
Median	4	-8	-4
Range		[redacted]	

Reviewer's Comments

- Alcohol had the highest effect in the increase of heart rate followed by vardenafil
- The two in combination had the maximal increase in heart rate among the three groups (based on comparing the means, medians and ranges among the 3 groups)
- There is no obvious trend in the individual heart rate – time data indicating that no one group was significantly different than the other (presented above in Fig. 18)

- No obvious trend was detectable in Table 26 for bleeding times other than the fact that there might be a prolonging of bleeding time around 1 hour following administration of alcohol and vardenafil

This reviewer does not believe that the interaction of alcohol with vardenafil is very significant, especially considering the fact that an additional alcoholic beverage (than what was used in this study, and which is a very practical scenario) by itself may have more pronounced effects in HR and BP than what was observed in this study.

Overall, there was not a really significant increase in the adverse events observed in the vardenafil + alcohol arm as compared to the vardenafil + placebo alcohol arm. **The significance of all the above PD changes are a clinical judgement, and a final decision on these PD-related issues is, therefore, deferred to the Medical Officer's review**

DDI: Nitroglycerine

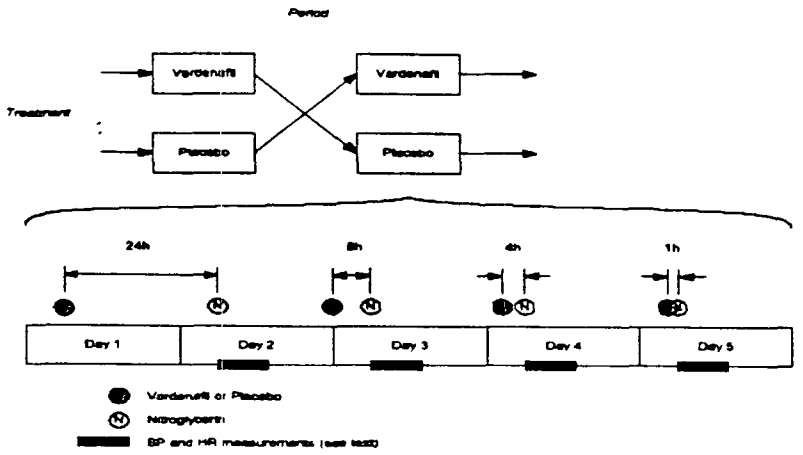
Erectile dysfunction (ED) is a common problem among patients with vascular diseases, eg, hypertension and coronary artery disease (CAD). These patients commonly use PDE-5 inhibitors. Since cGMP is found in cardiac tissue and may be susceptible to inhibition of breakdown by PDE-5 inhibitors, coronary blood flow could be affected by cGMP-mediated vasodilatation and any possible changes in cGMP concentration elicited by PDE-5 inhibitors. The vasodilatation effects of vardenafil may be potentiated by nitrates, particularly when the dose of nitroglycerin is given close to the dosing of the PDE-5 inhibitor. To assess the extent to which blood pressure was lowered and heart rate was increased following a dose of sublingual nitroglycerin (as a representative drug of the class of nitrates) on the background of vardenafil, a study was performed to evaluate the expected potentiation of these pharmacodynamic effects (Study100304).

The study was performed as a randomized, double-blind, placebo-controlled, 2-way crossover study in 18 healthy male subjects (age 40 – 65 years). The doses administered were 10 mg of vardenafil hydrochloride and 0.4 mg sublingual nitroglycerin (NTG) tablets (———). Each study period consisted of 5 in-house days. The subjects received the treatment as follows:

- Day 1: vardenafil or placebo administered at 8 am and NTG given 24 hours later
- Day 3: vardenafil or placebo administered at 12:01 am (just after midnight) and NTG given 8 hours later
- Day 4: vardenafil or placebo administered at 4 am and NTG given 4 hours later
- Day 5: vardenafil or placebo administered at 7 am and NTG given 1 hour later

The design of the study is schematically presented below in Fig. 19

Figure 19. Crossover design of study and relationship of NTG and study drug administration



Results:

Table 27. Effect of vardenafil on the systolic & diastolic blood pressure and heart rate response to NTG (Day 5 - with NTG administered after 1 hour of vardenafil/placebo)

Systolic

Variable	Placebo LS mean	Vardenafil LS mean	Estimate of difference	90%CI
Maximum change in SBP (mmHg) in period 0-60 min	-20.9	-19.2	1.7	-1.5 to 4.8
Change in mean SBP (mmHg) in period 0-60 min	-8.2	-8.9	-0.6	-3.1 to 1.8

Diastolic

Variable	Placebo LS mean	Vardenafil LS mean	Estimate of difference	90%CI
Maximum change in DBP (mmHg) in period 0-60 min	-17.9	-20.1	-2.1	-5.2 to 0.9
Change in mean DBP (mmHg) in period 0-60 min	-7.1	-8.0	-0.9	-2.7 to 0.9

Heart Rate

Variable	Placebo LS mean	Vardenafil LS mean	Estimate of difference	90%CI
Maximum change in HR (bpm) in period 0-60 min	15.6	13.9	-1.7	-4.3 to 0.9
Change in mean HR (bpm) in period 0-60 min	2.6	-0.2	-2.8	-4.7 to -0.9

Reviewer's Comments :

- Although there was a significant drop in systolic and diastolic blood pressure in the vardenafil + NTG arm, the data did not point towards a really significant difference between the placebo and vardenafil arms in the first 60 minutes
- There was no further increase in heart rate with the use of vardenafil as compared to that produce by NTG alone
- A look at the individual data for blood pressure and heart rates do not point towards any trends
- The highest proposed dose of vardenafil (20 mg) was not used in this study

Based on the above results, it may be concluded that there was not a significant PD drug interaction even when NTG was administered 1 hour after a 10 mg vardenafil dose. However, a final decision of the clinical relevance of the above PD changes is deferred to the Medical Officer's review.

