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RESEARCH**

APPLICATION NUMBER:
200179Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 200179	Submission Date(s): 08/26/2009; 11/16/2009; 03/02/2010; 05/28/2010
Brand Name	STAXYN
Generic Name	Vardenafil Hydrochloride
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Myong Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology III
OND Division	Division of Reproductive and Urologic Products
Sponsor	Bayer HealthCare Pharmaceuticals
Relevant NDA	021400 [Levitra®]
Submission Type; Review Type	Original NDA; Standard
Formulation; Strength	Orally Disintegrating Tablet (ODT); 10 mg
Indication	Erectile Dysfunction (ED)

As of June 15, 2010, the proposed trade name STAXYN (vardenafil hydrochloride) orally disintegrating tablet has been accepted by the Division of Medication Error Prevention and Analysis (DMEPA). In addition, on June 15, 2010 the sponsor submitted their revised labeling to project manager Ms. Eufrecina Deguia via E-Mail which has been reviewed by the Office of Clinical Pharmacology and found acceptable from a Clinical Pharmacology perspective. There are no other pending issues for this NDA from a Clinical Pharmacology perspective.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200179	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	VARDENAFIL HCL

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/s/

SANDHYA K APPARAJU
06/16/2010

MYONG JIN KIM
06/16/2010

Office of Clinical Pharmacology

Division of Clinical Pharmacology 3

Clinical Pharmacology Team Leader Memorandum

NDA: 200179
Compound: Vardenafil Hydrochloride Orally Disintegrating Tablets
Indication: Treatment of Erectile Dysfunction
Sponsor: Bayer HealthCare Pharmaceuticals Inc.

BACKGROUND:

Vardenafil hydrochloride (HCl) is a phosphodiesterase 5 (PDE5) inhibitor and it is currently approved for the treatment of erectile dysfunction (ED) as a film-coated immediate release (IR) tablets (NDA 021400, Levitra, Approval, 08/19/2003). For most patients, the recommended starting dose of Levitra is 10 mg, taken orally approximately 60 minutes before sexual activity. The dose may be increased to 20 mg or decreased to 5 mg based on efficacy and side effects. The following is the dosing recommendation in specific populations or patients on concomitant medication from the Levitra package insert:

- Geriatrics - A starting dose of 5 mg Levitra should be considered in patients \geq 65 years old.
- Alpha Blockers – Caution is advised for an additive effect on blood pressure. Concomitant treatment should be initiated only if patient is stable on his alpha blocker therapy. In those patients who are stable on alpha-blocker therapy, Levitra should be initiated at a dose of 5 mg (2.5 mg when used concomitantly with certain CYP3A4 inhibitors).
- CYP3A4 Inhibitors – 1) ritonavir - not to exceed a single dose of 2.5 mg Levitra in 72 hours; 2) – indinavir, saquinavir, atazanavir, ketoconazole 400 mg daily, itraconazole 400 mg daily, and clarithromycin – not to exceed a single dose of 2.5 mg Levitra in 24 hours; 3) ketoconazole 200 mg daily, itraconazole 200 mg daily and erythromycin – not to exceed a single dose of 5 mg Levitra in 24 hours
- Hepatic Impairment – 1) no dose adjustment in mild hepatic impairment (Child-Pugh A); 2) a starting dose of 5 mg Levitra is recommended in moderate hepatic impairment (Child-Pugh B), a maximum dose is 10 mg; 3) not evaluated in severe hepatic impairment (Child-Pugh C).
- Renal Impairment – No dose adjustment is required in mild, moderate or severe renal impairment. Levitra has not been evaluated in patients on renal dialysis.

SUMMARY OF CLINICAL PHARAMCOLOGY FINDINGS:

An orally disintegrating tablet (ODT) formulation of vardenafil HCl 10 mg has been developed by the sponsor for the treatment of ED. The proposed recommended dose is one vardenafil ODT tablet taken on-demand approximately 60 minutes before sexual activity.

In this current NDA, 3 Clinical Pharmacology studies in healthy or ED populations were submitted to address the single and multiple dose pharmacokinetics (PK) of vardenafil ODT, effects of food or water intake, effect of age, and relative bioavailability compared to Levitra IR 10 mg. In addition, 2 phase 3 clinical trials were submitted.

This Clinical Pharmacology Team Leader Memorandum will address only the issues related to safe use of vardenafil ODT in geriatrics and patients receiving concurrent vasodilators for hypertension and their relevant labeling sections. Please see the Clinical Pharmacology review by Dr. Sandhya Apparaju for detailed summary of Clinical Pharmacology findings (DARRTS, June 9, 2010).

Exposure of Vardenafil ODT 10 mg in Elderly (≥ 65 years) vs. Young Males (18-45 years) with ED:

- Cmax and AUC in the elderly were 21% and 38% higher, respectively, compared to the young males with ED.

Relative BA of Vardenafil ODT 10 mg Compared to Levitra 10 mg IR:

- Cmax and AUC values of vardenafil following a single dose administration of 10 mg ODT were 15% and 44% higher, respectively, in healthy young male volunteers (18 – 50 years).
- Cmax was lower (8%) and AUC was higher (29%) following a single dose administration of 10 mg ODT in young men with ED (18 – 45 years).

Relevant Findings from the Two Phase 3 Trials (Studies 12093 and 12094, refer to Medical Reviewer’s review by Dr. Donald McNellis):

- Exclusion Criteria include: 1) Resting hypotension with a resting systolic blood pressure of <90 mm Hg, hypertension with a resting systolic blood pressure > 170 mm Hg or a resting diastolic blood pressure > 110 mm Hg; 2) symptomatic postural hypotension within 6 months of Visit 1; 3) subjects taking alpha-blockers.
- Demographic characteristics of the 2 Phase 3 trial population:

	Vardenafil ODT (n=355)
Age Group	n (%)
<45 years	27 (7.6 %)
45 - <65 years	146 (41.1 %)
65 - <75 years	153 (43.1 %)
≥ 75 years	29 (8.2 %)
Age, mean (range)	61.5 (22 – 83)

Relevant Information Related to Geriatrics and Vardenafil ODT From the Previous Communication with Sponsor:

- During the End-of-Phase 2 meeting (4/17/2008), the following comments were conveyed to the sponsor:
 - Sufficient safety data will be needed in the elderly if the 10 mg ODT dose is pursued as the starting dose in this population. Exposure appears to increase with both age and the ODT drug formulation.
 - Include a sufficient number of elderly patients who are over the age of 75 years (ICH-E7). The exploration of a dose less than 10 mg ODT should also be considered for the elderly population.
- Pre-NDA meeting minutes (preliminary comments from 10/1/2008):

- The analysis submitted in the meeting package raises the issue of dizziness occurring in elderly subjects receiving doses greater than 5mg. This rate of dizziness in the elderly diverges from the rate seen in younger patients increasingly with increasing doses. The Division will re-analyze vital signs data from Phase 1 studies previously submitted. The incidence of dizziness and vasodilatory events in elderly subjects from clinical trial results and from post marketing experience will also be a review issue.

COMMENTS:

- In the phase 3 clinical trials, safety of vardenafil ODT 10 mg was assessed in only 29 patients ≥ 75 years of age (8% of the study population).
- In the phase 3 clinical trials, patients with symptomatic hypotension, resting hypotension with a resting systolic blood pressure <90 mm Hg or resting diastolic blood pressure >110 mm Hg were not studied. In addition, patients on alpha-blockers were excluded.
- In the Phase 3 clinical trials, the most common adverse events (seen in $>2\%$ of patients and more frequently than seen in placebo) were: headache, flushing, nasal congestion, dyspepsia, dizziness and back pain (refer to Dr. Donald McNellis' review)
- An age-related increase in dizziness was observed at the Levitra 10 mg and 20 mg dose levels. This increase was particularly notable in the patients ≥ 75 years of age (NDA 21400, refer to Dr. George Benson's review). However, the increase in dizziness with age was not seen in the vardenafil ODT studies (refer to Dr. Donald McNellis's review).
- Cmax and AUC in the elderly were 21% and 38% higher, respectively, compared to the young males with ED.
- Given that vardenafil exposure following a single dose administration of vardenafil HCl ODT 10 mg is higher in the elderly men, the risk for orthostatic hypotension in the elderly men needs to be addressed.

RECOMMENDATION:

NDA 200179 is acceptable from a Clinical Pharmacology perspective with a Post-marketing Requirement.

POST-MARKETING REQUIREMENT:

A drug interaction clinical trial to assess the potential for orthostatic hypotension in elderly men (age 65 – 80) with ED on vardenafil HCl ODT 10 mg whose hypertension is under control with a vasodilator who have been on a stable dose for at least four weeks. The design should be a randomized, double-blind, placebo-controlled, cross-over study stratified by age (n=20 in age 65-69, n=20 in age 70-80) with the following treatments: vardenafil 10 mg ODT or placebo administered concomitantly with a vasodilator. Blood pressure and heart rate should be measured 1 hour prior to administration of vardenafil and hourly for 10 hours following dosing. These measurements should be taken after being supine for 10 minutes, then after sitting for 1 minute, then after standing for 5 minutes.

The sponsor has agreed to conduct the post-marketing clinical trial and proposed the following timetable (June 9, 2010, sequence number 0017):

Final Protocol Submission: within 6 months of NDA approval date
Study Completion Date: within 20 months of NDA approval date
Final Report Submission: within 26 months of NDA approval date

LABELING

- Alpha-Blockers – recommend “In patients taking alpha-blockers, do not initiate vardenafil therapy with TRADEMARK”.
- Under Clinical Studies Experience – recommend to include “approximately 8% (n=29) were ≥ 75 years old”.
- Under Drug Interactions – replace Maalox with “an antacid based on magnesium-aluminum hydroxide”.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200179	ORIG-1	BAYER HEALTHCARE PHARMACEUTICA LS INC	VARDENAFIL HCL
NDA-200179	PMR/PMC-1	BAYER HEALTHCARE PHARMACEUTICA LS INC	VARDENAFIL HCL

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/s/

MYONG JIN KIM
06/11/2010

EDWARD D BASHAW
06/14/2010

Fully support the need for this study.

BIOPHARMACEUTICS REVIEW
Office of New Drugs Quality Assessment

Application No.:	NDA 200-179 (000)	Reviewer: Sandra Suarez Sharp, Ph.D	
Division:	DRUP		
Sponsor:	Bayer Healthcare Pharmaceuticals	Team Leader: Angelica Dorantes, Ph.D	
Trade Name:	(b) (4)	Supervisor: Patrick J. Marroum, Ph.D	
Generic Name:	Vardenafil Hydrochloride (b) (4)	Date Assigned:	April 30, 2010
Indication:	Erectile dysfunction (ED)	Date of Review:	Jun 03, 2010
Formulation/strength	(b) (4) Tablets, 10 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission dates	CDER Stamp Date	Date of informal/Formal Consult	DUE DATE
April 29, 2010	April 30, 2010	April 30, 2010	July 24, 2010
Type of Submission:	Original NDA		
Type of Consult:	Sponsor's response to comments on disintegration specification		

REVIEW SUMMARY:

LEVITRA[®] (vardenafil hydrochloride) 2.5, 5, 10 and 20 mg film-coated tablets were approved by the Agency on Aug 19, 2003 under NDA 21-400 as an oral treatment for ED. The sponsor is proposing a new formulation for vardenafil hydrochloride consisting of an orally disintegrating tablet (orodisperse) for the treatment of ED. This new formulation, (b) (4), contains the equivalent to 10 mg vardenafil and it has been formulated to rapidly disintegrate in the mouth. The recommended starting dose of Levitra (film-coated tablets) or (b) (4) (also referred in this document as (b) (4)) is 10 mg taken orally.

Disintegration testing is being proposed in lieu of dissolution as the quality control test of the orodisperse tablets. During the review of this NDA a different disintegration specification was recommended for (b) (4) (refer to Dr. Suarez's review of the original submission of this NDA entered in DARRTS on April 22, 2010). Thus, the following comment was conveyed to the sponsor on April 24, 2010:

- The data provided in your submission dated Dec 8, 2009, indicate that disintegration testing is appropriate to discriminate changes in the process parameters or manufacturing conditions of (b) (4) Tablets, 10 mg. Specifically, disintegration values of (b) (4) seconds were observed for (b) (4) tables under (b) (4) compared to (b) (4) seconds under normal manufacturing conditions. Therefore, to ensure consistent quality of the drug product, we recommend the following disintegration specification for both, shelf-life and product release.

Test	Specification	
	Shelf-life	Product Release
Disintegration	(b) (4)	(b) (4)

On April 30, 2010 the Agency received a communication from the sponsor stating the acceptability of the proposed disintegration specification.

RECOMMENDATION:

The ONDQA/biopharmaceutics team has reviewed the submission sent to NDA 200-179 (000) on April 30, 2010. The sponsor has accepted the following disintegration specification recommended by the Agency:

Test	Specification	
Disintegration	Shelf-life	Product Release
	(b) (4)	

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: JDavis, ADorantes, JSalemme, Dchristner, MJRhee

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200179	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	VARDENAFIL HCL

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/s/

SANDRA SUAREZ
06/08/2010

PATRICK J MARROUM
06/09/2010

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 200179	Submission Date(s): 08/26/2009; 11/16/2009; 03/02/2010; 05/28/2010
Brand Name	Pending
Generic Name	Vardenafil Hydrochloride
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Myong Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology III
OND Division	Division of Reproductive and Urologic Products
Sponsor	Bayer HealthCare Pharmaceuticals
Relevant NDA	021400 [Levitra®]
Submission Type; Review Type	Original NDA; Standard
Formulation; Strength	Orally Disintegrating Tablet (ODT); 10 mg
Indication	Erectile Dysfunction (ED)

An optional inter-divisional level OCP briefing was held for NDA 200179 on April 21, 2010 from 3-4 PM in White Oak Building 51, Conference room 3300. Attendees included Drs' Shiew Mei Huang, Dennis Bashaw, Hae Young Ahn, Myong Jin Kim, Suresh Kaul, Donald McNellis, John Lazor, Kellie Reynolds, Darrell Abernethy, Hyunjin Kim, LaiMing Lee, Chongwoo yu, Yangmee Shin and Sandhya Apparaju.

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1 Executive Summary

1.1 Recommendation: Division of Clinical Pharmacology III, Office of Clinical Pharmacology finds the Clinical Pharmacology and Biopharmaceutics information submitted in NDA 200179 [Vardenafil Orally Disintegrating Tablet 10 mg] to be acceptable. The Clinical Pharmacology-relevant labeling language has been agreed upon and is found to be acceptable as well.

1.2 Phase IV Commitments: None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

- Vardenafil Hydrochloride (HCl) is a phosphodiesterase type-5 (PDE5) inhibitor drug approved as film-coated immediate release (IR) tablets for the treatment of Erectile Dysfunction (ED) [NDA 021400, Levitra; Approval: August 2003]. As approved, Levitra IR is available in 2.5 mg, 5 mg, 10 mg and 20 mg strengths. The starting dose for most ED patients is 10 mg, with an option to increase the dose to 20 mg or decrease it to 5 mg for effectiveness or safety reasons. The 2.5 mg strength is used when dosing with certain potent CYP3A4 inhibitor drugs.
- An orally disintegrating tablet (orodispersible; ODT) 10 mg formulation of Vardenafil has been developed by Bayer to extend the product line and is the subject of this NDA 200179. The proposed recommended dose is one 10 mg ODT taken on-demand (p.r.n.) approximately 1 hour prior to sexual activity, not exceeding one dose over a 24-hour period. The tablet is intended for placement on the tongue where it disintegrates and dissolves in the salivary fluid, which is then swallowed. Dose should be taken without water.
- Three Clinical Pharmacology studies (#12769, #13396, #12093 (PK sub-study)) in healthy and ED populations evaluated single and multiple dose PK, food-effect, effect of concomitant water intake and age effect on systemic PK of vardenafil and its major metabolite M1. A mechanistic study 10021 evaluated the potential for absorption directly via the oral mucosa.
- The clinical and to-be-marketed formulations of Vardenafil ODT were identical.
- The development program included two phase 3 clinical trials (# 12093 and #12094) in ED patients to evaluate safety and efficacy of the 10 mg ODT formulation. The Bioanalytical methods used in the analyses of vardenafil and its metabolite M1 in the NDA were adequately validated.
- In healthy male volunteers (18-50 years), the C_{max} and AUC of vardenafil following a single dose administration of 10 mg ODT formulation was greater compared to Levitra 10 mg IR by 15 % and 44 %, respectively. In target ED patients 18-45 years of age, the C_{max} was somewhat lower (8 %) and AUC was greater by 29 % relative to IR. The T_{1/2} values were comparable across treatments (mean of ~4 hours) and T_{max} (median of 1.5 hours) was prolonged with the ODT formulation relative to IR (median of 0.75 hours). Once daily dosing of 10 mg ODT for ten days did not result in significant accumulation of vardenafil. T_{1/2} was unchanged with daily doses.
- Similar to the approved 10 mg IR formulation, elderly ED patients (≥ 65 years) had higher systemic exposure and longer T_{1/2} values of vardenafil and its

- metabolite M1 (activity 25 % that of vardenafil) compared to younger patients (18-45 years). For the 10 mg ODT formulation, the C_{max} and AUC estimates in the elderly were higher by 21 % and 38 % respectively, compared to the younger patients. For the metabolite M1, with the ODT formulation, the elderly patients had 40 % and 19 % increase respectively in C_{max} and AUC values following single dose administration, compared to younger patients.
- For the ODT formulation, food intake (high fat, high calorie) reduced the C_{max} of vardenafil by ~ 35 % while the AUC of vardenafil was not significantly affected. T_{max} was not altered with food. The major metabolite M1 had significantly lower C_{max} and AUC (~ 50 % and 32 % lower on average) in presence of food. In the phase 3 clinical trials of the ODT formulation, dosing was done on-demand without regard to food and thus ODT will be labeled for dosing irrespective of food intake.
 - The systemic exposure (AUC) of vardenafil from the ODT formulation was decreased by 29 % when dose was swallowed with water. Clinical trials for the ODT formulation were conducted without water. Thus the labeling will indicate that the dose should be administered without water.
 - Intrinsic and Extrinsic factors: Based on Clinical Pharmacology studies conducted for the approval of Levitra IR [NDA 21400] and the dose adjustments currently in place, sponsor recommends the following for Vardenafil ODT use which are acceptable per this reviewer's assessment:
 - Renal impairment: No dose adjustment for mild to severe renal impairment. Not recommended for use in renal dialysis.
 - Hepatic impairment: No dose adjustment for mild hepatic impairment. Not recommended for use in moderate to severe hepatic impairment.
 - Use with moderate to potent CYP3A4 inhibitors: not recommended
 - Dosing in geriatric patients (≥ 65 years): Sponsor proposes that the ODT formulation is safe for use in elderly and that no dosage adjustment is needed. The current labeling for Levitra IR notes that due to a potential for higher systemic exposure, a lower starting dose of 5 mg should be 'considered' in the elderly. Due to supra-bioavailability of the ODT relative to 10 mg IR (29 % in ED patients) and due to higher exposure potential with age (38 % higher AUC in ≥ 65 year old patients), it is estimated that compared to younger patients receiving the 10 mg approved IR formulation, elderly patients receiving 10 mg ODT formulation may have ~ 67 % higher AUC of vardenafil; when comparing to younger patients receiving ODT, elderly on ODT may experience ~ 38 % higher AUC; compared to elderly currently receiving 10 mg IR, elderly on 10 mg ODT may see ~ 20 % higher exposure.
 - In the two phase 3 clinical trials for TRADENAME, sponsor has prospectively enrolled ~ 52 % elderly patients (43 % patients ≥ 65 to < 75 years and 9 % patients ≥ 75 years) in order to obtain adequate safety and efficacy information for this population. In these studies elderly patients did not experience a greater frequency of adverse events with the ODT formulation use. Reviewer therefore finds the sponsor's proposal for geriatric use of the ODT to be reasonable as available data indicate acceptable safety of the 10 mg ODT formulation in elderly ED patients (≥ 65 years).

2 Question-Based Review

2.1 General Attributes

2.1.1. What is the relevant regulatory history for the proposed drug product?

- Vardenafil is a PDE5 inhibitor drug approved as film-coated IR tablets for the treatment of ED [NDA 021400, Levitra®; Approval: August 2003].
- The efficacy, safety, and tolerability for vardenafil (as IR tablets) have been shown for dose ranges from 2.5 mg to 20 mg by data from randomized clinical studies and post marketing experience. The approved starting dose of Levitra is 10 mg taken on-demand approximately 1 hour prior to sexual activity (not exceeding one dose during a 24-hour period). Dose can be decreased to 5 mg or increased to 20 mg for reasons of safety or effectiveness. An additional strength of 2.5 mg is marketed in the U.S. for use in presence of potent CYP3A4 inhibitor drugs.
- An orally disintegrating tablet (orodispersible; ODT) formulation of Vardenafil has been developed by the same sponsor and is the subject of this NDA 200179.
- The objective of the development program is to develop a vardenafil formulation that allows discreet intake without water thus potentially improving convenience to the patients. The ED patient places the ODT tablet on the tongue, where it disintegrates in the available salivary fluid and the resulting solution is swallowed.
- The proposed ODT formulation involves single dose strength of 10 mg.

2.1.2. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Drug Substance: Vardenafil HCl Trihydrate (b) (4)

- Vardenafil HCl trihydrate (b) (4) is a white to slightly brown or yellow solid substance. Its chemical name is 2-[2-Ethoxy-5-(4-ethyl-piperazine-1-sulfonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f] [1,2,4]triazin-4-one monohydrochloride trihydrate. The drug substance is an achiral compound.

Structural formula

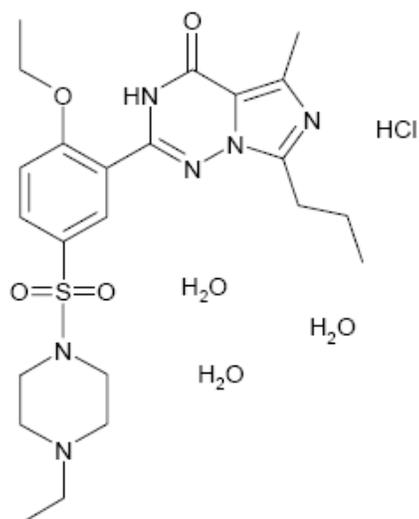


Figure 1: Structural formula for Vardenafil HCl.

- The molecular formula of the drug substance is $C_{23}H_{32}N_6O_4S \cdot HCl \cdot 3H_2O$; its molecular weight is 579.1 g/mole.
- The solubility of vardenafil HCl trihydrate (b) (4) in water at 25°C is 0.11 mg/mL. Vardenafil HCl trihydrate has an aqueous solubility high enough to dissolve the 10 mg dose strength in less than 250 mL water, 0.1 M HCl or phosphate buffers up to pH 4.5 (37 °C). Solubility is, however, pH dependent and decreases significantly at neutral pH.

Drug Product

- Vardenafil HCl ODT 10 mg is presented as a white, round, biconvex, (b) (4) unmarked tablet of a diameter of 9 mm and a radius of curvature of 15 mm. The tablet weight is 180 mg. Each tablet contains 11.85 mg of vardenafil HCl trihydrate (b) (4) corresponding to 10.0 mg vardenafil.
- The composition of Vardenafil HCl ODT 10 mg is listed together with the function of each component:

Table 1: Composition of Vardenafil ODT formulation (10 mg)

Composition	Reference to standard	Function	Amount [mg]
Drug substance			
Vardenafil hydrochloride trihydrate micronized specification		drug substance	11.85 ^a
Excipients			
Aspartame	Ph. Eur., NF specification ^b	(b) (4)	(b) (4)
Flavor peppermint	Ph. Eur., NF, Ph. Jap. specification	(b) (4)	(b) (4)
Magnesium stearate			
Pharmaburst B2 ^c consisting of:			
Crospovidone	Ph. Eur., NF		- ^c
Mannitol	Ph. Eur., USP		- ^c
Silica colloidal hydrated	Ph. Eur., NF		- ^c
Sorbitol	Ph. Eur., NF		- ^c
Weight			180.00

a corresponding to 10.0 mg vardenafil

b components of flavor peppermint are of Ph. Eur., FCC and BP quality

c exact specification of the commercially available blend Pharmaburst™ B2 is stated in the composition of (b) (4)

2.1.3. What are the proposed mechanism(s) of action and therapeutic indication(s)?

- Vardenafil ODT formulation is indicated for use in the treatment of ED. ED is multifactorial in etiology and frequently involves interplay of both psychological and organic factors.
- The mechanism of action of PDE5 inhibitors such as vardenafil is the inhibition of cGMP-specific PDE5, an enzyme responsible for the degradation of cGMP in the corpus cavernosum. Inhibition of this enzyme causes increased concentrations of cGMP, which in turn enhances smooth muscle relaxation and hence the erectile response.

2.1.4. What are the proposed dosage(s) and route(s) of administration?

- Vardenafil ODT formulation will be made available as a single 10 mg dose strength.
- The recommended dose in ED is one 10 mg ODT taken on-demand (p.r.n.) approximately 1 hour prior to sexual activity, not exceeding one dose over a 24-hour period.
- The tablet is intended for placement on the tongue where it disintegrates and dissolves in the salivary fluid, and the resulting liquid is then swallowed. Dose should be taken without water (i.e. not to be swallowed intact with water).
- Vardenafil ODT can be taken without regard to meals. Two controlled phase 3 clinical trials were conducted with the 10 mg ODT formulation and dosing was on-demand irrespective of meals. In addition, a food-effect study demonstrated 35 % decrease in vardenafil C_{max} and no significant change in AUC with food.
- As the ODT formulation is available only in a single 10 mg dose strength, for patients requiring lower or higher doses of vardenafil, physicians may need to prescribe the approved IR formulation. The ODT formulation is not scored.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The Clinical and Clinical Pharmacology program for the development of Vardenafil ODT included the following studies:

Clinical Pharmacology studies:

- Study 12769 [PH-35349]: Randomized, open-label, four-fold crossover study to investigate the effect of a high fat, high calorie breakfast and of water, respectively, on 10 mg vardenafil oral disintegrating tablet in comparison to one 10 mg commercial tablet in healthy, male subjects.
 - Study included 16 subjects (n = 13 with PK data) 18-45 years of age and is the primary source of information pertaining to the effect of food and effect of water intake with respect to ODT dosing.
 - Study also assessed the concentrations of M1, the major metabolite of vardenafil, reported to have PDE5 inhibitor activity approximately 28 % of that of vardenafil itself.
- Study 13396 [PH-35868]: Open-label, age-stratified group-comparison study to investigate the pharmacokinetics, safety and tolerability of multiple once daily doses of 10 mg vardenafil orodispersible tablet preceded by one single dose of 10 mg commercial tablet in young and elderly male patients with erectile dysfunction.
 - Study compared PK of the ODT in relation to the IR tablet across the age categories including < 45 years, 45-64 years and \geq 65 years. Study included 36 patients and is the primary source of PK comparisons across the < 45 vs. \geq 65 years age groups of ED patients (n = 14 per group) as well as the multiple dose PK of Vardenafil ODT.
- Study 10021 [PH 29915]: Randomized, non-blind, two-fold crossover study to investigate the absorption and relative bioavailability of BAY 38-9456 solution after single sublingual dosing of 10 mg in young healthy male subjects.
 - This was a mechanistic study evaluating the absorption of vardenafil via the sublingual route. Information is useful in explaining the observed supra-bioavailability of vardenafil from the ODT formulation.

Clinical studies:

- Study 12093 [A44851]: Pivotal phase III trial to investigate the efficacy and safety of an orodispersible tablet vardenafil versus placebo in the treatment of men with erectile dysfunction (ED)- a fixed-dose, double-blind, randomized multi-center trial- POTENT I.

- The primary objective of this study was to compare the efficacy and safety of vardenafil ODT 10 mg (PRN) after 12 weeks of treatment in a general population of men with ED (> 18 years). In this study, approximately 50% of the men on active treatment were 65 years-of-age or older. 362 patients were randomized (186 to the vardenafil 10 mg ODT, and 176 to the placebo).
- Study included a 24 patient PK sub-study. After the completion of the double-blind period and at least 48 hours after the last dose patients who were enrolled in the sub-study were given a single dose of vardenafil ODT under fasted conditions, without water. Single dose PK data for parent and M1 metabolite were obtained in the younger and elderly ED patients.
- Study 12094 [A45684]: Pivotal phase III trial to investigate the efficacy and safety of an orodispersible tablet vardenafil versus placebo in the treatment of men with erectile dysfunction (ED) – a fixed-dose, double-blind, randomized multi-center trial–POTENT II;
 - Study was identical to 12093 with the exception of not having a PK sub-group.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

- The primary efficacy outcomes evaluated in the two phase 3 clinical trials were:
 - (1) the erectile function domain scores of the international index of erectile function tool (IIEF-EF) at Visit 4 (Week 12);
 - (2) the response to the sexual encounter profile question # 2 (SEP2) related to the success rates of penetration at Visit 4 (Week 12) and
 - (3) the response to the sexual encounter profile question related to maintenance of erection (SEP 3) at Visit 4 (Week 12).

These endpoints are globally accepted standards and regulatory requirements for assessing ED drugs.
- The IIEF used in the two phase 3 trials is a multi-dimensional, self-report questionnaire that is standard for the assessment of male sexual function with 5 domains covering “erectile function,” “orgasmic function,” “sexual desire,” “intercourse satisfaction,” and “overall satisfaction.” The Erectile Function (EF) domain from the IIEF is comprised of items 1 to 5 and 15.
- Other secondary efficacy parameters evaluated include
 - Percentage of subjects achieving “back to normal” erectile function (IIEF-EF \geq 26) at Visit 4 (Week 12) or LOCF.
 - All diary questions other than SEP 2 and 3 that concern erectile function that were assessed over the entire treatment period.
 - Number of sexual attempts under medication till first successful attempt (SEP 3).

- The Treatment Satisfaction Scale (TSS); to be administered at the randomization visit and the final visit (or at Premature Discontinuation)
- A Global Assessment Question (GAQ) to be administered at the final visit only (or at Premature Discontinuation).

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

- Yes. Vardenafil and metabolite (M1) concentrations were determined using adequately validated LC-MS/MS methods. Based on the validation reports included in the submission and based upon the acceptable accuracy and precision for calibrators and quality-control samples analyzed concurrently with study samples, the reported concentrations for vardenafil and the M1 metabolite in the clinical studies were found to be valid for further evaluation.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy and safety?

- The clinical development program for NDA 200179 included only one dose strength (10 mg) of the ODT formulation. Hence no new dose-response information has been obtained from the new NDA.
- In the Clinical Pharmacology review of the original NDA [021400], reviewer notes the following about dose-response relationships for safety and efficacy:
 - [In the phase III clinical trials] “while all the three 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 diabetes (study 100250) there was a marginal higher efficacy with the 20 mg dose compared to the 10 mg”.
 - “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”

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

Note: From the Clinical Pharmacology review of NDA 21400 [07/23/2002]

2.2.5 What are the PK characteristics of the drug and its major metabolite?

Pharmacokinetic results in healthy male volunteers:

Study 12769: Single dose PK of vardenafil and its active M1 metabolite were evaluated as part of study 12769 in n = 13 healthy male subjects (18-50 years). The M1 metabolite is reported to have ~ 28 % of the pharmacological activity of parent vardenafil. Subjects in this study received the following 4 treatments in a randomized manner, separated by wash-out duration of 5 days between treatments:

Treatment 1: 10 mg ODT; without water; fasting (reference)

Treatment 2: 10 mg ODT; without water; 30 min after breakfast (Test 1)

Treatment 3: 10 mg ODT; with 180 mL water; fasting (Test 2)

Treatment 4: 10 mg IR Levitra tablet; with 180 mL water; fasting (Comparator)

The PK of vardenafil and its M1 metabolite in healthy males from the ODT alone group (Trt 1; administered without water) are summarized below. The other treatment groups are discussed under relevant sections of this review.

Results:

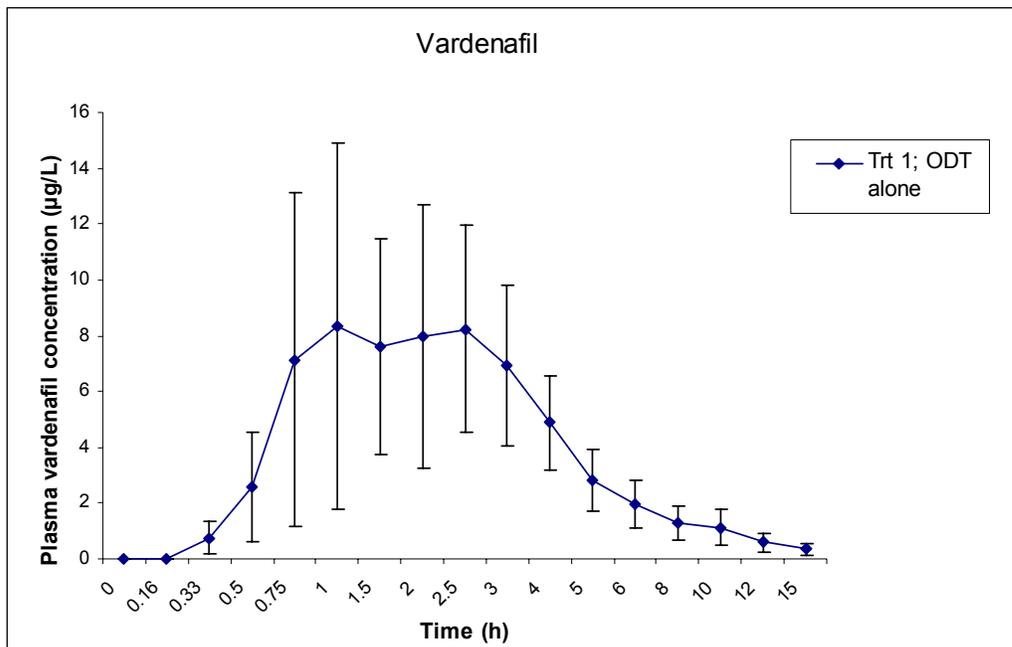


Figure 2: Plasma concentration-time profiles for vardenafil from the ODT formulation. Data shown is arithmetic mean \pm standard deviation values from n= 13 volunteers.

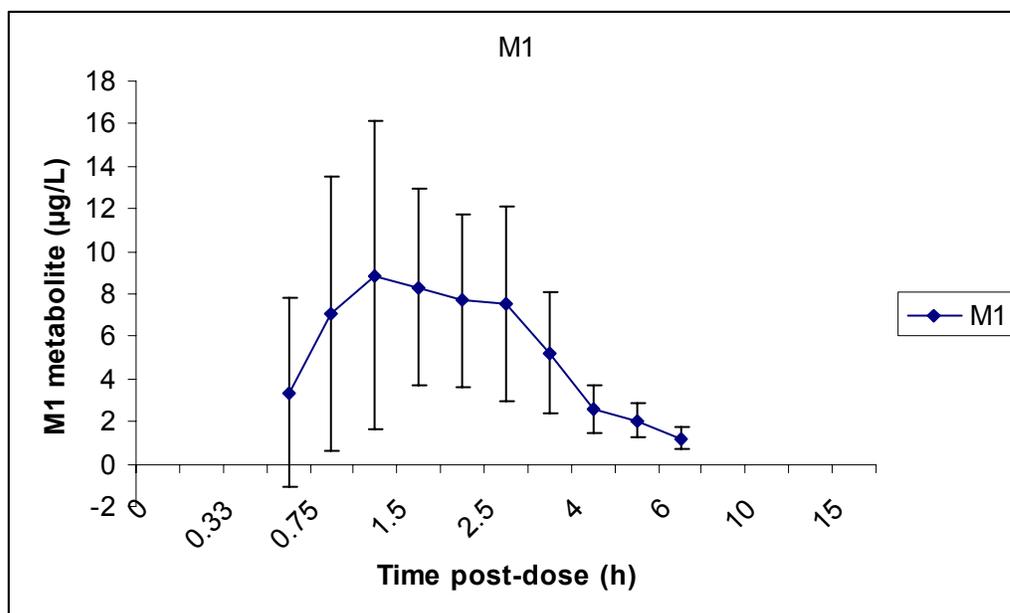


Figure 3: Plasma concentration-time profiles for M1 metabolite from the 10 mg ODT use; data shown is arithmetic mean \pm standard deviation values from n= 13 volunteers.

The plasma PK [arithmetic mean \pm S.D.] of vardenafil and its M1 metabolite following a single dose of 10 mg ODT formulation administered without water under fasted conditions (Trt 1) are shown in the table below:

Table 2: Plasma PK of Vardenafil and M1 following 10 mg ODT in healthy male volunteers (18-50 years).

PK Parameter	Vardenafil (n=13)	M1 metabolite (n=13)
Cmax (µg/L)	12.15 \pm 5.78	13.54 \pm 5.11
Tmax * (h)	1.5 [0.75-3.0]	1.0 [0.75-2.5]
AUCinf (µg h/L)	42.37 \pm 16.95	30.66 \pm 10.45
AUC0-tn (µg h/L)	41.42 \pm 16.58	28.5 \pm 10.3
T1/2 (h)	4.27 \pm 1.03	2.28 \pm 1.19

* median [range]

- Vardenafil: Following oral administration of 10 mg ODT formulation to healthy males, vardenafil concentrations were detectable at the first collection time of 10 minutes. Concentrations then increased to a peak concentration of 12.15 \pm 5.78 µg/L at a median Tmax of 1.5 hours [range: 0.75 – 3.0 h]. The AUCinf of vardenafil was 42.37 \pm 16.95 µg.h/L. The elimination half-life was ~ 4.3 hours following dosing of the 10 mg ODT formulation. Vardenafil concentrations were detectable throughout the PK sampling duration (15 h).

- Metabolite (M1): M1 is the major metabolite of vardenafil and is reported to have PDE5 inhibitor activity approximately 28 % of that of vardenafil itself. Following oral administration of the 10 mg ODT formulation, metabolite concentrations were below detection until 30 minutes post-dose, after which concentrations peaked with a median Tmax of 1.0 h [range: 0.75-2.0 h] and exceeded those seen for parent vardenafil. Cmax of the metabolite was $13.54 \pm 5.11 \mu\text{g/L}$, and the AUCinf after the single dose was $30.66 \pm 10.45 \mu\text{g.h/L}$. T1/2 of the metabolite was 2.3 hours. Metabolite concentrations were below detection after ~ 6-8 hours post dose.

2.2.5.2 How does the PK of the drug and its major active metabolite in healthy young male volunteers compare to that in young ED patients?

- Phase 1 study 13396 and a sub-study in the phase 3 clinical trial 12093 evaluated the PK of vardenafil and its M1 metabolite from the ODT in the target ED population. The phase 1 study in ED patients also included evaluation of multiple dose PK of the ODT formulation.
- Compared to data from healthy male volunteers in a similar age group from study 12769, the average vardenafil and metabolite plasma exposure data appears to be lower in the ED patients. The distribution of AUC and Cmax for the parent vardenafil was however comparable across healthy volunteers and patients of study 12769 and 13396. The distribution of metabolite exposure differed among populations with lower spread in the ED patients.

Study 13396: This was a single-center, non-randomized, non-blinded, non-controlled, age-stratified group comparison study in N =36 ED patients aged 18-80 years. There were approximately n = 34 patients valid for PK [n= 14 each for the ≤ 45 and ≥ 65 years age groups and n = 6 for the 46-64 years group].