Are there any addition PK or PD information relevant to OCPB?

Because of the pharmacology of PDE-5 inhibitors and chemistry, there are a few other studies that the sponsor conducted as follows:

<u>Effect on Bleeding time – Aspirin interaction study with vardenafil</u>

Since there has been evidence that PDE-5 (located also in the platelets) inhibitors may affect the functioning of platelets and hence have an effect on the bleeding time, sponsor conducted Study 100396. This vardenafil - aspirin interaction study was comprised of two phases. The first phase was an open label, non-randomized evaluation of the effect of a single 10 mg dose of vardenafil on bleeding time at 1 and 4 hours after dosing (Day 1). Aspirin (2 x 81 mg) was taken once daily for 7 days, Day 2 through Day 8. The second phase of the study was conducted in a randomized, double blind fashion. Nineteen healthy male subjects (age 18-36 years) were enrolled in this study. The effect of a single 10 mg dose of vardenafil or placebo, administered on the background of low-dose aspirin (162 mg), on bleeding time at 1 hour and 4 hours after dosing (Days 5 and 8) was evaluated.

Results:

Table 28A: Geometric mean (%CV) bleeding time at predose and 1 hour and 4 hours after administration of aspirin and placebo/vardenafil

	Bleeding time, minutes		
	Aspirin and placebo	Aspirin and vardenafil	Geometric LS mean ratio[a] (95% CI)
Predose	7.96 (24%)	7.61 (28%)	
1 hour postdose	8.93 (35%)	9.17 (27%)	1.04 (0.91 – 1.17)
4 hours postdose	8.50 (20%)	9.20 (29%)	1.09 (0.95 – 1.25)

a) Aspirin + vardenafil / aspirin + placebo

Table 28B: Change in bleeding time from predose (in minutes) 1 & 4 hour after administration of aspirin and placebo/vardenafil.

1 Hr

	Aspirin and placebo	Aspirin and vardenafil
Mean ± SD (range)	1.30 ± 3.09	1.59 ± 1.91

4 Hr

	Aspirin and placebo	Aspirin and vardenafil
Mean ± SD (range)	0.49 ± 1.95	1.69 ± 2.94

Sponsor also analyzed the data from phase 1 open label portion of the study:

Table 28C: Geometric mean (%CV) bleeding time at predose and 1 hour and 4 hours after administration of vardenafil on Day 1.

	Bleeding time, minutes	Geometric LS mean ratio[a] (95% CI)
Predose	5.43 (26)	
1 hour postdose	5.63 (28)	1.04 (0.95 – 1.13)
4 hours postdose	5.12 (19)	0.94 (0.86 – 1.03)

a) 1 hour and 4 hours postdose versus predose

Reviewer's Comments

- There is no statistical differences observed between the aspirin + placebo and aspirin + vardenafil arms with respect to change in bleeding times
- Clinical relevance of the differences observed with the change in bleeding times may be debatable and the Medical Officer's review on this should be decisive

Effect on Sperm Motility

Based on some literature evidence that PDE-5 inhibitors might have some effect on sperm motility, sponsor conducted Study 10373 to determine the effect of an acute (single 20 mg dose) exposure of vardenafil on sperm motility and morphology in 16 healthy young males.

The results of this study indicate that other than some variability on both sides, there were no significant changes in the sperm parameters (results not reported here). Whether these changes are clinically significant, or is this single dose study was the correct design for the chosen objective, is a clinical judgement.

Effect on Vision

Based on previous experience with PDE-5 inhibitors showing transient alterations in color vision from high doses, sponsor conducted Study 10197 to determine the effect of a single high (40 mg dose) of vardenafil on retinal function.

The results (not presented here) indicate a mild and transient impairment of color discrimination in the blue-green range (tritane axis) and in the purple range (tetertane axis). The most pronounced differences between the treatments were observed at 1h and 6h after drug administration. There were no differences between the vardenafil and placebo treatment groups at 24 hours. The clinical team review with relevant background should judge the clinical significance of these findings.

Exercise Tolerance Test

ED typically first appears in men over the age of 55 years many of whom may be patients with coronary artery disease (CAD). Since coronary blood flow could be affected by cGMP-mediated vasodilatation, the physical activities during sexual intercourse could potentiate the vasodilatation effects of PDE-5 inhibitors.

Sponsor conducted Study 100302 to assess the safety and tolerability of vardenafil in patients with stable CAD recruiting. Forty-one patients with exertional cardiac ischemia (age 48 – 77 years) were investigated in a randomized, double blind, placebo-controlled, 2-way crossover study to evaluate the pharmacodynamic effects of vardenafil as compared to placebo on the total treadmill time (onset of angina or appearance of ST-segment depression ≥ 1 mm on the ECG between 3 and 10 minutes of exercise). After qualifying for double-blind treatment, patients were given randomized, double-blind crossover treatment of 10 mg vardenafil or placebo with a minimum of 5 days between the 2 crossover treatments. The study drug was administered one hour before the exercise treadmill test (ETT). Results are as follows:

Table 29A. Exercise treadmill completion times, all patients valid per protocol (mean in seconds ± std. dev.)