- The marketed Levitra[®] 10 mg IR tablet was given as a single administration at the beginning of the treatment period (Day 1). After a wash-out phase (Day 2 and Day 3), a multiple-dose phase of 10 days with once-daily administrations of vardenafil 10 mg ODT followed (Days 4 - 13).
- On PK days (days 1, 4 and 13), study drug administrations were performed after a fasting time of at least 10 hours [ODT was administered without water]. On all other days of the treatment period, study drug administrations were performed after a standard breakfast at the study center.

Pharmacokinetic results- Single dose PK of the ODT formulation in ED patients:

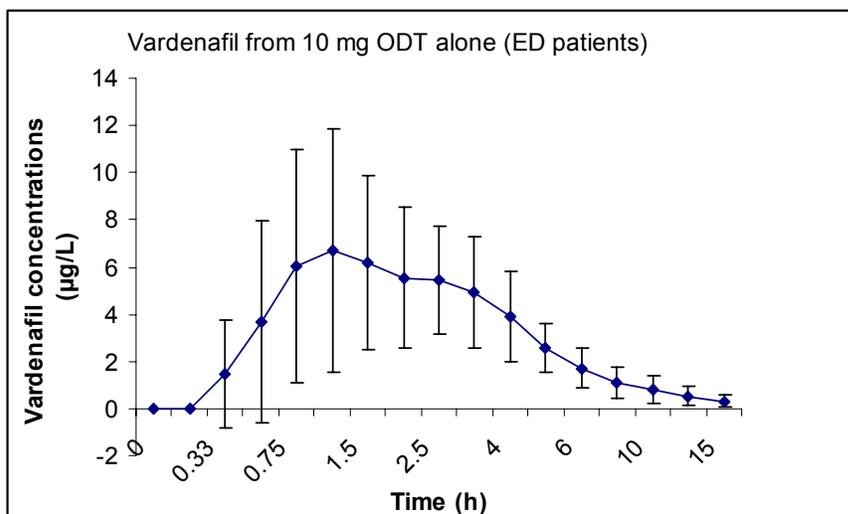


Figure 4: Plasma vardenafil concentrations following a single dose of Vardenafil 10 mg ODT in ED males of study 13396 (18-45 years).

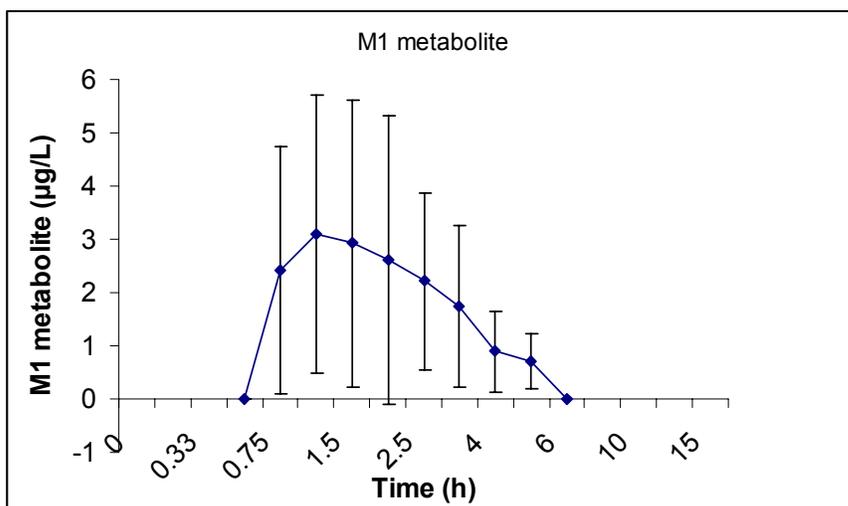


Figure 5: Plasma concentrations of the major metabolite M1 following a single dose of Vardenafil 10 mg ODT in ED males of study 13396 (18-45years).

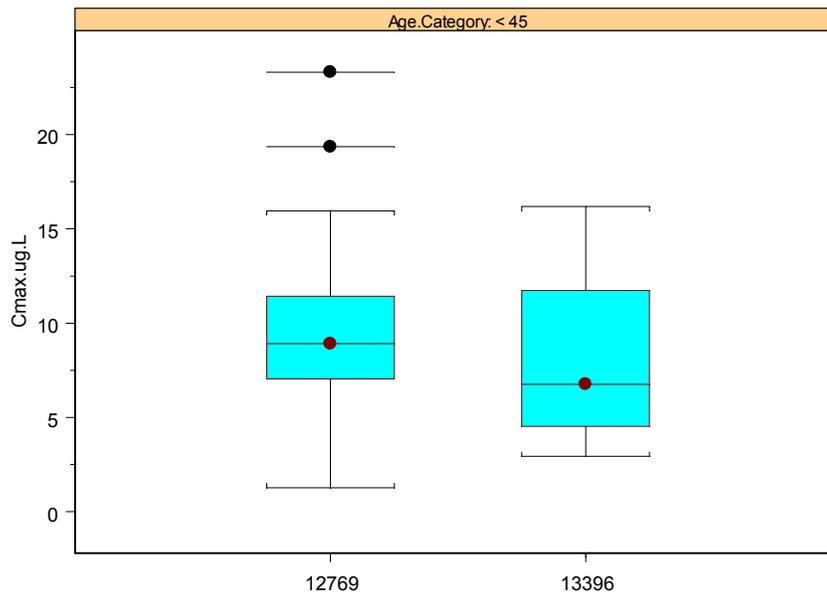
Table 3: Single dose pharmacokinetics of vardenafil and M1 metabolite from the ODT formulation in young ED patients (18- 45 years) of study 13396

Single dose PK for 10 mg ODT		
Mean ± SD (% CV)		
Parameter (Units)	Vardenafil	Metabolite M1
Cmax (µg/L)	8.4 ± 4.4 (52)	4.47 ± 2.99 (67)
Tmax (h)	1.5 [0.75 – 2.5]	1.5 [0.75 – 2.5]
AUC (µg.h/L)	34.58 ± 19.5 (56)	13.93 ± 9.21 (66)
AUC0-tn (µg.h/L)	32.9 ± 18.6 (56)	9.06 ± 7.55 (83)

AUC24 ($\mu\text{g}\cdot\text{h}/\text{L}$)	33.6 ± 18.3 (55)	13.85 ± 9.25 (66)
T1/2 (h)	4.6 ± 2.4 (52)	2.85 ± 0.93 (32)

- Vardenafil: In ED patients, following a single dose administration of 10 mg ODT formulation, vardenafil concentrations were below LLOQ for up to 20 minutes post-dose. Vardenafil concentrations then peaked at a median Tmax of 1.5 hours to a peak concentration of 8.4 $\mu\text{g}/\text{L}$ on average. The concentrations declined from plasma with a mean T1/2 value of 4.6 hours. Concentrations were detectable throughout the sampling duration.
- M1 metabolite: In ED patients, following a single 10 mg ODT formulation, M1 concentrations were below detection limit for approximately 45 minutes post dose. Metabolite concentrations then peaked to 4.47 $\mu\text{g}/\text{L}$ at a median Tmax of 1.5 h. Concentrations declined with an average T1/2 of 2.9 hours. Metabolite exposure was approximately 40 -50 % of parent vardenafil in this study. Metabolite exposure was generally below LLOQ at ~ 6-8 hours post-dose.

Vardenafil:



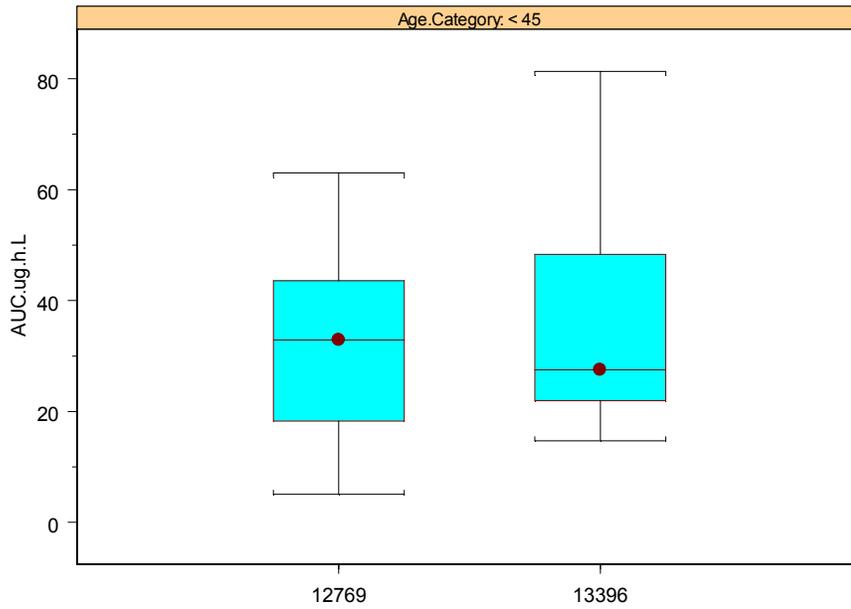
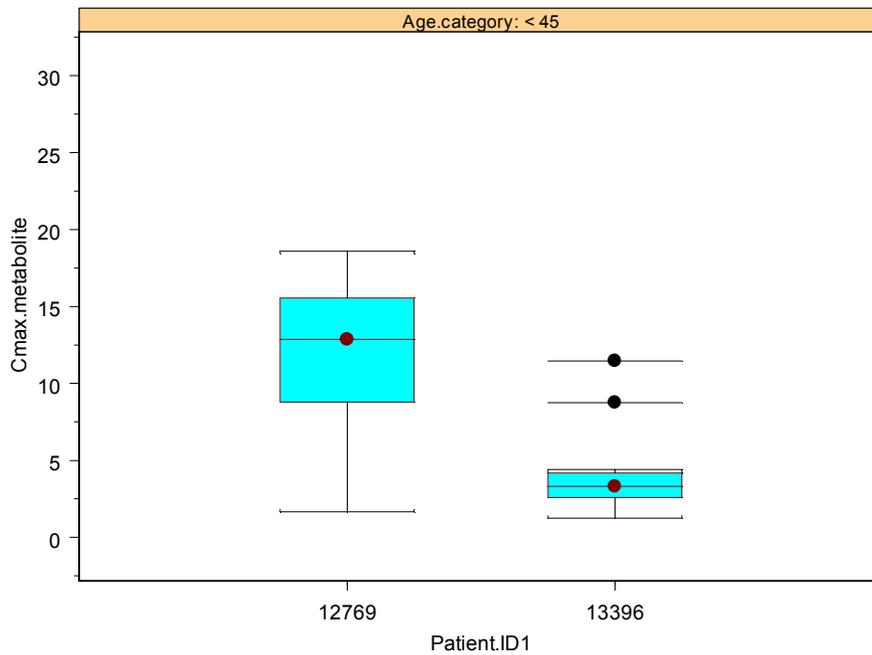


Figure 6: Box and Whisker plots showing the distribution of Vardenafil Cmax and AUC data in healthy volunteers (12769) and ED patients (13396) following a single dose administration of 10 mg ODT.

Metabolite:



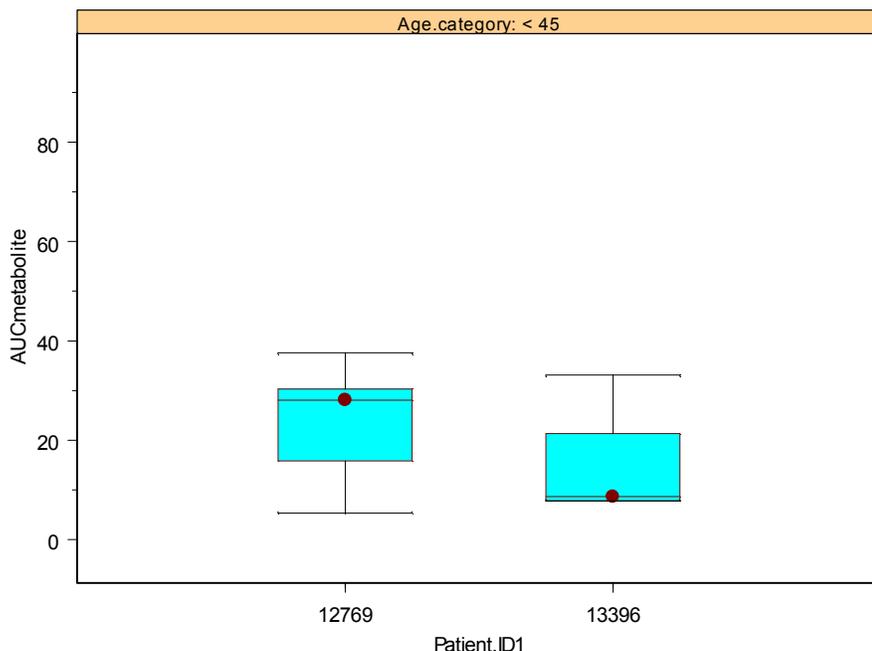


Figure 7: Box and Whisker plots showing the distribution of M1 metabolite Cmax and AUC data in healthy volunteers (12769) and ED patients (13396).

- Tmax and T1/2 values were comparable across healthy volunteers and ED patients of the same age group. The lower systemic exposure in ED patients compared to healthy volunteers was more pronounced for the M1 metabolite.
- Pharmacokinetics in elderly patients of this ED patient study and comparison of PK across age groups is described under the Geriatric section of this review.

2.2.5.3. How do the PK parameters change with time following chronic dosing?

- In study 13396, trough concentrations of vardenafil prior to day 10 of once-daily dosing and exposure on day 10 relative to day 1 for the ODT formulation suggested achievement of steady-state.
- Single and multiple dose PK (on day 10 of once-daily dosing of ODT without water) in ED patients (stratified by age category) are summarized below:

Table 4: Single and multiple dose PK (mean \pm SD, CV%) of vardenafil [study 13396]

Day 1 10 mg ODT SD	Parameter	18-45 years (N = 14)	46-64 years (N = 6)	65-69 years (N = 7)	70-80 years (N = 7)
	Cmax ($\mu\text{g/L}$)	8.4 \pm 4.4 (52)	7.25 \pm 2.67 (37)	10.3 \pm 5.5 (53)	10.2 \pm 6.3 (62)
	Tmax (h)	1.5	0.875	1.0	0.75
	AUC	34.58 \pm 19.5	30.2 \pm 8.7	49.5 \pm 20.6	41.2 \pm 13.3

	($\mu\text{g h/L}$)	(56)	(29)	(42)	(32)
	AUC ₂₄	33.6 \pm 18.3	29.5 \pm 8.2	47 \pm 19.3	40 \pm 12.8
	($\mu\text{g h/L}$)	(55)	(28)	(41)	(32)
	T _{1/2}	4.6 \pm 2.4	4.8 \pm 1.1	6.6 \pm 1.9	5.7 \pm 1.0
	(h)	(52)	(22)	(29)	(18)
	CL/F	368 \pm 169	360 \pm 127	248 \pm 140	266 \pm 92
	(L/h)	(46)	(35)	(57)	(38)
Day 10	Parameter	18-45 years	46-64 years	65-69 years	70-80 years
10 mg ODT MD		(N = 14)	(N = 6)	(N = 7)	(N = 7)
	C _{max,ss} ($\mu\text{g/L}$)	10.66 \pm 4.89	8.3 \pm 2.8	12.5 \pm 7.7	9.5 \pm 3.4
		(46)	(33)	(62)	(36)
	T _{max,ss} (h)	1.0	1.5	0.75	1.0
	AUC _{ss}	39.8 \pm 17.8	37.6 \pm 9.8	47.7 \pm 2.8	45 \pm 14.7
	($\mu\text{g h/L}$)	(45)	(26)	(50)	(32.5)
	T _{1/2}	4.68 \pm 1.38	4.28 \pm 0.88	6.16 \pm 2.57	5.8 \pm 1.5
	(h)	(30)	(21)	(42)	(26)
	CL _{ss} /F	313 \pm 166	285 \pm 93	248 \pm 96	245 \pm 93
	(L/h)	(53)	(32)	(39)	(38)

- Accumulation following once-daily dosing was not significant, with pre-dose concentrations for days in between at or below LLOQ for most patients during multiple-daily dosing.
- In the younger age group (18-45 years of age) of ED patients, the accumulation based on C_{max} was 15%, and increase in AUC was 8% relative to single dose. In the older age group (65 – 80 years of age), the accumulation based on C_{max} and AUC were 10 % and 2 % respectively.
- Statistical analyses of accumulation data of vardenafil and M1 metabolite (accumulation ratios R_A) are shown for two age groups of interest:

Table 5: Statistical findings of multiple dose data for vardenafil and M1 metabolite from ODT:

ODT MD vs. ODT SD	Vardenafil C _{max} Ratio [90 % CI range]	Vardenafil AUC Ratio [90 % CI range]	Metabolite C _{max} Ratio [90 % CI range]	Metabolite AUC Ratio [90 % CI range]
Study 13396 [ED males; 18-80 years; n = ~14 per group each age group]				
\leq 45 years	1.1588 [0.9074 – 1.4797]	1.0864 [0.9483 – 1.2445]	0.9333 [0.7720 – 1.1283]	0.9992 [0.8387 – 1.1903]
\geq 65 years	1.1135 [0.8879 – 1.3963]	1.0267 [0.9054 – 1.1644]	0.9421 [0.7904 – 1.1230]	1.1069 [0.9727 – 1.2596]

Known Absorption Distribution Metabolism and Excretion (ADME) characteristics of vardenafil (from the approved labeling for Levitra IR):

Vardenafil was approved as Levitra film-coated IR tablets in the 2.5 mg, 5 mg, 10 mg and 20 mg dose strengths. The ADME characteristics of Vardenafil were thoroughly evaluated in the original NDA [021400]. The following information from the approved package insert for Levitra summarizes these aspects:

Absorption: Vardenafil is rapidly absorbed with absolute bioavailability of approximately 15%. Maximum observed plasma concentrations after a single 20 mg dose in healthy volunteers are usually reached between 30 minutes and 2 hours (median 60 minutes) after oral dosing in the fasted state. Two food-effect studies were conducted which showed that high-fat meals caused a reduction in C_{max} by 18%-50%.

Distribution: The mean steady-state volume of distribution (V_{ss}) for vardenafil is 208 L, indicating extensive tissue distribution. Vardenafil and its major circulating metabolite, M1, are highly bound to plasma proteins (about 95% for parent drug and M1). This protein binding is reversible and independent of total drug concentrations. Following a single oral dose of 20 mg vardenafil in healthy volunteers, a mean of 0.00018% of the administered dose was obtained in semen 1.5 hours after dosing.

Metabolism: Vardenafil is metabolized predominantly by the hepatic enzyme CYP3A4, with contribution from the CYP3A5 and CYP2C isoforms. The major circulating metabolite, M1, results from desethylation at the piperazine moiety of vardenafil. M1 is subject to further metabolism. The plasma concentration of M1 is approximately 26% that of the parent compound. This metabolite shows a phosphodiesterase selectivity profile similar to that of vardenafil and an *in vitro* inhibitory potency for PDE5 28% of that of vardenafil. Therefore, M1 accounts for approximately 7% of total pharmacologic activity.

Excretion: The total body clearance of vardenafil is 56 L/h, and the terminal half-life of vardenafil and its primary metabolite (M1) is approximately 4-5 hours. After oral administration, vardenafil is excreted as metabolites predominantly in the feces (approximately 91-95% of administered oral dose) and to a lesser extent in the urine (approximately 2-6% of administered oral dose).

2.3 Intrinsic Factors

Summary of major intrinsic factors known to affect vardenafil exposure from the Levitra IR [NDA 021400; original NDA] and corresponding dosing recommendations for vardenafil ODT:

Renal Impairment (from IR labeling): In volunteers with mild renal impairment (CL_{cr} = 50-80 ml/min), the pharmacokinetics of vardenafil were similar to those observed in a control group with normal renal function. In the moderate (CL_{cr} = 30-50 ml/min) or severe (CL_{cr} <30 ml/min) renal impairment groups, the AUC of vardenafil was 20–30% higher compared to that observed in a control group with normal renal function (CL_{cr}

>80 ml/min). Vardenafil pharmacokinetics have not been evaluated in patients requiring renal dialysis. No dose adjustment is recommended for renal impairment.

Use of Vardenafil ODT in renal impairment: Sponsor proposes that vardenafil ODT is not recommended in patients on renal dialysis. No dosing recommendations are proposed for other renal impairment populations.

Based on the information known about the impact of renal impairment on vardenafil PK, this proposal appears reasonable.

Hepatic Impairment (from IR labeling): In volunteers with mild hepatic impairment (Child-Pugh A), the C_{max} and AUC following a 10 mg vardenafil dose were increased by 22% and 17%, respectively, compared to healthy control subjects. In volunteers with moderate hepatic impairment (Child-Pugh B), the C_{max} and AUC following a 10 mg vardenafil dose were increased by 130% and 160%, respectively, compared to healthy control subjects. Consequently, a starting dose of 5 mg is recommended for patients with moderate hepatic impairment, and the maximum dose should not exceed 10 mg. Vardenafil has not been evaluated in patients with severe (Child-Pugh C) hepatic impairment.

Use of Vardenafil ODT in hepatic impairment: Sponsor proposes that patients with moderate or severe hepatic impairment should not use vardenafil ODT.

Based on the information known about the impact of hepatic impairment on vardenafil PK, this proposal appears reasonable.

Geriatrics (from IR labeling): In a healthy volunteer study of elderly males (≥65 years) and younger males (18–45 years), mean C_{max} and AUC were 34% and 52% higher, respectively, in the elderly males. Consequently, a lower starting dose of LEVITRA (5 mg) in patients ≥65 years of age should be considered.

Use of Vardenafil ODT in geriatrics: (b) (4)

Discussion: This recommendation for geriatric use differs from that stated in the labeling for Levitra IR, where a lower starting dose of 5 mg is suggested for consideration in the elderly due to increased exposure. This section of the review will therefore further address this aspect by detailing the known exposure and safety of vardenafil ODT in geriatric patients:

Geriatrics- PK and safety information from Vardenafil ODT trials (NDA 200179):

Study 13396:

- In study 13396 the effect of patient age on pharmacokinetics of vardenafil and its metabolite were assessed using the target ED population for both IR and ODT

formulations. This study included patients ranging over 18-80 years of age [N= 14 for ≤ 45 years of age; N = 14 for ≥ 65 years of age and N = 6 between 46-64 years].

- As anticipated based on the higher exposure in elderly with the approved Levitra IR, the vardenafil exposure from the ODT formulation was higher in the elderly.

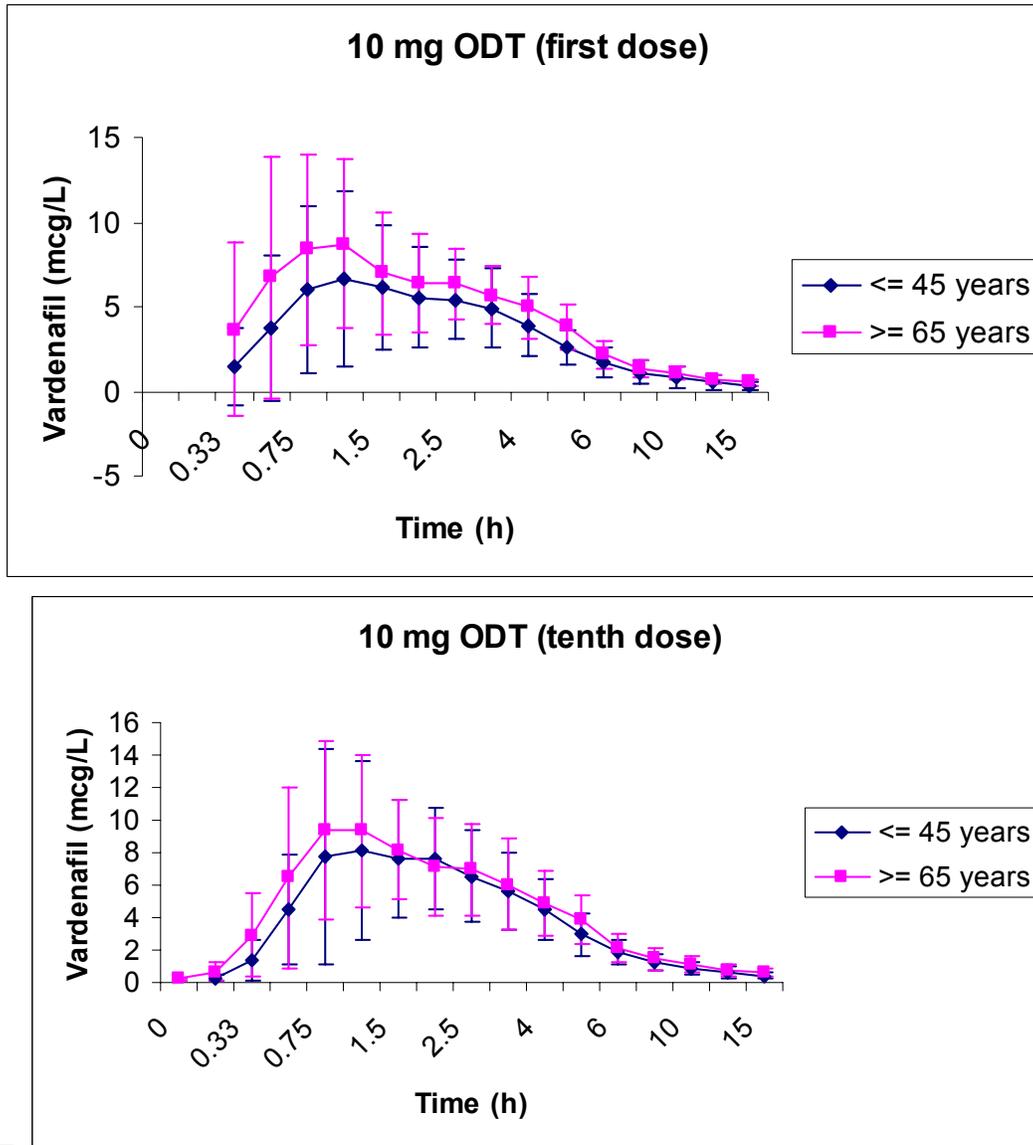


Figure 8: Single dose and multiple dose PK profile comparisons of vardenafil ODT across age groups [Study 13396]

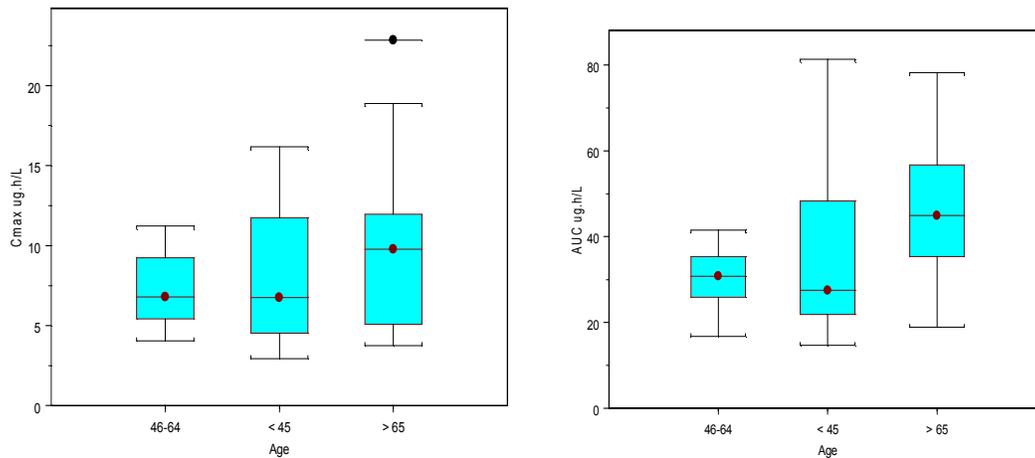


Figure 9: Box and Whisker plots comparing the distribution of Cmax and AUC data for parent Vardenafil PK distribution in study 13396 across age groups (n = 14 for ≤ 45 and ≥ 65 age groups each; n=6 for 46-64 years)

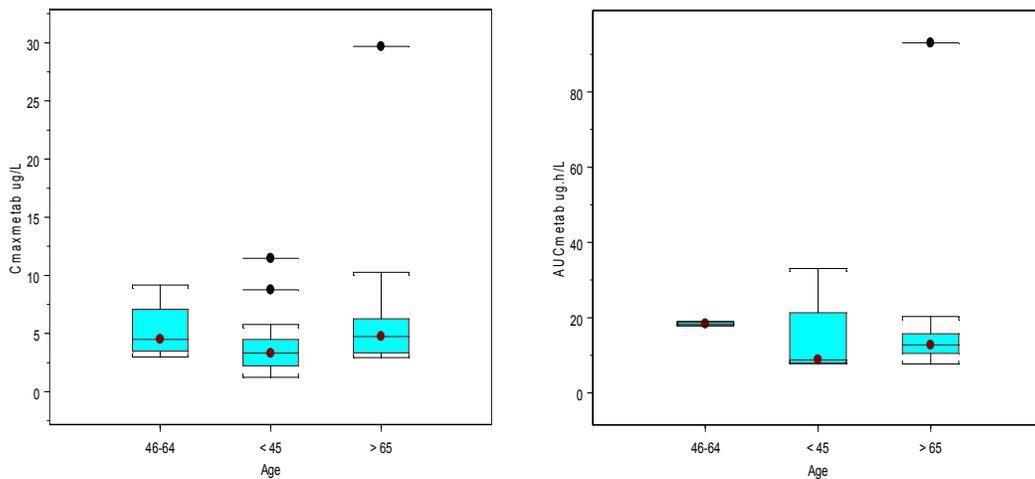


Figure 10: Box and Whisker plots comparing the distribution of Cmax and AUC of M1 metabolite in study 13396 across age groups (n = 14 for ≤ 45 and ≥ 65 age groups each; n=6 for 46-64 years)

- For the 10 mg ODT formulation, the Cmax and AUC estimates in the elderly were higher by 21 % and 38 % respectively, compared to the younger patients (18-45 years). The 90 % CI surrounding the point estimate (ratio) was outside the 0.8-1.25 range. On the last day of the multiple-dosing, vardenafil Cmax,ss and AUC τ ,ss [AUC(288-312)ss] were greater by 16 % and 31 %, respectively, in subjects aged ≥ 65 years.

- The magnitude of differences across age groups in this study was somewhat smaller for the ODT than the IR formulation [Cmax and AUC increases of 21 % and 38 % for ODT vs. 38 % and 48 % for IR; single dose data].
- For the metabolite M1, with the ODT formulation, the elderly patients had 40 % and 19 % increase respectively in Cmax and AUC values following single dose administration, compared to younger patients. The magnitude of increase in AUC of metabolite in the elderly was lower with the ODT formulation compared to IR (19 % vs. 60 %).

Table 6: Statistical findings comparing vardenafil and M1 PK across age groups.

Elderly vs. Young (>65 yr vs. <45 yr)	Vardenafil Cmax Ratio [90 % CI range]	Vardenafil AUC Ratio [90 % CI range]	Metabolite Cmax Ratio [90 % CI range]	Metabolite AUC Ratio [90 % CI range]
Study 13396 [ED males; 18-45, 65-80 years; n = ~14 per group]				
Levitra IR	138.5 [112.07-171.16]	148.3 [133.85 – 164.32]	137.96 [116.66 - 163.16]	160.13 [136.26 – 188.19]
Vardenafil ODT	121.12 [98.01 – 149.69]	138.72 [125.20 – 153.71]	140.03 [118.41 – 165.60]	119.54 [101.25 – 141.14]

- The T1/2 values for vardenafil and metabolite were somewhat longer in the elderly ED patients suggesting slower clearance, thereby resulting in increased systemic exposure with age.
- The mean \pm SD [95 % CI range] for T1/2 values comparing the \leq 45 years vs. \geq 65 years in study 13396 were as follows:
 - Vardenafil: 4.64 ± 2.41 hours [95 % CI: 3.24 – 6.03], vs. 6.14 ± 1.54 hours [95 % CI: 5.25 – 7.03].
 - Metabolite: 2.92 ± 0.96 hours [95 % CI: 2.03 – 3.81], vs. 4.01 ± 4.7 hours [95 % CI: 1.16 – 6.85].

Vardenafil

Metabolite M1

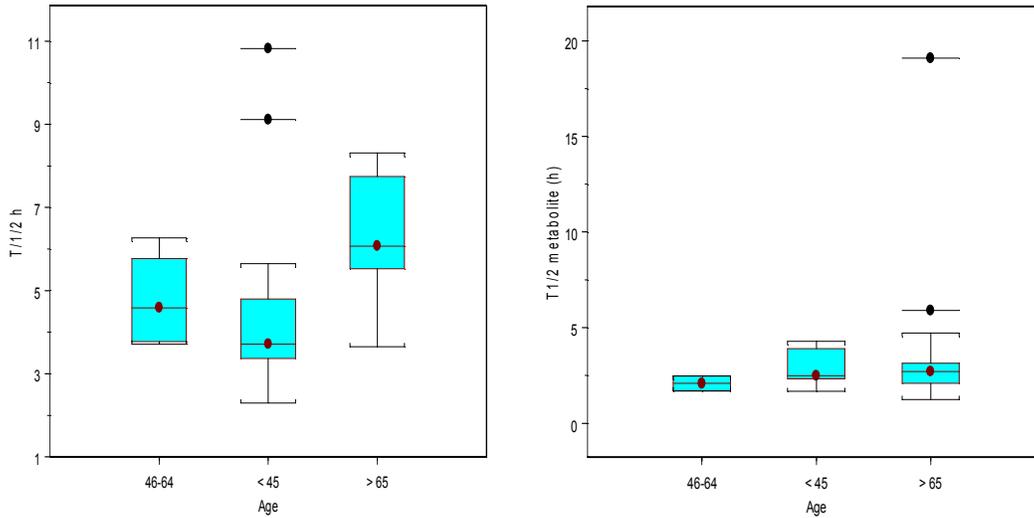


Figure 11: Distribution of T/12 values for vardenafil and metabolite M1 in 13396

PK sub-study 12093: In this 24 patient PK sub-study, vardenafil ODT single dose was administered to patients under fasted conditions, without water. These patients had completed the last dose of their phase 3 treatment (placebo or vardenafil ODT) no less than 48 hours prior to the PK phase. Patients were in the 18-64 years and ≥ 65 years age categories (roughly 12 in each).

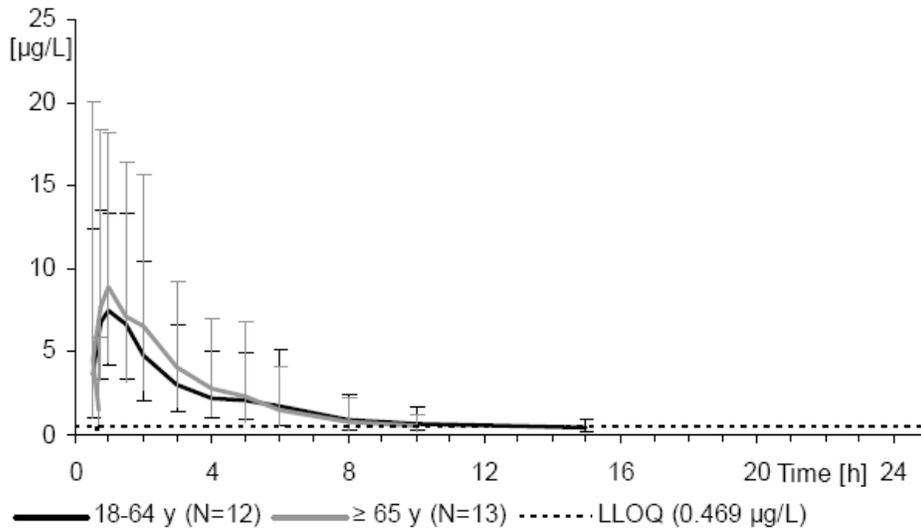


Figure 12: Plasma vardenafil concentration-time profiles in 18-64 years and ≥ 65 years old ED patients within the PK sub-study in 12093.

Table 7: Pharmacokinetic parameters following single dose of vardenafil ODT in a Phase 3 subset.

Vardenafil ODT	18- 64 years N = 12	≥ 65 years N =12
Cmax (µg/L)	11.9 (5.9)	15.0 (6.5)
Tmax * (h)	1.5 (0.5 – 2.5)	1.0 (0.5 – 3.5)
AUCinf (µg h/L)	56.1 (32.9)	60.6 (25.5)
AUC0-tn (µg h/L)	53.2 (30.7)	57.9 (24.7)
T1/2 (h)	5.65 (1.7)	6.12 (1.8)
CL/f (L/h)	253 (153)	200 (104)

Table 8: PK of M1 metabolite BAY 44-5576 following 10 mg ODT in phase 3 subset

	18- 64 years N = 12	≥65 years N =12
Cmax (µg/L)	10.76 (5.9)	14.4 (11.4)
Tmax * (h)	1.17 (0.5 – 2.5)	0.75 (0.5 – 3.0)
AUCinf (µg h/L)	39.9 (21.0)	55.1 (46.2)
AUC0-tn (µg h/L)	35.9 (20.8)	44.5 (42.8)
T1/2 (h)	4.34 (1.76)	5.68 (3.9)
CL/f (L/h)	355 (266)	282 (177)

Table 9: Statistical analyses: Point estimate ratio (≥ 65 years vs. 18-64 years) and 90 % CI for the parent and metabolite (study 12093).

Study 12093- PK Elderly vs. Young (≥65 yr vs. 18-64 yr) N = 24	Vardenafil Cmax Ratio [90 % CI range]	Vardenafil AUC Ratio [90 % CI range]	Metabolite Cmax Ratio [90 % CI range]	Metabolite AUC Ratio [90 % CI range]
ODT/no water/fasting	133.07 [87.46 – 202.46]	117.42 [79.59 – 173.23]	123.84 [80.12 – 191.42]	125.28 [73.65 - 213.11]

- The Cmax and AUC of vardenafil were on the average higher by 33 % and 17 % in elderly (≥ 65 years) vs. those who were 18-64 years of age. Earlier phase 1 PK study 13396 comparing PK in ≤ 45 years vs. ≥ 65 years categories demonstrated Cmax and AUC increases of 21 % and 38 % in the elderly.
- The ‘younger’ population included in this PK sub-study was considerably older compared to the study 13396, since majority of patients were above the age of 50

in this group. Only 3 patients in the PK sub-study were in the young 18-45 category. Thus the fold-increase in AUC going from the 18-64 years age group to ≥ 65 years age group was smaller.

Distribution of vardenafil PK across age categories in study 12093 (subset); note that only 3 patients were under 45 years old in this study;

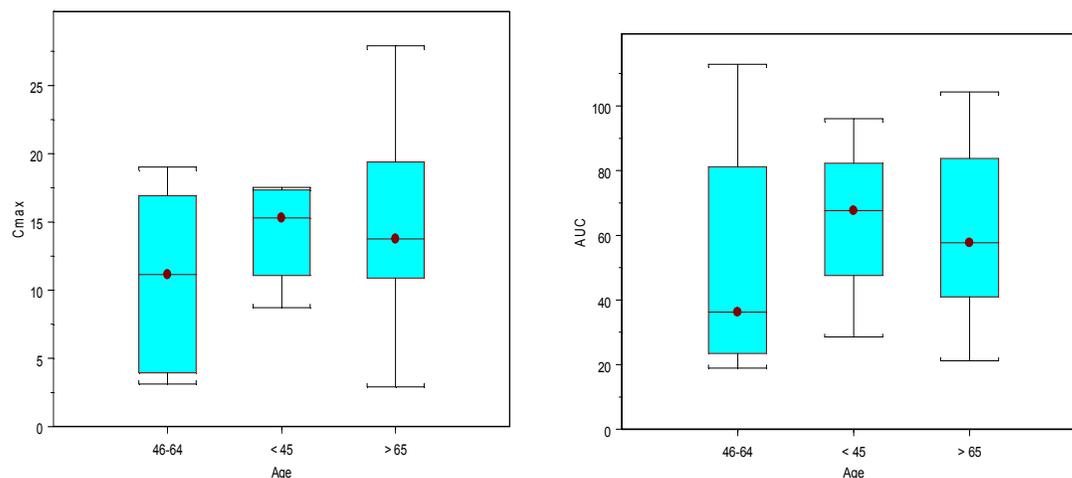


Figure 13: Box and Whisker plots comparing the distribution of vardenafil C_{max} and AUC data across age groups in PK sub-study 12093.