Parameter	n	10 mg vardenafil	Placebo
Total Treadmill Exercise Time	39	433 ±109	426 ±105
Total Time to Angina Pectoris (first awareness)	34	291 ±123	292 ±110
Total Time to ST-Segment depression of 1 mm or greater change from baseline	31	380 ±108	334 ±108

Table 29B: Analysis of exercise treadmill completion times (all patients valid per protocol)

Parameter	n	Ratio of LS means (vardenafil/placebo)	p-value for difference
Total treadmill exercise time	39	1.015	0.394
Total time to angina pectoris (first awareness)	34	0.976	0.594
Total time to ST-segment depression of 1 mm or greater change from baseline	31	1.155	0.0004

Reviewer's Comments

- The study *did not* use the highest possible dose of vardenafil (i.e. 20 mg)
- There is a high statistically significant increase in the total time to ST-segment depression of 1 min or greater for the vardenafil as compared to placebo – however the clinical relevance of this finding should be determined by the Medical Officer

QT Prolongation

The sponsor attempted to address the issue whether vardenafil is responsible for clinically relevant prolongation of the QT segment of electrocardiograms, a phenomenon that may lead to serious arrhythmia and has been the reason for the market-withdrawal of several drugs in recent times.

In Studies 10010 and 10011, the sponsor determined the heart rate and corresponding QT prolongation following administration of upto 40 mg of vardenafil and presented a formal analysis (to the clinical section of the NDA) to address this safety issue. Additionally, as a routine safety assessment, the sponsor conducted ECG determinations in many of the Phase 1 and 2 studies that they conducted, including the studies designed to assess drug interaction with ketoconazole and erythromycin.

Reviewer's Comments

- Based on the possibly multiples (10 – 16 fold) of vardenafil exposure than normal as seen when the drug was administered with ketoconazole or indinavir, it may be said that the 'worst-case' risk assessment (for QT prolongation) has not been addressed in this NDA (since the sponsor only achieved 2-fold the maximal proposed dose, 20 mg, in their QT studies)
- For Studies 10010 and 10011 where QT prolongation was studied formally, the ECG sampling (recording) was at 2.5 hours following vardenafil administration, clearly beyond the T_{max} ($\approx$ 1 hr)
- The Division of Cardio Renal Drug Products (DCRDP) formally evaluated the QT prolongation issue (as a consult). Based on their review on the QT prolongation potential for vardenafil, there were no particularly significant concerns regarding the arrhythmogenic potential from *commonly anticipated levels/scenarios of vardenafil exposure.*

Biopharmaceutics

Is the proposed to-be-marketed formulation identical to the pivotal clinical trial formulation?

According to the sponsor, the proposed to-be-marketed formulation is *identical* to formulation used in all the Phase 3 studies. Hence, no 'linking' bioequivalence studies were required or conducted.

What are the absolute and relative bioavailabilities?

Sponsor conducted Study 20297 (randomized, non-blinded, 2-way-crossover) to determine the absolute bioavailability after a single 10 mg oral tablet and a 2 mg i.v. administration of vardenafil. Results are below:

Figure 20: Vardenafil - plasma concentration/time data (geo. means) following 10 mg oral tablet and 2 mg iv (n = 12; Study 10297)

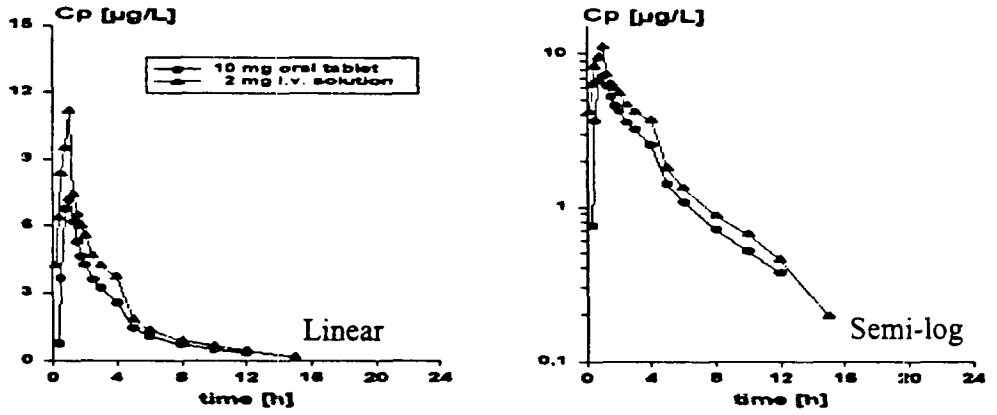


Table 30: Pharmacokinetic parameters in plasma following a single dose of 10 mg vardenafil as oral tablet and 2 mg vardenafil as iv infusion over 1 hour (geo. means/SD; n = 12, Study 10297)

parameter	unit	tablet 10 mg	iv solution 2 mg
AUC	µg*h/L	25.7 / 1.48	35.4 / 1.23
AUC_{norm}	g*h/L	217 / 1.49	1499 / 1.15
C_{max}	µg/L	8.74 / 1.42	11.7 / 1.32
$C_{max,norm}$	g/L	73.9 / 1.48	495 / 1.29
t_{max}	h	0.75 [a]	1.00 [a]
$t_{½}$	h	3.84 / 1.45	3.80 / 1.32
CL/f	L/h	390 / 1.48	-
CL	L/h	-	56.4 / 1.23
V_z/f	L/kg	25.5 / 1.88	-
V_z	L/kg	-	3.65 / 1.32
	L		309 / 1.40
V_{ss}	L/kg	-	2.46 / 1.23
	L		208 / 1.30
F_{abs} [b]	%	14.5	-

a) median (range)
b) geo. mean (range)

Reviewer's comments:

- Absolute BA is around 15% (range 8 – 25 % and 95% CI 12 – 18%)
- Low levels of the detected metabolites following the i.v. administration (results not shown here) confirm that first pass is a major factor in drug degradation
- Clearance of 56 L/h implies that vardenafil is possibly a high extraction drug and the extraction is probably dependent on blood flow
- High values of V_z (309 L) and V_{ss} (208 L) implies that the drug probably distributes into tissues
- In the 2 mg i.v. arm of the study, there were three patients with QTc change from baseline (ΔQTc) between 31 – 60 msec 12 hours post drug administration. Sponsor concluded that this was possibly due to 'circadian rhythm'

- *Relative Bioavailability:* In separate studies, sponsor determined the mean rel. BE of the Phase III tablet to an encapsulated tablet is around 97%, and that for the Phase II tablet to an oral solutions was around 93% (mean). The rel. BA for the encapsulated tablet compared to the oral solution was 83%. The detailed results for these two studies are not presented here.