Safety information for ODT use in the Elderly:

- As noted above in study 13396, elderly (≥ 65 years) ED patients had 21 % higher C_{max} and 38 % higher AUC compared to younger (≤ 45 years) ED patients. Safety information from phase 1 and phase 3 clinical trials was considered to assess whether the higher systemic exposure in elderly translated to increased incidence of adverse events.
- In each of the two phase 3 clinical trials of the ODT formulation, 50 % of enrolled patients were > 65 years of age (in total N = 180 men with ED were treated with vardenafil within each of the age groups studied).
- The safety information for the ODT formulation across the age groups is summarized; where relevant additional factors such as the timing of dose relative to food, timing of AE relative to dosing were also explored:

Study 13396 (Phase 1 study in ED patients):

- In total, 33 of 36 subjects (92 %) experienced at least 1 treatment-emergent adverse event. Most treatment-emergent adverse events were of mild intensity. The 3 most frequent treatment-emergent adverse events could be explained by the mode of action, i.e. flushing, nasal congestion, and headache.

- While the overall incidence of AEs was higher in the elderly [87 % in ≤ 45 years; 100 % in (≥ 65 years of age)], the incidence of treatment-emergent adverse events did not demonstrate a consistent pattern suggestive of an increased incidence with age; for e.g. flushing (subjects aged <45 years vs. subjects aged (≥ 65 years: 40 % vs. 67 %), nasal congestion (40 % vs. 20 %), and headache (40 % vs. 7 %).
- 7 subjects (19 %) experienced moderate or severe treatment-emergent adverse events, 6 of them were aged <45 years. Moderate drug-related adverse events were headache, back pain, dyspepsia, and flushing.
- Dizziness occurred in equal incidence across age groups (one in each age group).
- One individual Subject # 24 (44 years old) experienced loss of consciousness at approximately 4 h and 30 minutes after the dose on the last day of ODT administration during the multiple dose phase. The sponsor attributes this to vasovagal shock unrelated to study drug as the subject reportedly admitted to manipulating indwelling catheter prior to the event. Dosing appeared to have occurred around 9 AM that day (under fasting conditions during PK days) and the event occurred ~ 4 h 30 minutes later. The T_{max} in this individual was 0.75 hours on that day. Systemic exposure did not appear to be vastly different from other individuals of this study.
- Nasal congestion and flushing of the face occurred mostly close to the T_{max} of the drug i.e. within 1-2 hours post-dose. The incidence of myalgia pains was generally noted several hours after dosing, while back pain, headache and heartburn occurred without a particular trend in timing relative to dose.
- Although nasal congestion and flushing related AEs were reported more frequently on PK days (3 and 12) when dose was administered under fasted conditions, it was also observed in few individuals in the days in between when dosing occurred with a standard (continental) breakfast. Thus the correlation with food intake is not clear.

Study 12093 (POTENT I; Phase 3 clinical trial in ED);

- The average age of all safety subjects was about 62 years in this study. The average age in the younger patient stratum was about 53 years, while elderly subjects had an average age of approximately 70 years. The calculated age at entry in the study ranged from 21 to 84 years. Patients were predominantly white.

Major demographic characteristics: Safety population [Study 12093]

Parameter		Vardenafil 10 mg ODT		Placebo	
		< 65 years	≥ 65 years	< 65 years	≥ 65 years
Race n (% , rounded)	White	55	68	53	64
	Black	3	4	2	5
	Asian	6	3	2	2
	Missing	20	16	19	16
Age (years)	Mean \pm SD	52.8 \pm 9.0	69.7 \pm 4.2	52.7 \pm 8.5	69.8 \pm 4.9
Weight (kg)	Mean \pm SD	87.1 \pm 11.7	81.6 \pm 11.4	88.0 \pm 15.0	82.6 \pm 11.9
BMI (kg/m ²)	Mean \pm SD	27.5 \pm 3.5	26.9 \pm 3.2	27.9 \pm 4.3	27.1 \pm 3.6

- The total incidence rate of AEs was higher in the 10 mg ODT group compared to placebo [38.6 % vs. 20.7 %]. Within each treatment group, there were approximately 50 % of elderly patients.
- The incidence of adverse events was higher in the <65 years age group compared to the elderly in the vardenafil ODT group [42.5 % vs. 35.1 %].

AE type	Vardenafil 10 mg ODT		Placebo	
	< 65 years N=87	≥ 65 years N=97	< 65 years N=81	≥ 65 years N=93
Treatment emergent AEs	37 (42.5%)	34 (35.1%)	16 (19.8%)	20 (21.5%)
Drug-related treatment emergent AEs	27 (31%)	25 (25.8%)	7 (8.6%)	9 (9.7%)
Treatment emergent AEs leading to discontinuation	1 (1.1%)	1 (1.0%)	0 (0%)	1 (1.1%)
Serious adverse events (SAEs)	0 (0%)	4 (4%)	0 (0%)	1 (1.1%)
SAEs with outcome death	0 (0%)	0 (0%)	0 (0%)	0 (0%)

- [Note: Information was not available to determine whether dosing in each individual occurred with or without food in this study. The phase 3 instructions were to take the dose as needed 1 hour prior to sexual activity, irrespective of food. As described earlier, food reduces the C_{max} (by 35 %) but not AUC. The time of onset and duration of the AEs was not available for most cases. The CRF forms were not required to capture this information. In addition, study did not capture food intake information relative to dosing].
- Back pain, dysgeusia, dyspepsia, muscle spasms, supraventricular extrasystoles were some of the AEs observed more frequently in the elderly in this trial. Most other AEs including headache, flushing, dizziness, nasal congestion, and diarrhea were higher in the younger age group.
- The majority of AEs reported in the study were of mild to moderate severity. Younger subjects in the vardenafil group reported slightly more mild and moderate AEs than the elderly subjects whereas in the placebo group the frequency of reports of mild and moderate AEs were similar in both age groups.

		Mild	Moderate	Severe
Vardenafil 10 mg ODT	Total (N=184)	53 (28.8%)	15 (8.2%)	3 (1.6%)
	< 65 years (N=87)	29 (33.3%)	8 (9.2%)	0 (0%)
	≥ 65 years (N=97)	24 (24.7%)	7 (7.2%)	3 (3.1%)
Placebo	Total (N=174)	30 (17.2%)	6 (3.4%)	0 (0%)
	< 65 years (N=81)	14 (17.3%)	2 (2.5%)	0 (0%)
	≥ 65 years (N=93)	16 (17.2%)	4 (4.3%)	0 (0%)

- Serious AEs were seen at higher frequency in the elderly. Serious AEs included acute coronary syndrome, femoral arterial stenosis, gastrointestinal hemorrhage, and syncope. With the exception of the syncopal event reported in patient # 37007-003, the medical officer for this NDA review has concluded that all other serious AEs were unrelated to treatment. All of these subjects were reported to have recovered.
- Subject number 37007-003 (age 73) in the vardenafil ODT group developed syncope of moderate intensity. No information is available for this subject with respect to timing of syncope in relation to dose or food intake. Patient completed the trial as planned.
- The following excerpt is from the medical officer's draft review related to this syncopal AE:

- *Subject 12093-37007-0003: The subject is a 73 year-old male who has had hypertension since 1987. He has had “inner ear disease” – not further defined. His medication on study entry was losartan/HCTZ. He was randomized to vardenafil ODT on September 23, 2008. His last dose of vardenafil, prior to the event, was December 9, 2008 at 23:10. On [REDACTED] (b) (4), time unavailable, he was hospitalized following a syncopal episode. He was treated with ASA and cinnarizin and was listed as “cured” on [REDACTED] (b) (4). No further details are available regarding his hospital course. He was not withdrawn from the study, however he took no study medication following hospitalization since his scheduled final visit occurred on December 14, 2008.*
- *[Medical] Reviewer’s comment: The time interval between administration of vardenafil and the syncopal episode is not known. No definitive explanation for the syncope was established. This event should be considered as possibly related to vardenafil.*
- A total of 3 dizziness events were reported in this study. Patient ages were in the range of 52 – 68 years. All events were coded as mild in severity. One of the subjects had PK information [370100005]. Tmax, Cmax and AUC information was not out of ordinary.

Study 12094 (POTENT II; Phase 3 clinical trial in ED):

- The average age of all safety subjects was about 62 years. The average age in the younger patient stratum is about 53 years, while elderly subjects have an average age of approximately 70 years. The calculated age at entry in the study ranges from 22 to 88 years. Patients were predominantly white.

Major demographic characteristics- safety population [study 12094]

Parameter		Vardenafil 10 mg ODT		Placebo	
		< 65 years	≥ 65 years	< 65 years	≥ 65 years
Race n (% , rounded)	White	53 (62%)	65 (77%)	54 (64%)	60 (73%)
	Black	7 (8%)	1 (1%)	7 (8%)	2 (2%)
	Asian	6 (7%)	4 (5%)	2 (2%)	1 (1%)
	Hispanic	20 (23%)	15 (18%)	21 (25%)	18 (22%)
Age (years)	Mean±SD	52.5±8.6	70.3±4.9	53.5±7.8	70.5±5.3
Weight (kg)	Mean±SD	89.7±17.0	86.0±14.3	88.8±15.1	87.4±14.2
BMI (kg/m ²)	Mean±SD	29.1±5.0	28.7±3.7	28.8±4.4	28.7±4.1

Incidence rates of adverse events by treatment group and stratum (safety population) N (%)

AE type	Vardenafil 10 mg ODT		Placebo	
	< 65 years N=86	≥ 65 years N=85	< 65 years N=84	≥ 65 years N=82
Treatment emergent AEs	34 (39.5%)	31 (36.5%)	18 (21.4%)	20 (24.4%)
Drug-related treatment emergent AEs	20 (23.3%)	14 (16.5%)	5 (6.0%)	4 (4.9%)
Treatment emergent AEs leading to discontinuation	2 (2.3%)	1 (1.2%)	0 (0%)	1 (1.2%)
Serious adverse events (SAEs)	2 (2.3%)	0 (0%)	1 (1.2%)	0 (0%)
SAEs with outcome death	0 (0%)	0 (0%)	0 (0%)	0 (0%)

- Similar to POTENT I trial (12093), the incidence of AEs was higher in this study in the vardenafil ODT group compared to placebo. In addition, the incidence of AEs was higher in the younger (< 65 years) age group compared to the elderly (≥ 65 years).

		Mild	Moderate	Severe
Vardenafil 10 mg ODT	Total (N=171)	47 (27.5%)	16 (9.4%)	2 (1.2%)
	< 65 years (N=86)	24 (27.9%)	9 (10.5%)	1 (1.2%)
	≥ 65 years (N=85)	23 (27.1%)	7 (8.2%)	1 (1.2%)
Placebo	Total (N=166)	24 (14.5%)	13 (7.8%)	1 (0.6%)
	< 65 years (N=84)	11 (13.1%)	7 (8.3%)	0 (0%)
	≥ 65 years (N=82)	13 (15.9%)	6 (7.3%)	1 (1.2%)

- Incidence of vardenafil AEs including headache, flushing, nasal congestion, dizziness, dyspepsia, were higher in the < 65 years old patients. Cough, dry mouth, diarrhea, and dysphagia were higher in the elderly. Muscle spasm, neck pain and back pain incidence was similar among age groups.
- Three serious adverse events in the vardenafil treated patients were reported during this study and all three were in the < 65 years old age group. Events included hypertension, chest pain and arrhythmia; events were concluded by the medical officer to be unrelated to drug treatment.

Dizziness events across both clinical trials:

- Dizziness was observed in 3 patients during study 12093 and 5 patients during study 12094. Age of the patients was in the 54- 68 range. Dizziness was generally described as mild (7 instances). There was one instance of ‘moderate’ dizziness.
- Study did not provide information related to time of food intake relative to dosing or the onset of AE relative to dosing. Therefore it is not possible to establish relationship between food status and AEs (In an earlier Phase 1 study vardenafil C_{max} was shown to be lower by 35 % in fed conditions for the ODT).
- Patients varied in the time of day when they took the drug (on-demand). Both AM and PM dosing was noted in individuals and sometimes within the same individual on different occasions. Dizziness events were observed with both AM and PM doses and therefore no relationship could be established with respect to the time of dosing and the AE.
- All subjects who experienced dizziness had a history of hypertension and some had stroke or cardiovascular conditions, hypercholesterolemia as well. All patients were on concomitant medications to treat these existing conditions.
- The duration of the dizziness was captured in the CRF as start and stop dates of event or on two occasions in the additional comments box. In 4 patients mild dizziness was noted to have been experienced through out the study duration, possibly due to the AE occurring after each of the doses taken. In one moderate case of dizziness, the event lasted for 2-3 days after each of the doses. Of these 5 cases, four were under the age of 65 years and one was 65 years old. In other 3 cases, the dizziness was infrequent.

- Based on discussions with the medical officer, with the exception of a patient who discontinued the study due to moderate dizziness lasting 2-3 days after dose (#400040008 in study 12094; age 62 years), dizziness in other patients appeared to be associated with a particular dose and would've been mild since none of these patients discontinued the study due to this AE.
- According to the medical reviewer, subject 400040008 with moderate dizziness interestingly, also had the AE of "hypertension" reported during the period he was dizzy several times. While there was no vital sign data taken in relation to the dizziness, the medical reviewer feels that this is reasonable evidence that his dizziness was not related to low BP. Patient had multiple other medical problems including diabetes, history of CVA twice, glaucoma and was taking Atacand (not known whether for hypertension or for a history of heart failure). Overall, patient is presumed to have been that he was much more sensitive to dizziness/flushing than is usually seen, with his multiple medical problems and multiple medications likely to have played a part. In addition, the cardiovascular disease history of these patients could've made them more susceptible to these AEs.
- Only one patient who experienced dizziness had PK data and this information did not suggest any marked differences compared to average PK data from the remaining subjects [370100004; Tmax: 1.5 h; Cmax: 10 ug/L; AUC: 47.2 ug.h/L].

Study 12093 (PK sub-study):

Safety information (AEs) during the post-study period (includes PK visit 5) in the patients who participated in the PK subset during the conduct of the double-blind period of phase 3 study were available. Only two events in one patient coded as neuralgia and hypotension (shown as **) were listed as occurring on PK day at visit 5.

Patient ID	Age	Parent Cmax (ug/L)	Parent AUC (ug h/L)	Metab Cmax (ug/L)	Metab AUC (ug.h/L)	AEs during Post- study period (including SD PK phase**)
370100002	59	15.6	96.9	9.841	59.10	Increased neuropathic pain in feet** Hypotension** High blood iron; Premature supraventricular complexes

Dosing Considerations in the Elderly:

- The approved starting dose for Levitra IR is 10 mg taken orally. Patients have an option to decrease the dose to 5 mg or increase it to 20 mg for safety or efficacy considerations. The approved labeling states that a lower starting dose of 5 mg should be 'considered' in elderly ED patients.
- In young ED patients, vardenafil 10 mg ODT formulation provides a 29 % higher AUC of the parent drug compared to Levitra 10 mg IR. [The magnitude of increase with the ODT relative to IR was higher (by 44 %) in healthy young volunteers for reasons unknown]. Elderly patients (≥ 65 years) also demonstrate ~

- 21 % and 38 % higher C_{max} and AUC of vardenafil compared to younger patients (≤ 45 years) with the ODT formulation.
- Thus compared to young ED patients, elderly patient receiving the ODT may experience ~ 67 % increase in AUC and a modest increase in C_{max}. This estimated increase is similar to the observed absolute increases of ~ 60 % on average in study 13396 when comparing the AUC values of young ED males (18-45 years; 28.3 $\mu\text{g}\cdot\text{h/L}$) receiving Levitra IR 10 mg to that of the AUC values in elderly ED males (≥ 65 years; 45.35 $\mu\text{g}\cdot\text{h/L}$) receiving ODT 10 mg; C_{max} values were comparable.
 - With ODT use in younger patients, the increase in metabolite AUC was ~ 9 % relative to Levitra IR use. In elderly patients, there was a further increase of ~ 20 % with age. Therefore, compared to younger ED patients, elderly patients receiving the ODT formulation may experience ~ 29 % higher AUC of metabolite and a modestly higher C_{max}. When the absolute increases in AUC were compared for younger (18-45 years) ED males receiving Levitra IR vs. older (≥ 65 years) ED males receiving 10 mg ODT in study 13396, there was a 40 % overall increase in metabolite AUC [14.04 $\mu\text{g}\cdot\text{h/L}$ vs. 19.7 $\mu\text{g}\cdot\text{h/L}$]. The increase in C_{max} was modest (9 %).
 - In an elderly patient currently receiving Levitra 10 mg IR, switching to the ODT 10 mg formulation will potentially result in ~ 20 % increase in systemic exposure [based on relative bioavailability estimates in study 13396 for elderly ED patients receiving both treatments after adequate wash-out].
 - For an elderly patient currently on a 5 mg dose of Levitra IR, it is anticipated that the net increase in AUC would be more than doubled when switched to the 10 mg ODT formulation, due to the supra-bioavailability of the ODT relative to IR.
 - Safety of the ODT 10 mg formulation was established in the two phase 3 clinical trials of NDA 200179, where approximately 50 % of enrolled ED patients were > 65 years of age [approximately N = 180 elderly and N = 180 younger ED patients received vardenafil treatment in two ODT trials]. The mean age of all subjects in phase 3 trials was 61.7 ± 11.0 yrs ranging from 21 to 88 yrs in the placebo group and 22 to 83 yrs in the ODT 10 mg group. Overall, across the two trials, about 8% of subjects were <45 yrs (n = 28), 41% were ≥ 45 to <65 yrs (n = 137), 43% were ≥ 65 to <75 yrs (n = 153), and 9% were ≥ 75 yrs of age (n = 29). According to the medical reviewer, the elderly subjects in these trials were representative of the population. Almost 50% had high blood pressure, 33% with diabetes, 10% with ischemic cardiac disease etc. There was no apparent trend for increased incidence of AEs with increasing age in these studies. The overall exposure to the study drug during on-demand usage was 37.6 ± 21.85 doses in the <65 years age group and 28.8 ± 20.21 doses in patients > 65 years (elderly). The calculated average doses per week were 3.2 and 2.4 in these two groups.
 - ***Since the safety of the ~ 70 % higher systemic exposures of vardenafil in the elderly (age range 65- 88 years) has been adequately assessed and found to be unremarkable in the two phase 3 clinical trials that included 50 % elderly (of which ~ 10 % were above the age of 75 years), it is this reviewer's opinion that the ODT 10 mg can be administered to elderly ED patients as the starting dose.***

- ***This recommendation also relies partly on the fact that for all ED patients including the elderly, there is a possibility of down-titrating the dose to 5 mg if tolerability becomes an issue. This can be achieved in the context of ODT use by switching to the marketed 5 mg Levitra IR dose.***

2.4 Extrinsic Factors

The following are known drug-drug interactions with vardenafil and the associated dosing recommendations as extracted from the approved labeling for Levitra IR:

In vivo studies: Cytochrome P450 Inhibitors

- Cimetidine (400 mg b.i.d.) had no effect on vardenafil bioavailability (AUC) and maximum concentration (C_{max}) of vardenafil when co-administered with 20 mg LEVITRA in healthy volunteers.
- Erythromycin (500 mg t.i.d.) produced a 4-fold increase in vardenafil AUC and a 3-fold increase in C_{max} when co-administered with LEVITRA 5 mg in healthy volunteers. It is recommended not to exceed a single 5 mg dose of LEVITRA in a 24-hour period when used in combination with erythromycin.
- Ketoconazole (200 mg once daily) produced a 10-fold increase in vardenafil AUC and a 4-fold increase in C_{max} when co-administered with LEVITRA (5 mg) in healthy volunteers. A 5-mg LEVITRA dose should not be exceeded when used in combination with 200 mg once daily ketoconazole. Since higher doses of ketoconazole (400 mg daily) may result in higher increases in C_{max} and AUC, a single 2.5 mg dose of LEVITRA should not be exceeded in a 24-hour period when used in combination with ketoconazole 400 mg daily.
- ***HIV Protease Inhibitors:***
- Indinavir (800 mg t.i.d.) co-administered with LEVITRA 10 mg resulted in a 16-fold increase in vardenafil AUC, a 7-fold increase in vardenafil C_{max} and a 2-fold increase in vardenafil half-life. It is recommended not to exceed a single 2.5 mg LEVITRA dose in a 24-hour period when used in combination with indinavir.
- Ritonavir (600 mg b.i.d.) co-administered with LEVITRA 5 mg resulted in a 49-fold increase in vardenafil AUC and a 13-fold increase in vardenafil C_{max}. The interaction is a consequence of blocking hepatic metabolism of vardenafil by ritonavir, a highly potent CYP3A4 inhibitor, which also inhibits CYP2C9. Ritonavir significantly prolonged the half-life of vardenafil to 26 hours. Consequently, it is recommended not to exceed a single 2.5 mg LEVITRA dose in a 72-hour period when used in combination with ritonavir.
- ***Other CYP3A4 inhibitors:*** Although specific interactions have not been studied, other CYP3A4 inhibitors, including grapefruit juice would likely increase vardenafil exposure.
- ***Other Drug Interactions:*** No pharmacokinetic interactions were observed between vardenafil and the following drugs: glyburide, warfarin, digoxin, Maalox, and ranitidine. In the warfarin study, vardenafil had no effect on the prothrombin time or other pharmacodynamic parameters.

- Nifedipine: Nifedipine did not alter the plasma levels of vardenafil when taken in combination.

Effect of vardenafil on other drugs:

- Nifedipine: Vardenafil 20 mg, when co-administered with slow-release nifedipine 30 mg or 60 mg once daily, did not affect the relative bioavailability (AUC) or maximum concentration (C_{max}) of nifedipine, a drug that is metabolized via CYP3A4. Nifedipine did not alter the plasma levels of vardenafil when taken in combination. In these patients whose hypertension was controlled with nifedipine, vardenafil 20 mg produced mean additional supine systolic/diastolic blood pressure reductions of 6/5 mmHg compared to placebo.
- Ritonavir and indinavir: Upon concomitant administration of 5 mg vardenafil with 600 mg BID ritonavir, the C_{max} and AUC of ritonavir were reduced by approximately 20%. Upon administration of 10 mg of vardenafil (film-coated tablets) with 800 mg TID indinavir, the C_{max} and AUC of indinavir were reduced by 40% and 30%, respectively.
- Aspirin: Vardenafil 10 mg (film-coated tablets) and 20 mg did not potentiate the increase in bleeding time caused by aspirin (two 81 mg tablets).

Use with alpha-blockers:

- In some patients, concomitant use of these two drug classes can lower blood pressure significantly leading to symptomatic hypotension (e.g., fainting). Concomitant treatment should be initiated only if the patient is stable on his alpha blocker therapy. In those patients who are stable on alpha-blocker therapy, LEVITRA should be initiated at a dose of 5 mg (2.5 mg when used concomitantly with certain CYP3A4 inhibitors).

Alcohol:

- Alcohol (0.5 g/kg body weight: approximately 40 mL of absolute alcohol in a 70 kg person) and vardenafil plasma levels were not altered when dosed simultaneously. Vardenafil 20 mg did not potentiate the hypotensive effects of alcohol during the 4-hour observation period in healthy volunteers when administered with alcohol (0.5 g/kg body weight).

Nitrates:

- The blood pressure lowering effects of sublingual nitrates (0.4 mg) taken 1 and 4 hours after vardenafil and increases in heart rate when taken at 1, 4 and 8 hours were potentiated by a 20 mg dose of LEVITRA in healthy middle-aged subjects. These effects were not observed when LEVITRA 20 mg was taken 24 hours before the NTG. Potentiation of the hypotensive effects of nitrates for patients with ischemic heart disease has not been evaluated, and concomitant use of LEVITRA and nitrates is contraindicated.

Use of Vardenafil ODT in presence of interacting drugs: Sponsor proposes the following language with regard to pharmacokinetic and pharmacodynamic interactions:

Based on the known potential for drug interactions with Levitra and the dosing restrictions currently in practice, sponsor's proposal to not allow use of vardenafil ODT with moderate to potent CYP3A4 inhibitors is acceptable. Based on the current recommendation that patients on alpha-blockers initiate Levitra at the lowest dose, it is acceptable not to recommend vardenafil ODT as the starting dose in such patients. Contraindication of vardenafil ODT with nitrates is acceptable.

2.5 General Biopharmaceutics

2.5.1 What is the relative bioavailability of the proposed to-be-marketed ODT formulation to the approved immediate release formulation of Levitra (IR; 10 mg dose)?

Relative bioavailability of ODT vs. IR in healthy volunteers (study 12769):

- As described in the PK section of this review, study 12769 evaluated single dose PK of both ODT and IR formulations in healthy volunteers (18-50 years).
- Plasma concentration-time profiles as well as PK data of vardenafil are summarized below for both formulations:

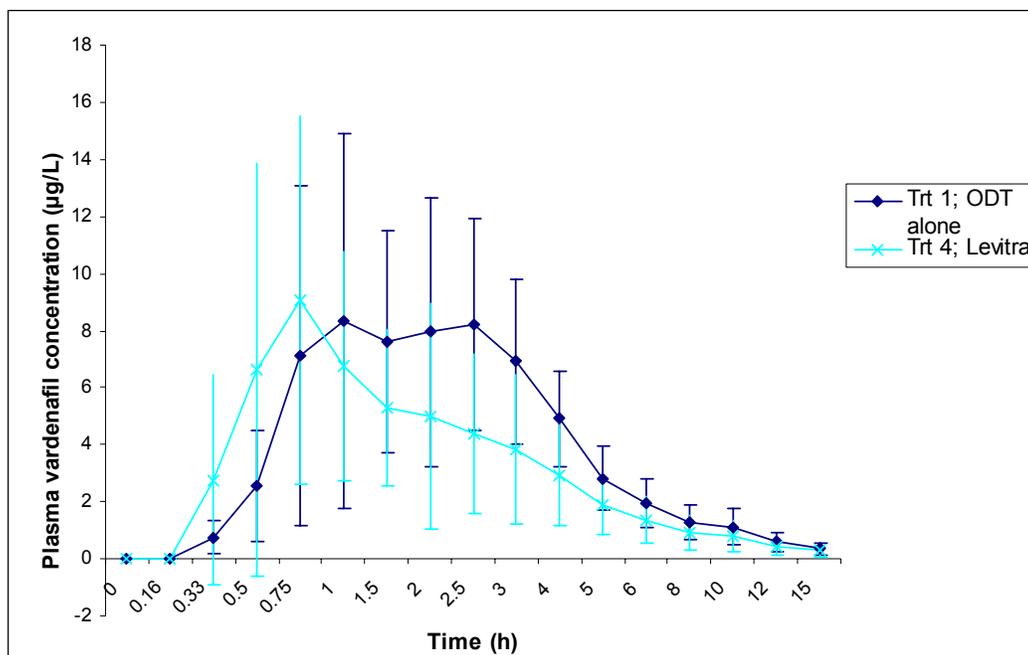


Figure 14: Plasma concentration-time profiles comparing PK of vardenafil for the 10 ODT vs. 10 mg Levitra IR.

Table 10: Plasma Vardenafil PK comparing ODT vs. IR (10 mg) in healthy volunteers of study 12769

Vardenafil PK	ODT alone TRT 1 (n=13)	LEVITRA IR TRT 4 (n=13)
Cmax (µg/L)	12.15 ± 5.78	10.78 ± 6.4
Tmax* (h)	1.5 [0.75-3.0]	0.75 [0.5-2.0]
AUCinf (µg h/L)	42.37 ± 16.95	30.48 ± 16.39
AUC0-tn (µg h/L)	41.42 ± 16.58	29.4 ± 16.1
T1/2 (h)	4.27 ± 1.03	3.99 ± 1.15

- The ODT 10 mg formulation when administered under fasted conditions without water results in an increased bioavailability (BA) of vardenafil (by 44 %) compared to the AUC of 10 mg Levitra formulation. The increased BA from the ODT is speculated to be due to the contribution of a local absorption component in the oral cavity that bypasses the first-pass metabolism.
- As the overall rate of absorption from the oral cavity is slower, there appears to be a reduced effect on vardenafil Cmax from the ODT (15 % higher compared to Levitra) and a prolonged Tmax (1.5 h vs. 0.75 h with Levitra).
- Although not apparent in all individuals, the peak concentrations of vardenafil resulting from the ODT formulation were sustained for a longer duration

compared to Levitra IR, as seen from the average profile above and in some of the individual profiles shown below.



- Metabolite M1 pharmacokinetics across the two formulations are summarized:

Table 11: Plasma M1 metabolite pharmacokinetics comparing ODT vs. IR (10 mg) in healthy volunteers of study 12769

Metabolite PK	ODT alone TRT 1 (n =13)	LEVITRA IR TRT 4 (n =13)
Cmax (µg/L)	13.54 ± 5.11	13.94 ± 6.41
Tmax * (h)	1.0 [0.75-2.5]	0.75 [0.5-2.0]
AUCinf (µg h/L)	30.66 ±10.45	27.39 ± 10.1
AUC0-tn (µg h/L)	28.5 ± 10.3	24.1 ± 10.2
T1/2 (h)	2.28 ± 1.19	2.19 ± 0.7

- The metabolite Cmax values were comparable while the metabolite AUC was modestly higher with the ODT formulation. Following the ODT 10 mg formulation (administered without water under fasting conditions), the AUC values of the M1 metabolite were 17 % higher, compared to those seen with

Levitra 10 mg formulation. The T1/2 values of the metabolite (~ 2.2 h) were also comparable across treatments.

Table 12: Statistical results comparing relative bioavailability of ODT vs. IR (healthy)

ODT vs. IR (10 mg)	Vardenafil Cmax Ratio [90 % CI range]	Vardenafil AUC Ratio [90 % CI range]	Metabolite Cmax Ratio [90 % CI range]	Metabolite AUC Ratio [90 % CI range]
Study 12769 [healthy males; 18-50 years; n = 13]				
Conditions of dosing: ODT/fasting/no water	114.66 [94.04- 139.8]	144.12 [131.7- 157.8]	100.27 [83.19-120.87]	117.56 [107.86 – 128.13]

Relative bioavailability of ODT vs. IR in ED patients (study 13396):

- As described in the PK section of this review, study 13396 evaluated the single dose PK of both ODT and the IR formulations in ED patients.

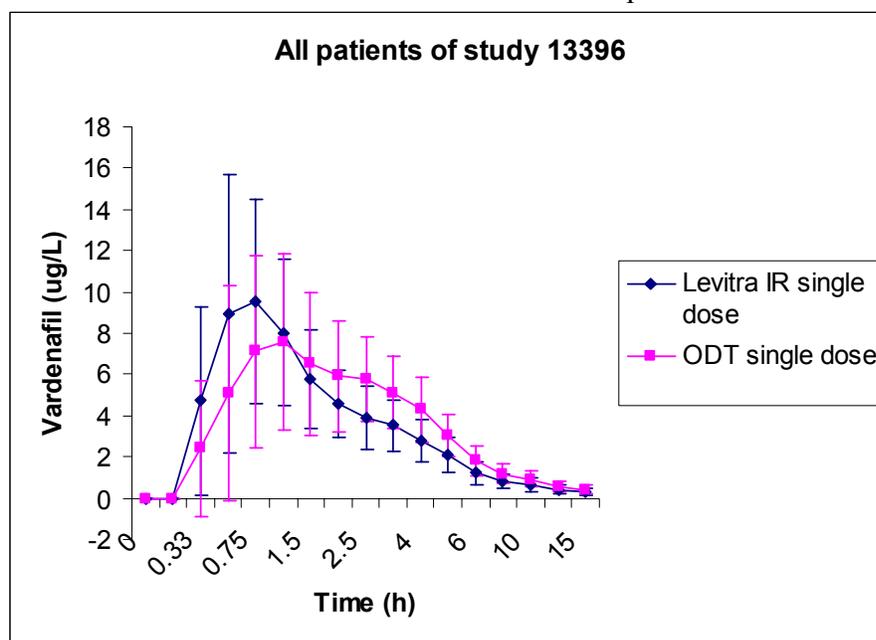


Figure 15: Plasma concentration-time profiles comparing single dose PK of vardenafil from ODT (no water) vs. IR (10 mg) formulations in ED patients; all patients regardless of age

- Similar to the phase 1 study in healthy volunteers (age 18-50), the ODT provided a greater AUC of vardenafil, although the magnitude seen in this study of ED patients (age ≤45) was lower (29 % vs. 44 %). The Cmax of vardenafil exhibited a modest decrease relative to IR in this study, while it was somewhat higher in healthy volunteer study 12769.

- The lowering of the vardenafil C_{max} relative to IR was much more pronounced in the elderly than in younger ED patients (20 % vs. 8 %), while the metabolite M1 C_{max} was lower by ~ 27 % in both age groups.
- Additionally, in the elderly ED patients, the AUC of M1 metabolite was lower by ~ 19 % relative to the IR formulation.

Table 13: PK parameters of Levitra IR and ODT 10 mg formulations after a single dose in ED patients of study 13396 [formulation and age effects are shown]

PK parameters:		Mean ± SD (% CV)			
10mg IR; single dose	Parameter	18-45 years (N = 14)	46-64 years (N = 6)	65-69 years (N = 7)	>70 years (N = 7)
	C _{max} (µg/L)	10.22 ± 7.18 (70.3)	9.23 ± 3.3 (36)	12.2 ± 4.9 (40)	12.3 ± 6.3 (51)
	T _{max} (h)	0.75	0.5	0.75	0.75
	AUC (µg h/L)	28.3 ± 18.25 (65)	24.13 ± 5.79 (24)	37.4 ± 9.8 (26)	35.4 ± 12.0 (34)
	AUC _{0-tn} (µg h/L)	26.8 ± 17.6 (65)	22.7 ± 5.3 (23)	35.4 ± 9.12 (26)	34 ± 11.8 (35)
	T _{1/2} (h)	4.92 ± 1.62 (33)	4.04 ± 0.80 (20)	6.9 ± 2.1 (30.5)	5.86 ± 1.02 (18)
10 mg ODT; single dose	Parameter	18-45 years (N = 14)	46-64 years (N = 6)	65-69 years (N = 7)	>70 years (N = 7)
	C _{max} (µg/L)	8.4 ± 4.4 (52)	7.25 ± 2.67 (37)	10.3 ± 5.5 (53)	10.2 ± 6.3 (62)
	T _{max} (h)	1.5	0.875	1.0	0.75
	AUC (µg h/L)	34.58 ± 19.5 (56)	30.2 ± 8.7 (29)	49.5 ± 20.6 (42)	41.2 ± 13.3 (32)
	AUC _{0-tn} (µg h/L)	32.9 ± 18.6 (56)	29.1 ± 8.6 (30)	46.5 ± 19.8 (43)	39.4 ± 13.2 (34)
	T _{1/2} (h)	4.6 ± 2.4 (52)	4.8 ± 1.1 (22)	6.6 ± 1.9 (29)	5.7 ± 1.0 (18)

Table 14: Statistical results comparing relative bioavailability of ODT vs. IR in ED patients (young and elderly).

ODT vs. IR (10 mg)	Vardenafil C _{max} Ratio [90 % CI range]	Vardenafil AUC Ratio [90 % CI range]	Metabolite C _{max} Ratio [90 % CI range]	Metabolite AUC Ratio [90 % CI range]
Study 13396 [ED males; 18-80 years; n = 14 per each age group]				
≤ 45 years	92.39 [74.76 – 114.17]	129.22 [116.63 – 143.18]	72.80 [61.56 – 86.10]	109.09 [91.06 – 130.70]
≥ 65 years	80.80 [65.38 – 99.85]	120.88 [109.09 – 133.93]	73.89 [62.48 – 87.39]	81.44 [70.02 – 94.73]

- **Overall, these results suggest that the ODT formulation provides greater systemic exposure of vardenafil (~ 29 %) in younger ED patients relative to the**

approved IR formulation. The net increase in elderly with the ODT formulation was somewhat smaller, ~ 20 % relative to IR. Sponsor attributes this lower relative increase in elderly to potentially lower salivary flow (dry mouth) in these individuals, thereby reducing the fraction of locally absorbed drug. The effect on Cmax was variable across studies, with the ED patient study showing a small decrease in Cmax relative to IR. The potential variability of absorption associated with the local route for the ODT formulation may have had a more pronounced effect on Cmax.

2.5.3 What is the effect of food on the BA of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

- As described in the pharmacokinetic section of this review, food-effect on PK from ODT formulation was evaluated in study healthy volunteers (age 18-50) of study 12769.
- In the fasted group, the study drug was administered in the morning after a fasting period of at least 10 hours. In the fed-group, subjects received a breakfast containing 42 g proteins (1 g = 4.2 kcal), 67 g carbohydrates (1 g = 4.2 kcal), 63.5 g fat (1 g = 9.2 kcal), i.e. 1051 kcal in total.

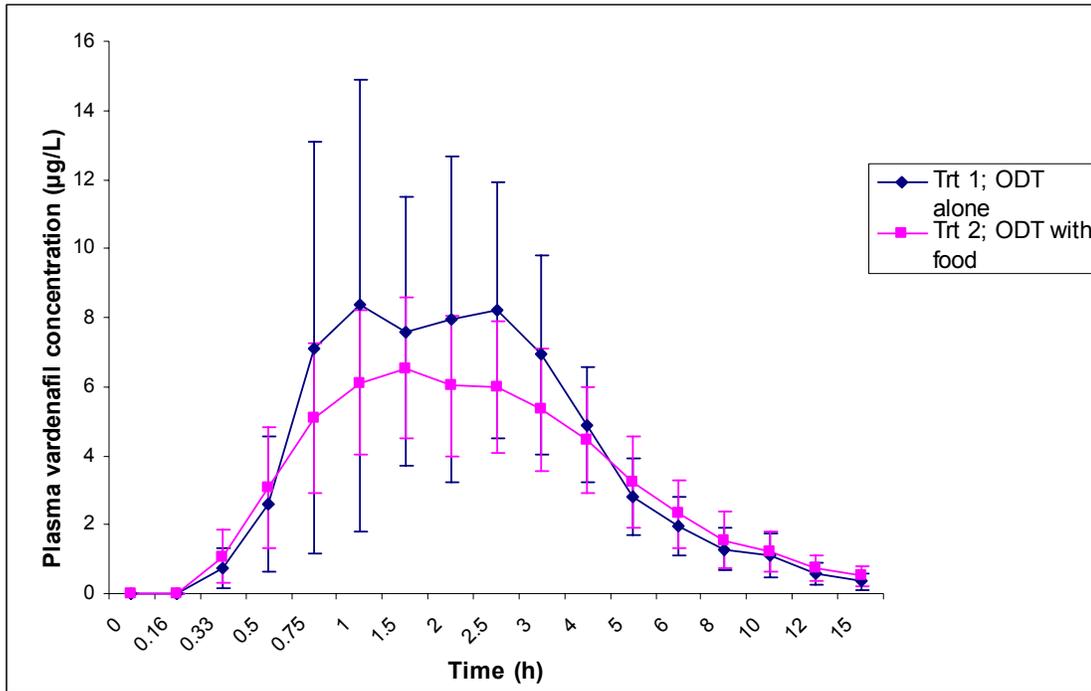


Figure 16: Plasma concentration-time profiles of vardenafil when the ODT was administered with or without food.