Is there an effect on food and time of dosing on Vardenafil PK?

In Study 10119, sponsor determined the effect of a standard American breakfast on a single 20 mg oral dose of vardenafil in 12 healthy males. Results follow:

Table 31: Vardenafil PK parameters:

Parameter	Unit	BAY 38-9456 + breakfast N=12	BAY 38-9456 N=12
AUC	µg*h/L	56.7/1.67	62.1/1.82
AUC_{norm}	10^{-3}*kg*h/L	255/1.73	279/1.90
$AUC_{(t_{last})}$	%	3.47/1.62	2.37/1.57
C_{max}	µg/L	11.0/1.55	21.2/1.79
$C_{max,norm}$	10^{-3}*kg/L	49.4/1.60	95.3/1.84
t_{max}*	h	2.75	0.75
$t_{½}$	h	4.57/1.23	4.92/1.26
MRT	h	7.23/1.34	5.04/1.20
V_z/f	L/kg	25.9/1.63	25.5/1.67
CL/f	L/h	353/1.66	322/1.82

*Median (Range)

M1 PK parameters:

Parameter	Unit	BAY 38-9456 + breakfast N=12	BAY 38-9456 N=12
AUC	µg*h/L	11.7/1.56	20.5/1.40
AUC_{norm}	10^{-3}*kg*h/L	55.9/1.60	98.0/1.46
$AUC_{(t_{last})}$	%	12.9/1.35	14.3/1.46
C_{max}	µg/L	3.77/1.43	10.4/1.42
$C_{max,norm}$	10^{-3}*kg/L	18.0/1.42	49.5/1.44
t_{max}*	h	2.75	0.75
$t_{½}$	h	1.82/1.64	3.04/1.44
MRT	h	4.30/1.60	3.32/1.34
V_z/f	L/kg	46.9/1.29	44.8/1.58
CL/f	L/h	1608/1.56	917/1.40

*Median (Range)

Reviewer's comments:

- For vardenafil, there was a significant decrease in C_{max} in the fed state (and increase in T_{max}), critical for the way this drug is going to be used
- Relative bioavailability remain almost similar
- Since a more appreciable effect was observed on M1 (reduction in AUC and C_{max} and an increase in T_{max} in the fed state), it is possible that the GI metabolism of the drug is also affected

Sponsor conducted another Study (#100335) to determine the effect of AM and PM dosing in the fed and fasted state in 23 subjects. This study had 4 arms:

Treatment A: Vardenafil 20 mg administered after an overnight fast (at approximately 8 AM)
Treatment B: Vardenafil 20 mg administered immediately following a high-fat breakfast (at approximately 8 AM; high fat breakfast identical to that in the draft FDA Guidance Document on Food-Effect Bioavailability and Bioequivalence Studies)
Treatment C: Vardenafil 20 mg administered without an evening meal (at approximately 6 PM)
Treatment D: Vardenafil 20 mg administered immediately following a typical evening meal (at approximately 6 PM)

Results: Study 100335

Figure 21.

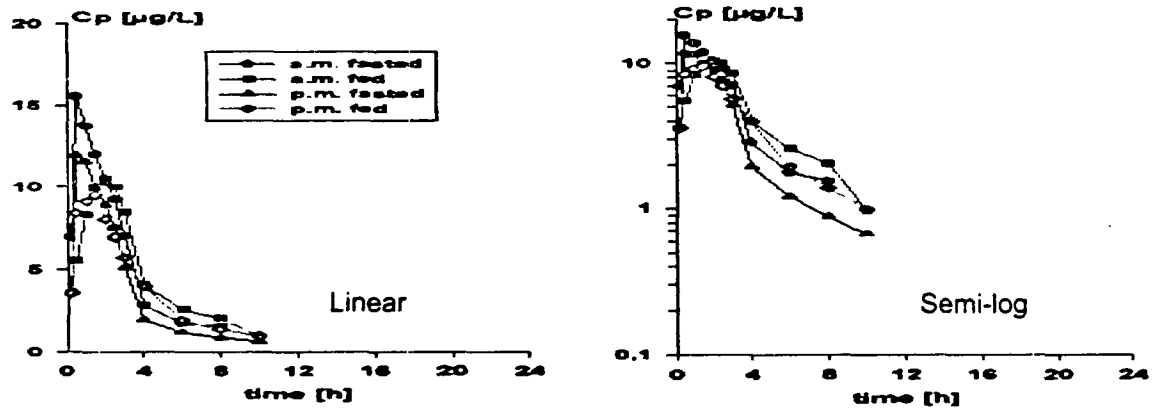


Table 32A: Vardenafil - PK parameters in plasma in the fasted and fed state in the morning & evening following a single dose of 20 mg vardenafil tablet (geo. means/SD; n = 22/24)

parameter	unit	am fasted (n = 22)	am fed (n = 22)	pm fasted (n = 24)	pm fed (n = 24)
AUC	µg*h/L	66.8/1.95	67.1/1.81	52.0/2.06	59.1/1.74
C_{max}	µg*h/L	17.1/1.92	14.0/1.96	14.2/2.02	13.0/1.92
$t_{½}$	h	3.32/1.64	3.30/1.51	3.90/1.93	3.79/1.48
t_{max} [a]	h	1.0 —	2.0 —	1.0 —	1.0 —

a) median (range)

Table 32B: Ratios of geometric LS means and 90% confidence intervals

parameter	am fed/am fasted	pm fed / pm fasted
AUC	1.01 [0.74 – 1.36]	1.14 [0.85 – 1.52]
C_{max}	0.82 [0.61 – 1.11]	0.92 [0.69 – 1.23]

Reviewer's comments:

- The effect of food was more on the C_{max} and T_{max} than on AUC (as in the previous study)
- The effect of food was more pronounced with the AM breakfast than PM evening meal
- Information on the effect of food on vardenafil derived from these two studies will be included in the product label

What are the specifications and methods for dissolution?

This reviewer could not locate any document that summarizes the method for dissolution of the vardenafil tablets, or for the proposed dissolution specifications. However, on discussion with the CMC Reviewer, the following is the opinion of the CMC reviewer:

To: Dhruba J. Chatterjee
From: Jila H. Boal
Subject: NDA 21-400, Dissolution Specification (Release and Stability, and the Acceptance Criteria for Dissolution)
Date: May 6, 2002

The following comments are the chemist's conclusion on the dissolution specification.
The proposed dissolution test method may not be sensitive enough and the dissolution media may have to be changed to a milder pH buffer (——— Also the dissolution acceptance criteria may need to be changed, if the dissolution media is changed.
Here are my thoughts from my review.

Dissolution: This is an immediate release solid oral dosage form. The drug substance as a hydrochloride salt is soluble in aqueous acidic media. A tablet dissolution of [redacted] in 15 minutes in 900 ml of acid media implies Case 1 (highly permeable, highly soluble tablet) according to *"Guidance for Industry, Dissolution Testing of Immediate Release Solid Oral Dosage Forms (Issued 8/1997)"*. Therefore a single point dissolution test at release and stability is sufficient to describe the dissolution specification of the tablets.

Dissolution profile of the tablets used in the phase III clinical trials and the commercial scale tablets are examined in the following media: 0.1 M HCl and buffers of pH 4.5 and pH 6.8.

It is shown (See pages 2-17 of document T.02.40-03) that the dissolution profile in the media of pH 0.1 M HCl and buffer pH 4.5 are similar whereas in buffer pH 6.8 due to the lower solubility of the drug substance no sink conditions are reached in this medium and the dissolution curves do not show complete dissolution within the specified time window.

During scale-up from pilot scale to commercial production scale debossed tablet markings were introduced.
The f_2 values were calculated to be higher than 55, which is within the acceptable criteria of 50-100 as indicated in the "*Guidance for Industry, Dissolution Testing of Immediate Release Solid Oral Dosage Forms*". The value of 55 corresponded to the 5 mg tablets that were tested in buffer pH of 6.8, whereas

the f_2 values for the other strengths were all higher than 70. In addition, the percent coefficient of variation at the 5, 15, 30, 45 and 60 minute time points comply with the FDA guidance, *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*. The recommendation is that the percent coefficients of variation is not more than 20% for the early time points and not more than 10% for the other time points. Therefore, based on this in-vitro dissolution test, the tablets manufactured with and without debossing can be considered to be equivalent (see pages 2-17 of T.02.40-03 document).

The debossing process does not affect tablet dissolution at release. However, the impact of debossing the tablets should be evaluated on tablets at stability (See the discussion on the stability specifications of commercial scale debossed tablets).

The comparability between the debossed commercial tablets and pilot non debossed tablets should be reviewed by the Biopharmaceutics reviewer and is pending.

The dissolution acceptance criteria of Q=[redacted]% at 15 minutes may not be sensitive enough to differentiate the quality attributes of the tablets in future productions. The dissolution rate of Q=[redacted]% at 15 or [redacted] minutes in buffer pH 4.9 might be more discriminatory.

Reviewer's comments:

- Based on review of the 3 different methods (dissolution media) used, this reviewer concurs with the CMC reviewer that the pH = 4.5 medium might be marginally more discriminative than the currently chosen 0.1M HCl medium, however the magnitude of the difference may be practically negligible
- This reviewed concurs with the sponsor that **the dissolution acceptance criteria for this product be Q=[redacted]% @ 15 min**

Analytical

Q. Which moieties have been selected for analysis and why?

Based on information available from the parent and its metabolic fate, vardenafil and its primary metabolite M1 were assayed in most of the studies. In several other studies, two more minor metabolites M4 and M5 were also analyzed.

Q. What bioanalytical methods are used to assess concentrations, and how reliable are the methods?

For the assay of vardenafil and M1, a validated [redacted] method was used following either [redacted] methods for sample preparation. In some assays, particularly which involved M4 and M5, a fluorescence detection method was also used. Inter and Inter-day precision and accuracy values for vardenafil and the 4 metabolites ranged between [redacted]% in plasma, urine and semen. A few rare values in plasma were as high as around [redacted]%. The method was satisfactorily specific and linear. The limit of quantification for vardenafil and M1 ranged mostly between [redacted] µg/L and [redacted] µg/L for most studies (in most of the studies, plasma levels stayed well above [redacted] µg/L for almost all of the time even from the lowest dose). The

sponsor characterized the stability of all biological samples and adequately stored the samples for optimal stability. Overall, the analytical methods/validations were acceptable.