Table 15: Pharmacokinetics of Vardenafil when ODT was taken with or without food

	ODT alone	ODT with food
--	-----------	---------------

	TRT 1 (n=13)	TRT 2 (n=13)
C _{max} (µg/L)	12.15 ± 5.78	7.52 ± 2.33
T _{max} * (h)	1.5 [0.75-3.0]	1.5 [0.75-2.5]
AUC _{inf} (µg h/L)	42.37 ± 16.95	40.66 ± 14.26
AUC _{0-tn} (µg h/L)	41.42 ± 16.58	39.06 ± 13.85
T _{1/2} (h)	4.27 ± 1.03	4.8 ± 1.06
CL/f (L/h)	273.3 ± 109.4	274.4 ± 92.6

Table 16: Pharmacokinetics of M1 metabolite when ODT was taken with or without food:

Metabolite M1	ODT alone TRT 1 (n=13)	ODT with food TRT 2 (n=13)
C _{max} (µg/L)	13.54 ± 5.11	6.82 ± 3.18
T _{max} * (h)	1.0 [0.75-2.5]	1.5 [0.75-3.0]
AUC _{inf} (µg h/L)	30.66 ± 10.45	20.94 ± 7.04
AUC _{0-tn} (µg h/L)	28.5 ± 10.3	18.9 ± 9.5
T _{1/2} (h)	2.28 ± 1.19	2.21 ± 1.15
CL/f (L/h)	357 ± 163	509 ± 199

- Food intake reduced the C_{max} of vardenafil by ~ 35 % while the AUC of vardenafil was not significantly affected with food. T_{max} was not altered with food. The major metabolite M1 had significantly lower C_{max} and AUC in presence of food. Concomitant food intake appears to affect both systemic absorption and GI metabolism of vardenafil.

Table 17: Statistical results comparing food-effect on vardenafil and M1 PK.

Food-Effect on PK	Vardenafil C _{max} Ratio [90 % CI range]	Vardenafil AUC Ratio [90 % CI range]	Metabolite C _{max} Ratio [90 % CI range]	Metabolite AUC Ratio [90 % CI range]
Study 12769 [Healthy males; 18-50 years; n = 13]				
ODT fed/ODT fasted	64.66 [53.03 – 78.83]	97.94 [89.48 – 107.20]	48.45 [40.20 – 58.41]	68.95 [63.38 – 75.02]

- *In the two randomized, placebo-controlled phase 3 clinical trials of vardenafil ODT formulation (12093 and 12094) dosing was done without regard to food. Therefore, it is reasonable to label the drug for dosing with or without food as safety and efficacy in these scenarios have been assessed in the clinical trials.*

2.5.4 What is the effect of concomitant water intake with the ODT formulation instead of allowing the ODT to dissolve in the mouth and then swallow the liquid (i.e. per phase 3 and labeling instructions)?

- As described in the pharmacokinetic section of this review, the effect of concomitant water intake (i.e. ODT swallowed with 180 mL water) on the pharmacokinetics from the ODT formulation were evaluated in healthy volunteers (age 18-50) of study 12769.

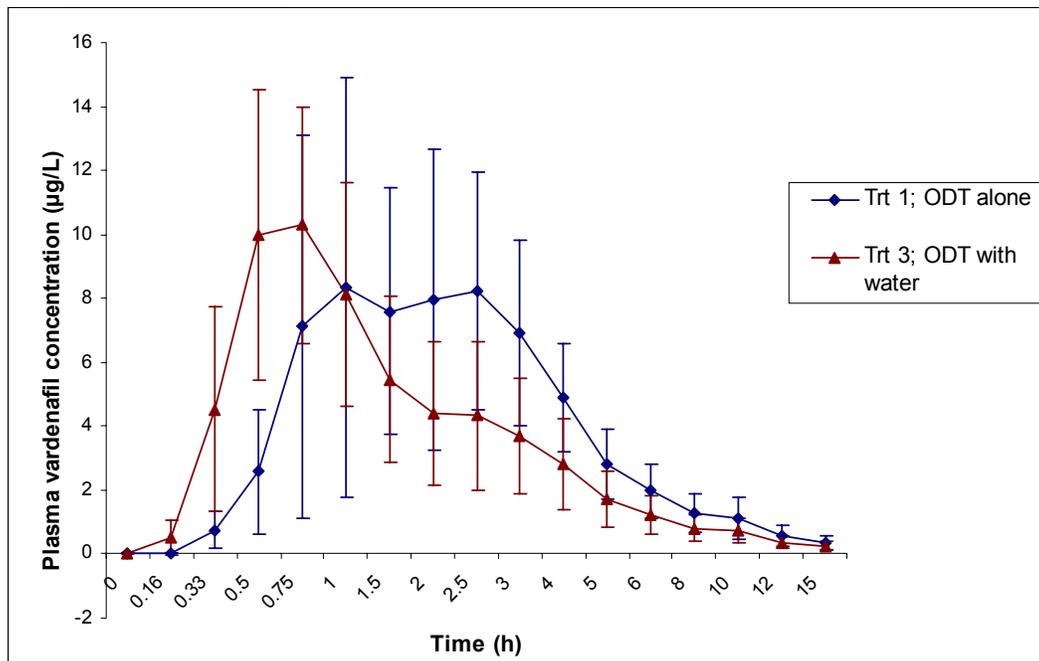




Figure 17: The plasma concentration-time profiles of vardenafil from the ODT formulation when administered with or without water

Table 18: Plasma pharmacokinetic parameters of vardenafil when the ODT formulation was administered with or without water

Vardenafil	ODT alone TRT 1 (n =13)	ODT with water TRT 3 (n = 13)
Cmax ($\mu\text{g/L}$)	12.15 \pm 5.78	11.49 \pm 4.84
Tmax * (h)	1.5 [0.75-3.0]	0.5 [0.5-1.0]
AUCinf ($\mu\text{g h/L}$)	42.37 \pm 16.95	30.56 \pm 13.31
AUC0-tn ($\mu\text{g h/L}$)	41.42 \pm 16.58	29.45 \pm 13.04
T1/2 (h)	4.27 \pm 1.03	3.94 \pm 1.23
CL/f (L/h)	273.3 \pm 109.4	383.4 \pm 147.5

Table 19: Plasma pharmacokinetic parameters of M1 metabolite when the ODT formulation was administered with or without water

Metabolite M1	ODT alone TRT 1 (n=13)	ODT with water TRT 3 (n = 13)
Cmax (µg/L)	13.54 ± 5.11	15.42 ± 4.45
Tmax * (h)	1.0 [0.75-2.5]	0.75 [0.5-1.0]
AUCinf (µg h/L)	30.66 ±10.45	26.8 ± 9.72
AUC0-tn (µg h/L)	28.5 ± 10.3	24.7 ± 9.2
T1/2 (h)	2.28 ± 1.19	2.21 ± 0.87
CL/f (L/h)	357 ± 163	407 ± 178

- When ODT was administered with water the PK parameters were similar to those seen with the IR formulation taken with water. This observation corroborates the earlier conclusion that ‘supra-bioavailability’ from the ODT formulation was due to a small amount of drug absorbed directly from the oral mucosa bypassing the first-pass effect.

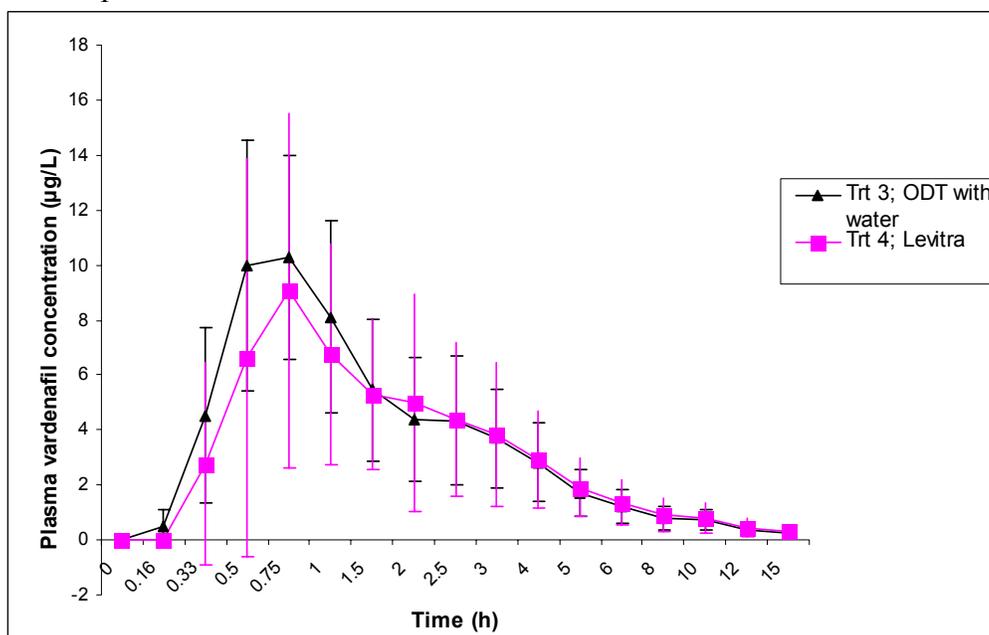


Figure 18: Plasma concentration-time profiles for vardenafil after the ODT was administered with water in relation to Levitra IR (Study 12769)

Table 20: Statistical results for comparing PK of ODT administered with or without water.

Effect of swallowing the ODT with water on PK	Vardenafil Cmax Ratio [90 % CI range]	Vardenafil AUC Ratio [90 % CI range]	Metabolite Cmax Ratio [90 % CI range]	Metabolite AUC Ratio [90 % CI range]
Study 12769 [Healthy males; 18-50 years; n = 13]				
ODT with water/ODT without water	96.23 [79.11 – 117.05]	71.39 [65.29 – 78.05]	116.75 [97.08 – 140.40]	87.75 [80.74 – 95.36]

- ***Clinical trials for the ODT formulation were conducted without water. Thus the labeling will indicate that the dose should be administered without water. The above evaluation was helpful in assessing the safety of the resultant exposure if the dose is inadvertently taken with water during clinical use.***

2.6 Analytical

Study 12769:

- Bioanalytical assay: Bioanalyses for vardenafil and M1 metabolite were conducted at Bayer HealthCare AG (Wuppertal, Germany) using a validated HPLC method with mass spectrometric detection. Concentrations of vardenafil and its metabolite were determined after solid/liquid extraction using C18 cartridges by HPLC coupled with a tandem mass spectrometer. [2H5] BAY 38-9456 was used as internal standard for vardenafil, [2H5] BAY 44-5576 was used as an internal standard for the metabolite M-1. Vardenafil was determined and calculated as free base.
- Calibration range: The method is validated within a working range of 0.1 to 50.0 µg/L (Vardenafil) and 0.5 to 50.0 µg/L (M1). Calibration data demonstrate acceptable precision and accuracy of the back-calculated values.
- Selectivity: Chromatograms of 6 ammonium heparin blank plasma samples from different donors did not reveal any relevant peak interfering with the peak of Vardenafil or BAY 44-5576. The method can therefore be regarded as selective.
- Stability information: Stability has been characterized under various conditions as shown:

Matrix	Storage conditions	Container used	Period
Sample (in autosampler)	Room temperature	(b) (4)	at least 72 hours
Plasma	<= -15°C		at least 3 freeze-thaw cycles
Whole blood	Room temperature, daylight (window sill) 2 – 8°C		at least 6 hours
Plasma	Room temperature 2 – 8°C <= -15°C		at least 24 hours at least 24 hours at least 12 months

- Recovery: Data for vardenafil and its M1 metabolite are shown:

Vardenafil:

Concentration [µg/L]	1.00	25.0
Recovery (n=6)	80.2	82.1
[%]		

BAY 44-5576:

Concentration [µg/L]	1.00	25.0
Recovery (n=6)	84.8	87.3
[%]		

- Precision and Accuracy: Acceptable precision ($\leq 15\%$) and accuracy ($\pm 15\%$) values were noted for QC samples including at lower limit of quantitation (LLOQ) for vardenafil and M1 metabolite.

Vardenafil:

Concentration [$\mu\text{g/L}$]		0.100	0.300	1.50	9.00	30.0
		= LOQ				
<u>Intra-assay precision</u>						
Series 1	N	6	6	6	6	6
	Accuracy [%]	96.3	102.9	101.8	97.9	100.8
	Precision [%]	8.1	5.4	1.8	3.2	2.8
Series 2	N	6	6	6	6	6
	Accuracy [%]	110.4	97.0	97.5	98.0	100.9
	Precision [%]	15.4	12.6	3.7	4.1	0.8
Series 3	N	6	6	6	6	6
	Accuracy [%]	111.7	104.8	102.9	101.4	103.1
	Precision [%]	20.4	15.0	2.6	2.5	5.1
<u>Inter-assay precision</u>						
All samples	N	18	18	18	18	18
	Accuracy [%]	106.2	101.6	100.7	99.1	101.6
	Precision [%]	16.5	11.5	3.5	3.5	3.4

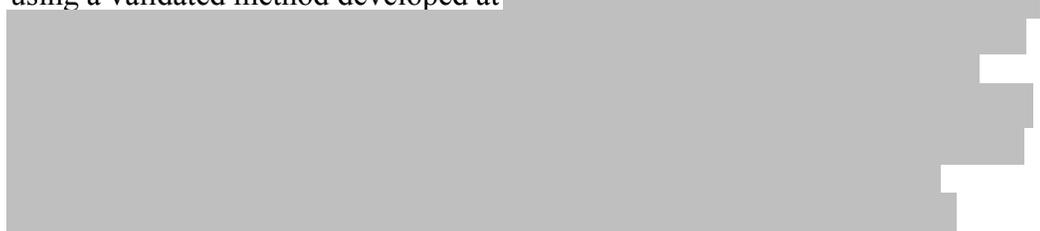
BAY 44-5576:

Concentration [$\mu\text{g/L}$]		0.500	1.50	9.00	30.0
		= LOQ			
<u>Intra-assay-precision</u>					
Series 1	N	6	6	6	6
	Accuracy [%]	108.8	99.9	97.8	101.2
	Precision [%]	11.0	3.7	1.9	2.0
Series 2	N	6	6	6	6
	Accuracy [%]	94.5	98.2	98.0	100.2
	Precision [%]	6.4	3.0	3.7	1.3
Series 3	N	6	6	6	6
	Accuracy [%]	106.3	97.7	99.7	99.1
	Precision [%]	10.1	7.3	2.0	4.0
<u>Inter-assay-precision</u>					
All samples	N	18	18	18	18
	Accuracy [%]	103.2	98.6	98.5	100.1
	Precision [%]	11.0	4.8	2.7	2.7

- ***Overall, the LC-MS/MS analytical method for the detection of vardenafil and its metabolite M-1 from human plasma appears adequately validated.***

Study 13396 and Study 12093 (PK subset):

- Bioanalyses for vardenafil and M1 metabolite in these studies were conducted using a validated method developed at (b) (4)





(b) (4) Results of the validation are presented in the following Table.

Vardenafil Results of pre-study validation (including the LLOQ)

Nominal concentration [$\mu\text{g/L}$]	N	Accuracy [%]	Precision [%]
0.123 (LLOQ)	6	104.5	5.6
0.357	6	90.5	3.6
1.290	6	99.1	7.6
14.253	6	100.0	3.2
38.922	6	96.9	2.8

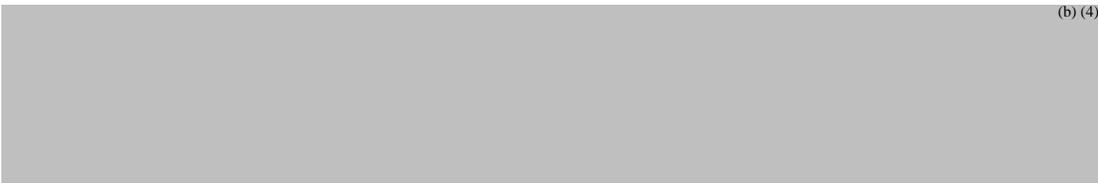
Metabolite (M-1) results of pre-study validation (including LLOQ)

Nominal concentration [$\mu\text{g/L}$]	N	Accuracy [%]	Precision [%]
0.469 (LLOQ)	5	107.9	5.4
1.300	6	105.1	4.8
14.366	6	103.5	2.6
39.229	6	103.9	2.6

- Results of the pre-study validation were within acceptable limits for precision and accuracy.

Conclusions: *The LC-MS/MS methods for bioanalyses of vardenafil and metabolite M1 in human plasma has been adequately validated for use in the assay of study samples.*

3 Detailed Labeling Recommendations

-  (b) (4)
- Sponsor has since submitted a separate labeling for their ODT formulation in physicians labeling rule (PLR) format. This proposed labeling for vardenafil ODT has been reviewed and the format and content appear acceptable pending minor revisions. Most of the information is similar to the approved Levitra labeling, including those pertaining to Pharmacokinetic and Pharmacodynamic drug-drug interactions, and QT prolongation effect.
- Changes to reflect reorganization into the PLR format and new Clinical and Clinical Pharmacology information to the Clinical Pharmacology, Dosage and Administration and Clinical sections of the labeling have been proposed. Clinical Pharmacology relevant sections of the draft labeling are shown below.
- Revisions (if any) are proposed as follows: additions are shown as underlined text and deletions are shown as ~~strikethroughs~~.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200179	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	VARDENAFIL HCL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANDHYA K APPARAJU
06/02/2010

MYONG JIN KIM
06/09/2010

A separate TL's memo will address OCP's post-marketing requirement and labeling issues.

BIOPHARMACEUTICS REVIEW			
Office of New Drugs Quality Assessment			
Application No.:	NDA 200-179 (000)	Reviewer: Sandra Suarez Sharp, Ph.D	
Division:	DRUP		
Sponsor:	Bayer Healthcare Pharmaceuticals	Team Leader: Angelica Dorantes, Ph.D	
Trade Name:	(b) (4)	Supervisor: Patrick J. Marroum, Ph.D	
Generic Name:	Vardenafil Hydrochloride (b) (4)	Date Assigned:	Sep 15, 2009
Indication:	Erectile dysfunction (ED)	Date of Review:	March 13, 2009
Formulation/strength	(b) (4) Tablets, 10 mg		
Route of Administration	Oral		
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission dates	CDER Stamp Date	Date of informal/Formal Consult	DUE DATE
Aug 26, 2009, Dec 8, 2009	Aug 26, 2009, Dec 8, 2009	Sep 15, 2009	Nov 13, 2009
Type of Submission:	Original NDA		
Type of Consult:	Disintegration method and specifications		
REVIEW SUMMARY:			
<p>LEVITRA[®] (vardenafil hydrochloride) 2.5, 5, 10 and 20 mg film-coated tablets were approved by the Agency on Aug 19, 2003 under NDA 21-400 as an oral treatment for ED. The sponsor is proposing a new formulation for vardenafil hydrochloride consisting of an orally disintegrating tablet (orodisperse) for the treatment of ED. This new formulation, (b) (4), contains the equivalent to 10 mg vardenafil and it has been formulated to rapidly disintegrate in the mouth. The recommended starting dose of Levitra (film-coated tablets) or (b) (4) (also referred in this document as (b) (4)) is 10 mg taken orally.</p> <p>Disintegration testing is being proposed in lieu of dissolution as the quality control test of the orodisperse tablets. This review summarizes the data supporting this proposal and makes conclusions and recommendations about the value of in vitro disintegration testing and its applicability for assessing the product's quality in lieu of dissolution testing.</p> <p>The use of disintegration as a surrogate for dissolution testing is feasible under certain circumstances as delineated by the ICH Q6A guidelines (e.g. high solubility, rapidly dissolving drug product). Specifically, disintegration testing can be used as a surrogate for conventional compendial dissolution tests for highly soluble drug substances in which the intrinsic rate of solubilization is rapid and the overall drug release rate is dominated by the cohesive properties of the formulation. In the case of (b) (4), the liberation of the drug substance from the drug product occurs in less than 30 seconds and the drug substance exhibits high solubility at gastric pH levels and up to pH 6. In addition, vardenafil is a weak base (pKa about 9) and Tmax occurs at about 0.75 hr to 1.5 hrs post administration, indicating that the absorption of the drug occurs in the upper intestine since it is highly ionized at acidic pH. Therefore, these characteristics together with the higher discriminatory power of disintegration testing over dissolution testing justify the characterization of (b) (4) by disintegration testing alone.</p>			

Different disintegration specifications are recommended in this review for (b) (4). Stability batches met the reviewer's proposed specifications.