Labeling Comments

Appendix (Pharmacometrics Review)

HE SUN, PH.D. DPE 2

PHARMACOMETRICS REVIEWERS' COMMENTS:

Report Number PH-31238
PPK study 004

Title: Investigation on the population pharmacokinetics and pharmacodynamic/pharmacokinetic relationship of BAY 38-9456, a multi study evaluation using data from studies BYA 38-9456/10128, 100249 and 100250.

A total number of 1028 patients supplying in total 2822 valid concentration measurements were taken in the evaluation. The samples were mostly taken between 4 and 12 weeks of treatment. The majority of the samples were between 0.25 and 0.75 hours and between 1 and 2 hours after dose.

The pharmacokinetics of vardenafil after sparse sampling in patients with erectile dysfunction was best described by a one compartmental model which is mainly due to the fact that most samples were taken within 2 hours after dose thus mostly within the absorption phase. It has to be noted that the $T_{½}$ and AUC/Dose were probably underestimated by applying the one compartment model.

The comedications found to be influencing the exposure (increase AUC) of vardenafil are only the calcium channel blockers and cytochrome 3A4 substrates (independent of specific drug). Whether the influence of comedications is due to the comedications or whether the comedications just acted as surrogates for the underlying disease state of the patient can not be stated. Consider the data distribution, it is not conclusive. Since comedications were not tested in any population evaluation before and some (levothyroxine, amlodipine and atenolol) were only given to a small proportion of the patients, they need to be validated based on data from a different study.

Reviewers comments:

1. *The blood samples were most collected at 0.5 to 2 hours window, thus any pharmacokinetic parameters relating to drug elimination/clearance are not seems can be reliably estimated.*

2. *The covariate analyses for the effect of demographic variables and co-medications on drug clearance therefore also can not be concluded.*

3. *The pharmacodynamic measurements were diastolic blood pressure, heart rate and systolic blood pressure. The change of drug concentration on eractile function was not reported.*

4. *Overall, this population pharmacokinetic analysis provided no additional clinical important information for the product.*

APPEARS THIS WAY
ON ORIGINAL

Report Number PH-30607

Study title: Investigation of the population pharmacokinetics of BAY 38-9456, a multi study evaluation using data from studies 000094, 010006, 010021, 100195, 010036, 010045, 010047, 010010, 010011, 010050, 010052, 100196, 300020 by non-compartment mixed effect modeling.

This report presents a non-compartmental population pharmacokinetic evaluation to determine the effect of c several covariates on the pharmacokinetics of BAY38-7268 (free base of BAY 38-9456). The number of patients in this evaluation was 247 supplying a total of 419 values for AUC. The PK parameters used in this evaluation were AUC, C_{max}, $t_{1/2}$, and t_{max}.

The inclusion of subject specific covariates (demographics, clinical chemistry or vital body parameters) did not result in a large reduction of the inter-subject variability for all pharmacokinetic parameters. Thus although some covariates were detected and the effect of pre-treatment-blood pressure confirmed in an other evaluation, none of them would justify a dose adaptation based on this evaluation.

Reviewer's comments:

1. *The method used in this analysis is a commendable effort.*

2. *It was found that Total Protein and Heart-Rate are major factors affect total drug AUC (i.e. the AUC value differ largely from the low end to the high end of the covariate. See results table). It is unclear how the change in total AUC due to Protein will impact the free drug concentration/clinical outcome (see Leslie Benet, CPT 7(3):115, 2002). The impact of heart rate on drug clearance should be further investigated. Again, the heart rate effect could be confounded by comedications.*

Study review details

Report Number PH-31238
PPK study 004

Title: Investigation on the population pharmacokinetics and pharmacodynamic/pharmacokinetic relationship of BAY 38-9456, a multi study evaluation using data from studies BYA 38-9456/10128, 100249 and 100250.

Objectives

The primary objectives of this study with respect to the pharmacokinetics of vardenafil in patients were:

- to find the structural pharmacokinetic model describing the pharmacokinetics of vardenafil and its variability in the target population

- to evaluate which of the covariates below, estimated at pre-treatment, possibly influence the pharmacokinetics of vardenafil: Demographics: body weight (WGHT, kg), body height (HGHT, cm), age (AGE, years), and race (RACE, 1=Caucasian, 2=black, 3=Asian/Oriental, 4=American Indian, 6=other or not specified, 7=Hispanic).

Materials and Methods

Data of 3 studies (10128, 100249, 100250) were used in this evaluation.

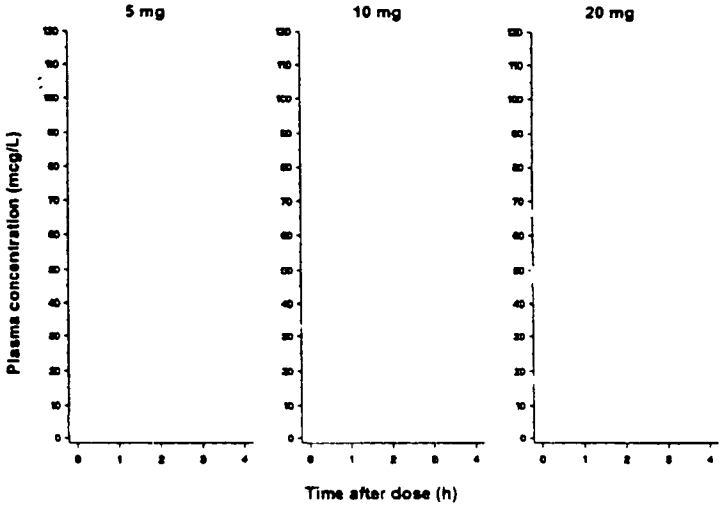
Entries of study medication in the diary on the day of a PK dosing might have been related to a dose taken before a sexual attempt or might be an entry erroneously made by the patient based on the PK dose. Thus the following assumption was made to classify the two possibilities:

> Sponsor's statement "5 hours was assumed to be the interval after the PK sample was taken, in which it was unlikely that sexual activity occurred due to the time spent in the clinic and traveling home afterwards and thus that dose was probably an entry of the clinical dose used to estimate pharmacokinetics."

Reviewer's Comments: Data analyses on co-medication effects with this kind of assumption may prevent its reliability.

A total number of 1028 patients supplying in total 2822 valid concentration measurements were taken in the evaluation. The samples were mostly taken according to protocol after a dose of 5, 10 or 20 mg vardenafil given at the clinical Visit 3 and 4 for the European and Visit 3 and 5 for the North American studies, thus between 4 and 12 weeks of treatment. The majority of the samples were between 0.25 and 0.75 hours and between 1 and 2 hours after dose, see below:

Figure 11-1: Measured concentrations by dose group versus time after dose



Reviewer's comments: With this type of spares sample, the estimation of drug elimination related pharmacokinetic parameters are not reliable. It was noted that the t½ and AUC/Dose were underestimated by applying the one compartment model.

The pharmacokinetics of vardenafil after sparse sampling in patients with erectile dysfunction was best described by a one compartmental model which is mainly due to the fact that most samples were taken within 2 hours after dose thus mostly within the absorption phase. For the estimation of covariates the pre-treatment demographic values were used except for the co-medications and blood pressure that the actual values during the studies were taken.

RESULTS:

Table 1: Pharmacokinetic parameters

Table 1-1: Final Model for the population pharmacokinetics of vardenafil in patients

Parameter (units)	Change in OFV on deletion	Mean population value	Influence of covariate on mean value	95% confidence interval limits lower ; upper	SE/Mean (%)
KA (1/h) intercept		0.9940		0.5420 ; 1.4460	22.7
2nd population group	+ 718.2	1.7600		1.3780 ; 2.1420	10.9
Acetylsalicylic acid comedication	+ 30.7		x 0.6980	0.5726 ; 0.8234	9.0
Serum creatinine (µmol/L)	+ 14.6		- 0.0047 x (SCRE-83.2)	-0.0073 ; -0.0021	27.7
Serum-glutamate-pyruvate-transaminase (U/L)	+ 17.6		+ 0.0084 x (SGPT-27)	0.0012 ; 0.0155	42.7
Atenolol comedication	+ 8.6		x 0.6320	0.4786 ; 0.7854	12.1
Levothyroxine comedication	+ 23.0		x 0.5230	0.3816 ; 0.6644	13.5
Total testosterone (nmol/L)	+ 12.8		- 0.0165 x (TTST-14.5)	-0.0258 ; -0.0072	28.2
V2 (L) 5 mg dose		103.0000		70.0000 ; 136.0000	16.0
10 mg + 20 mg dose	+ 13.0	91.4000		66.8000 ; 116.0000	13.5
Age (Y)	+ 45.1		-0.9170 x (AGE-56.6)	-1.5890 ; -0.2450	36.6
Height (cm)	+ 40.9		1.0800 x (HGHT-176.3)	0.4800 ; 1.6800	27.8
Diuretic comedication	+ 6.7		x 1.1500	0.9782 ; 1.3218	7.5
Diastolic blood pressure (mmHg)	+ 29.2		-0.6650 x (DBP1-81.7)	-1.1030 ; -0.2270	32.9
K (1/h)		0.5300		0.4114 ; 0.6486	11.2
Total bilirubin (mg/dL)	+ 21.7		-0.2880 x (BILI-0.5)	-0.3576 ; -0.2184	12.1
Calcium channel blockers comedication	+ 109.4		x 0.1850	0.1308 ; 0.2392	14.6
Amlodipine comedication	+ 22.0		x 2.9300	1.3680 ; 4.4920	25.7
Cytochrome 3A4 inducing comedication	+ 13.3		x 1.5200	1.1740 ; 1.8660	11.4
ALAG1 (h) intercept	+ 214.3	0.1810		0.1674 ; 0.1946	3.8
2nd population group	+ 205.1	0 fixed			
Location North America	+ 24.1		x 0.8340	0.7906 ; 0.8774	2.6
Cytochrome 3A4 substrate comedication	+ 22.6		x 1.1800	1.0820 ; 1.2780	4.2
Total testosterone (nmol/L)	+ 17.6		-0.0035 x (TTST-14.5)	-0.0061 ; -0.0010	36.4
F1 intercept		0.14 fixed			
2nd population group	+ 45.8	0.2320		0.1622 ; 0.3018	15.0
Fraction of patients belonging on the mean to main population group		0.6580		0.6098 ; 0.7062	3.7
Intersubject variability on					
V2 (ETA1)	+ 16.5	21.6%		12.3288 ; 27.9285	33.7
KA (ETA2) 1st profile	+ 18.1	42.5%		19.4936 ; 56.9210	39.5
KA (ETA3) 2nd profile	+ 49.3	63.5%		40.1248 ; 80.3119	30.0
Constant CV residual error	—	52.5%		48.6004 ; 56.1961	7.2

Table 1-2: Pharmacokinetic parameters geom. mean/geom. SD based on individual (posthoc) estimated values

	1st group	2nd group
Percentage of patient population	65.8%	34.2%
AUC / dose (per 1mg)	2.96/1.41 µg×h/L	5.36/1.57 µg×h/L
C_{max} / dose (per 1mg)	0.70/1.36 µg/L	1.44/1.37 µg/L
Volume of distribution	91.4/1.23 L	90.2/1.27 L
Elimination half life	1.38/1.48 h	1.54/1.70 h
Absorption half life	0.85/1.48 h	1.35/1.64 h
Bioavailability	0.14 (SD n.a.*)	0.23 (SD n.a.*)
Lag time of absorption	0.168/1.16 h	0.00033/31. 5 h
Time of C_{max}	1.60/1.26 h	1.14/1.37 h

*n.a. = not applicable

Even though several covariates (see Table 1) were detected that influenced the pharmacokinetic behavior, none of the covariables found explained the variability of vardenafil pharmacokinetics to a large extent as measured by the reduction in the residual variability. The final model still showed a large residual error of 53 % as well as large within patient variability in the rate of absorption between 42 and 64 %.

Reviewer's comments: Again, this is mostly due to the blood samples are distributed at the early absorption phase. Phase I population pharmacokinetic evaluations showed similar results with a 68% variability in absorption rate, and a residual variability between 23 and 37 %. This residual variability was somewhat lower than that found in this Phase III evaluation, this as a result of more concentration measurements per subjects and thus a better definition of a multi-compartmental pharmacokinetics and more possibilities to include within and between subject error terms.

Note: Vardenafil exhibited a three compartment behavior found in a compartmental population pharmacokinetic evaluation with data from single and multiple dose studies in the dose range from 5 to 80 mg single dose and multiple dose of 40 mg once or twice daily.

Pharmacokinetic parameters after inclusion of data from multiple dose studies were somewhat different from the parameters based on the single dose data alone. In both evaluations a major influence was seen from blood pressure at pre-treatment on the AUC and Cmax and a slight non-linearity at a dose level of 80 mg. Blood pressure changes during treatment had no effects on the pharmacokinetics.

The combined single and multiple dose evaluation showed a positive correlation between body size estimates (ie, weight or calculated amount of fat) and Cmax. Other covariates explained only a minor part of the overall variability. The residual variability was moderate at 25% but the intersubject variability was between 19 and 68 % for the different pharmacokinetic parameters

The number of subjects in this evaluation was limited (n=44). For vardenafil no concentration versus effect relationship was seen for heart rate, blood pressure and QTc.

A non-compartmental population pharmacokinetic evaluation of Phase I data in the dose range from 5 to 80 mg single dose and multiple dose of 40 mg once or twice daily, showed that the inclusion of subject specific covariates (demographics, clinical chemistry or vital body parameters) did not result in a large reduction of the inter-subject variability for all pharmacokinetic parameters (the between subject variability in clearance for example was reduced by only 15% from 45.2% to 38.6%). Thus although some covariates were detected and the effect of pre-treatment blood pressure was confirmed, none of them were of a magnitude justifying a dose adaptation based on this evaluation. The residual variability was 23 % for AUC, 37 % for Cmax, 30 % for t½ and 61 % for Tmax

No clear difference on AUC, Cmax, T½ and Tmax was seen between the Japanese population and other subjects.

Discussion

As described, the samples were mainly taken within 2 hours after dosing and thus most of the patient were still in the absorption phase it was therefore not possible to get estimates for more complex models than the one compartmental model. The T½ as mentioned in Table 11-1 is therefore probably a mixture between distribution and elimination t½. The difference in t½ between the two groups could also be due to the occurrence of a flip/flop effect in which the elimination is faster than the absorption. The model was not always stable with respect to absorption and elimination with a high correlation between the parameters, which is to be expected under a flip-flop effect for at least some of the subjects (1.9 % had a Ka < Ke and thus a slow absorption in both periods and 11.8 % in one of the two periods) and the restrictions in the sampling scheme.

As can be seen from the predicted concentrations versus measured concentrations in the goodness of fit plots, the fit of the final model is showing some model misspecification at high concentrations and a large spread around the line of unity. This could also be due to an insufficient description of the absorption phase or the use of the simple 1 compartmental model. It is likely a combination of both, since Phase I data showed that a more complex compartmental model was appropriate coupled with the fact that a first order absorption model does not sufficiently describe an absorption process which is highly influenced by variations in passage time through the stomach as is the case for the class of high clearance drugs to which vardenafil belongs. This insufficiency of the model is also evident from the rather large residual error of more than 50 %. As mentioned, a multi compartment model was not better (Table 16.4, Runs 1-4 and Runs 6-30) and very unstable with implausible estimates of the pharmacokinetic parameters which was to be expected based on the sampling windows.

As can be seen all the models show no bias but large standard deviations. The final model performs only slightly better in value and standard deviation of the (absolute) prediction error.

Conclusion

The pharmacokinetics of vardenafil after sparse sampling in patients with erectile dysfunction was best described by a one compartmental model which is mainly due to the fact that most samples were taken within 2 hours after dose thus mostly within the absorption phase. It has to be noted that the T½ and AUC/Dose were probably underestimated by applying the one compartment model.

The comedications found to be influencing the exposure (increase AUC) of vardenafil are only the calcium channel blockers and cytochrome 3A4 substrates (independent of specific drug). Whether the influence of comedications is due to the comedications or whether the comedications just acted as surrogates for the underlying disease state of the patient can not be stated. Consider the data distribution, it is not conclusive. However the evaluation of Phase I healthy volunteer data as well as this evaluation in patients clearly showed an influence of blood pressure and body size on AUC and C_{max}. The comedications that were found to have an influence on the pharmacokinetics are mostly intended for the treatment of cardiovascular disease or have an influence on the blood pressure and thus it is postulated that all the observed effects are just surrogates for processes linked to hepatic clearance.

Since comedications were not tested in any population evaluation before and some (levothyroxine, amlodipine and atenolol) were only given to a small proportion of the patients, they need to be validated based on data from a different study.

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Ameeta Parekh
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I concur