RECOMMENDATION:

The ONDQA/biopharmaceutics team has reviewed NDA 200-179 (000) submitted on Aug 26, 2009 and Dec 8, 2009. We found this NDA acceptable from the biopharmaceutics perspective. The following comment should be conveyed to the sponsor:

- The data provided in your submission dated Dec 8, 2009, indicate that disintegration testing is appropriate to discriminate changes in the process parameters or manufacturing conditions of (b) (4) Tablets, 10 mg. Specifically, disintegration values of (b) (4) seconds were observed for (b) (4) tables under (b) (4) compared to (b) (4) seconds under normal manufacturing conditions. Therefore, to ensure consistent quality of the drug product, we recommend the following disintegration specification for both, shelf-life and product release.

Test	Specification	
Disintegration	Shelf-life	Product Release
	(b) (4)	(b) (4)

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: NDA 200-179 (000), JDavis, ADorantes, JSalemme, Dchristner, MJRhee

INTRODUCTION

LEVITRA[®] (vardenafil hydrochloride) 2.5, 5, 10 and 20 mg film-coated tablets are approved in the United States as an oral treatment for erectile dysfunction (ED). The tablets contain the equivalent of 2.5 mg, 5 mg, 10 mg and 20 mg vardenafil. Vardenafil is a potent and selective phosphodiesterase type-5 (PDE5) inhibitor.

The sponsor is proposing a new formulation for vardenafil hydrochloride, (b) (4) consisting of an orally disintegrating tablet (orodisperse) for the treatment of ED. This new formulation contains the equivalent to 10 mg vardenafil and it has been formulated to rapidly disintegrate in the mouth. The median time to reach Cmax (Tmax) in patients receiving 10 mg (b) (4) in the fasted state varied between 45 to 90 minutes. After administration of 10 mg (b) (4) to patients mean vardenafil AUC was increased from 21 to 29 % while mean Cmax was 8 to 19 % lower in comparison to 10 mg LEVITRA film coated tablet. A high fat meal had no effect on vardenafil AUC and Tmax in healthy volunteers and reduced Cmax by 35%. Based on these results (b) (4) can be taken before or after food. If (b) (4) is taken with liquid, the AUC is reduced by 29 % and median Tmax is shortened by 60 minutes while Cmax is not affected. (b) (4) should be taken without liquid.

CHEMISTRY

Drug Substance

According to the sponsor, [REDACTED] (b) (4)

[REDACTED] It appears as vardenafil *mono* hydrochloride trihydrate (HCL 3H₂O) is stable over a wide range of environmental humidity and is not hygroscopic under typical production conditions. In solid form it shows acceptable temperature, hydrolytic and photolytic stability.

Formulation

[REDACTED] (b) (4) is a white, round orodispersible tablet with no debossing. The components and composition of the product are summarized in Table 1.

Table 1. Components and composition for [REDACTED] (b) (4) tablets, 10 mg

Composition	Reference to standard	Function	Amount [mg]
Drug substance			
Vardenafil hydrochloride trihydrate [REDACTED] (b) (4)	specification	drug substance	11.85 ^a
Excipients			
Aspartame	Ph. Eur., NF	[REDACTED] (b) (4)	[REDACTED] (b) (4)
Flavor peppermint	specification ^b	[REDACTED]	[REDACTED]
Magnesium stearate	Ph. Eur., NF, Ph. Jap.	[REDACTED]	[REDACTED]
Pharmaburst B2 ^c consisting of:	specification	[REDACTED]	[REDACTED]
Crospovidone	Ph. Eur., NF	[REDACTED]	- ^c
Mannitol	Ph. Eur., USP	[REDACTED]	- ^c
Silica colloidal hydrated	Ph. Eur., NF	[REDACTED]	- ^c
Sorbitol	Ph. Eur., NF	[REDACTED]	- ^c
Weight			180.00

^a corresponding to 10.0 mg vardenafil

^b components of flavor peppermint are Ph. Eur., FCC and BP quality

^c exact specification of the commercially available blend Pharmaburst™ B2 is stated in the composition of [REDACTED] (b) (4)

Dissolution Method for Vardenafil IR Tablets

The approved dissolution method and specifications for Levitra IR tablets is as follows^{1,2}:

USP Apparatus	Media Volume	Temperature	Medium	Specifications
II (paddle)	900 mL	37 °C	0.1 N HCl	Q= (b) (4) in 15 min

Proposed Disintegration Method

The sponsor is proposing disintegration as a surrogate for dissolution testing. The following method and specifications are being proposed:

(b) (4)

Reviewer's Comments

Disintegration testing is being proposed in lieu of dissolution as the quality control test of the orodisperse tablets. The ICH Q6A guidance outlines that disintegration may be substituted for dissolution if:

- a product contains a drug which is highly soluble throughout the physiological range (dose/solubility volume < 250 mL from pH 1.2 to 6.8).
 - Based on BCS definition, a drug substance is considered *highly soluble* when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1-7.5.
- the drug product is rapidly dissolving (dissolution >80% in 15 minutes at pH 1.2, 4.0 and 6.8)
- a relationship to dissolution has been established or
- disintegration is shown to be more discriminating than dissolution

However, based on the data provided in the submission dated Aug 24, 2009, vardenafil hydrochloride did not appear to be classified as a highly soluble compound. In addition, information about dissolution of (b) (4) was not provided. The sponsor claimed that the disintegration method for (b) (4) is more discriminating than dissolution testing. However, the data provided to support this claim was insufficient. Therefore, the following issues regarding the use of disintegration as a surrogate for dissolution testing were identified during the filing period of this NDA and submitted to the sponsor on October 24, 2009:

¹ FDA Dissolution Method online

² Sponsor's submission to NDA 200179 dated Dec 8, 2009.

1. Your proposal of using disintegration testing as a quality control test in lieu of dissolution is not acceptable for the following reasons:
 - Vardenafil hydrochloride does not appear to be a highly soluble substance. The ICH Q6A guidance outlines that disintegration may be substituted for dissolution if a product contains a drug which is highly soluble throughout the physiological range (dose/solubility volume < 250 mL from pH 1.2 to 6.8).
 - Information on [REDACTED] (b) (4) dissolution throughout the physiological pH was not been provided. Disintegration may be used in lieu of dissolution if the drug product is rapidly dissolving (dissolution >80% in 15 minutes at pH 1.2, 4.0 and 6.8).
 - The relationship between dissolution and disintegration has not been established.
2. Your claim in terms of [REDACTED] (b) (4) disintegration method being more discriminating than the dissolution method is inconclusive due to a lack of sufficient information (e.g. dissolution method development report and validation).
3. Based on the statements delineated in points 1 and 2, in addition to your proposed disintegration method, you are requested to develop a more discriminating dissolution method which will serve as a quality control test.

On December 9, the Agency received the sponsor's response to the above comments as follows:

- *Vardenafil hydrochloride does not appear to be a highly soluble substance. The ICH Q6A guidance outlines that disintegration may be substituted for dissolution if a product contains a drug which is highly soluble throughout the physiological range (dose/solubility volume < 250 mL from pH 1.2 to 6.8).*

Bayer's Response:

[REDACTED] (b) (4)

Table 2. Solubility of Vardenafil in various dissolution media

Dissolution medium ^a	Vardenafil hydrochloride trihydrate dissolved at 37°C [g/900 mL]
0.1 M hydrochloride (pH 1)	(b) (4)
0.01 M hydrochloride (pH 2)	
de-ionized water (pH approx. 5.8)	
USP Acetate buffer pH 4.5	
USP Phosphate buffer pH 6.8	
USP Phosphate buffer pH 6.8 + 0.1 % SLS	
USP Phosphate buffer pH 6.8 + 0.2 % SLS	

a The buffer solutions referred to in this document were prepared according to USP.

b SLS: sodium lauryl sulfate (required to reach threefold sink-conditions)

Reviewer's Comments

The data presented in Table 2 shows that vardenafil is highly soluble up to pH about 6. At pH 6.8 its solubility greatly decreases (b) (4)

- *Information on (b) (4) dissolution throughout the physiological pH was not been provided. Disintegration may be used in lieu of dissolution if the drug product is rapidly dissolving (dissolution >80% in 15 minutes at pH 1.2, 4.0 and 6.8).*

Bayer's Response:

Vardenafil hydrochloride orodispersible tablets dissolve rapidly over the entire relevant pH-range from pH 1 to pH 6.8 (dissolution > 80% in 15 minutes at pH 1.2, 4.0 and 6.8). Figure 1 shows the dissolution characteristics over the entire relevant pH range of 1 to 6.8 evaluated at 50 rpm using 900 mL media without SLS. Despite the lower solubility at pH 6.8, the observed dissolution rates indicate that the drug substance solubility is not limiting and no regular dissolution medium would offer any discriminatory power for quality assessment.

Figure 1: Dissolution at different pH values (for n = 12 tablets), 50 rpm



Reviewer's Comments

The data provided in Figure 1 indicates that the (b) (4) is a rapidly dissolving drug product.

- 2. Your claim in terms of (b) (4) disintegration method being more discriminating than the dissolution method is inconclusive due to a lack of sufficient information (e.g. dissolution method development report and validation).*

Bayer's Response:

According to the sponsor, it is possible to prove that disintegration tests can reveal differences between acceptable and minor product qualities whereas the discriminatory capabilities of the dissolution test are very poor/limited. The use of a disintegration test instead of a dissolution test provides the detection of differences in quality-related properties resulting from variations in the manufacturing process. This demonstrates that the disintegration test is an appropriate method for quality control for Levitra Rapid Dissolve. As a result it was decided to implement only the disintegration test for routine quality testing of Levitra® Rapid Dissolve.

Summary of Dissolution method development

According to the sponsor based on the experience with this drug substance in the already approved Levitra® IR tablet formulation the method development for the dissolution test of the orodispersible formulation was started with 0.1 M hydrochloride as the dissolution medium. The test conditions were as follows:

Apparatus: USP apparatus 2 (paddle)

Dissolution medium: 900 mL 0.1 M hydrochloride (pH approx. 1)

Rotation speed: 50 rpm

Analytical procedure: UV/VIS spectrophotometry or HPLC with UV/VIS detection.

Dissolution profiles with sampling time points between 5 and 60 min were recorded using a paddle speed of 50 rpm. A specification limit of $Q = \text{[redacted]}^{(b) (4)}$ after $t = 15$ min was stipulated.

Media selection

The sponsor states that over the pH range from 1 to 6 drug release is very fast and complete after $\text{[redacted]}^{(b) (4)}$ as the drug substance is highly soluble. No differentiation between the dissolution profiles in the different media (0.1 M HCl, 0.01 M HCl, acetate buffer pH 4.5 and water) is possible (see Figure 1). At pH 6.8 the dissolution profile reflects the limited solubility (of the free base of Vardenafil) at this pH and potential difference in dissolution profile are therefore not indicative of relevant difference in drug product performance (see Figure 1). To achieve 3-fold sink conditions, as suggested in the relevant guidelines, requires the addition of a surfactant (e.g. 0.1 % SLS). Under these conditions the dissolution profile was indistinguishable from those observed at lower pH values.

Rotation Speed

The rotation speed of the reference method used for Levitra® IR tablets was already set at the lower end of a paddle dissolution method (i.e. 50 rpm). A slower rotation speed was not considered.

Testing discriminatory properties of dissolution test with regard to process variables

The discriminatory power of the dissolution test with respect to changes in the process parameters or whether there is a potential impact of altered manufacturing conditions on the dissolution properties some modified (experimental) tablet batches of Vardenafil orodispersible tablets were checked using the dissolution test method described above (same as for the market product Levitra® IR). The manufacturing conditions were deliberately altered to obtain drug product batches with different pharmaceutical quality (details are given Table 3). As demonstrated in Figure 2 a complete drug substance release was found already after about $\text{[redacted]}^{(b) (4)}$ for all tested batches, regardless the respective variations of the manufacturing process.

Table 3. Modified manufacturing conditions and their effect on disintegration times

$\text{[redacted]}^{(b) (4)}$



Figure 2. Influence of modifications of the manufacturing process and the quality of tablet ingredients on the dissolution behavior of Vardenafil hydrochloride ODT.



Figure 3. Influence of  on dissolution in different media.



Figure 4. Influence of (b) (4) on dissolution in different media.



Reviewer’s Comments

The data presented in the above section support the lack of discriminatory power of the dissolution method.

Disintegration Method Discriminatory Power

The discriminatory power of the disintegration test with regard to changes of ingredients or process parameters was evaluated by modifying the quality of the drug substance and excipients or by modifying the manufacturing conditions beyond the normal range of process parameters as described in Table 2. The disintegration times of such modified tablets were determined and compared with that of a typical reference batch (#060110) (see Table 4).

Table 4: Modified manufacturing conditions and their effect on disintegration times

Reviewer’s Comments

Dissolution of drug from a dosage form involves at least two consecutive steps: liberation of the solute or drug from the formulation matrix (disintegration), followed by dissolution of the drug (solubilization of the drug particles) in the liquid medium. The overall rate of dissolution depends on the slower of these two steps. According to the Q6A guidance, disintegration testing can be used as a surrogate for conventional compendial dissolution tests for highly soluble drug substances in which the intrinsic rate of solubilization is rapid and the overall drug release rate is dominated by the cohesive properties of the formulation.

In the case of (b) (4), the liberation of the drug substance from the drug product occurs in less (b) (4) and the drug substance exhibits great solubility at gastric pH levels and up to pH 6. In addition, vardenafil is a weak base (pKa about 9), Tmax occurs at about 0.75 hr to 1.5 hrs post administration, (b) (4). Therefore, these characteristics together with the higher discriminatory power of disintegration testing over dissolution testing justify the characterization of (b) (4) by disintegration testing alone.

Reviewer’s Conclusion

The sponsor has provided enough information to support the use of disintegration as a surrogate for dissolution.

Disintegration Specifications

The proposed disintegration specification for (b) (4) (shelf-life and release) is as follows:

Test	Specification	
	Release	Shelf-life
Disintegration	Max. (b) (4) seconds	Max. (b) (4) seconds

Test results of three consecutive batches of Vardenafil hydrochloride orodispersible tablet 10 mg which were manufactured for the prospective process validation of the commercial process are summarized in the table below .

Batch number	Disintegration (seconds)
BXA1G4U	(b) (4)
BXA1G4V	
BXA1G4W	

Data taken from batch-analysis section (3.2.P.5.4)

According to the sponsor, Vardenafil hydrochloride orodispersible tablets 10 mg also meet the requirements of the Ph. Eur. for this type of oral dosage form (general monograph on tablets) and the specification limit for the disintegration time is also in line with the recommendations given in the ‘Guidance for Industry on Orally Disintegrating Tablets’, (released by FDA-CDER in December 2008). The guidance states that disintegration should not be higher than 30 sec for these kinds of drug products.

Long-term stability data of 3 commercial scale batches of Vardenafil ODT 10 mg in the push through aluminum blister stored at 30 °C/75 % RH are available covering a storage period of 18 months. Moreover, 3 months stability data are currently available for the same 3 commercial scale batches packaged in the child-resistant blisters and stored at 25 °C/60 % RH. Additionally, 18 months data are available for one laboratory scale batch packaged in the push-through blister after storage at 25 °C/60 % RH and at 30 °C/75 % RH. Table below summarizes the batches including in the stability testing.



Reviewer’s Comments

The maximum disintegration values observed for tablets under stability studies was (b) (4) (conclusion from data presented in stability-data section P.8.3 and not shown in here). These values were observed for tablets under stress stability (40°/75% RH) for 18 months. Table 4 indicates that disintegration values of (b) (4) seconds were observed for tablets under (b) (4). Therefore, this reviewer recommends the following disintegration specification for both, shelf-life and product release:

Test	Specification	
	Release	Shelf-life
Disintegration	(b) (4)	(b) (4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200179	ORIG-1	BAYER HEALTHCARE PHARMACEUTICA LS INC	VARDENAFIL HCL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANDRA SUAREZ
03/18/2010

PATRICK J MARROUM
03/22/2010

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
	Information		Information	
NDA Number	200179	Brand Name	(b) (4)	
OCP Division	DCP3	Generic Name	Vardenafil HCl	
Medical Division	DRUP	Drug Class	PDE5 inhibitor	
OCP Reviewer	Sandhya Apparaju	Indication(s)	Erectile Dysfunction	
OCP Team Leader	Myong Jin Kim	Dosage Form	Orally disintegrating tablet	
		Dosing Regimen	On demand (p.r.n.)	
Date of Submission	August 26, 2009	Route of Administration	Oral	
Estimated Due Date of OCP Review	April 25, 2010	Sponsor	Bayer	
PDUFA Due Date	June 25, 2010	Priority Classification	Standard	
Division Due Date	April 26, 2010			
Clinical Pharmacology and Biopharmaceutics 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			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	X			

multiple dose:				
Patients-				
single dose:	X			
multiple dose:	X			
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:	X			
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X			vs. Levitra (approved)
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				

Food-drug interaction studies:	X			
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	4			
Filability and QBR comments				
	“X” if yes	Comments		
Application filable ?	X			
Comments sent to firm ?		The bioanalytical method validation report and study sample analysis report for the PK sub-study 12093 couldn't be located in the NDA. Submit this information or if already submitted, indicate its location in the NDA.		
QBR questions (key issues to be considered)	Revision of starting dose in elderly to 10 mg.			
Other comments or information not included above				
Primary reviewer	Sandhya Apparaju			
Secondary reviewer	Myong Jin Kim			

Filing Memo

Clinical Pharmacology and Biopharmaceutics Review

NDA: 200179

Compound: (b) (4) (Vardenafil HCl) 10 mg orally disintegrating tablet ((b) (4))

Sponsor: Bayer

Date: 10/09/2009

Reviewer: Sandhya Apparaju

Background: Vardenafil HCl is a potent inhibitor of PDE5 and is currently approved as film-coated tablets for p.r.n. (as needed) usage for Erectile Dysfunction (ED) in the doses of 2.5, 5, 10 and 20 mg dose strengths. The starting dose is 10 mg and dose may be increased to 20 mg or decreased to 5 mg depending on individual need for efficacy/tolerability.

Bayer HealthCare Pharmaceuticals Inc has developed an orally disintegrating tablet (ODT) of Vardenafil HCl (Levitra) for ED called (b) (4) . (b) (4) is formulated to rapidly disintegrate in the mouth. This feature permits the convenience of administration without water. Sponsor has submitted an original New Drug Application (NDA) for vardenafil hydrochloride to seek approval for the ODT formulation.

(b) (4)

(b) (4)

Proposed labeling (related to Dosage and Administration):

(b) (4)

Clinical trial database: Sponsor has conducted two clinical phase 3 safety and efficacy trials in the ED population (studies 12093 and 12094) and 3 clinical pharmacology studies (studies 13396, 12769, 10021) in support of their new formulation (see tables below). In addition, one of the phase 3 clinical trials includes a 25-patient PK sub-study (Study 12093). The sponsor has included a population analyses report that includes data from 3 completed clinical trials original NDA studies with PK data to explore the treatment-emergent adverse event frequencies for the approved film-coated formulation by drug concentration (Cmax or AUC) ranges (PH- 32067; 2002).

Tabulated list of clinical trials:

Type of Study Clinical Phase	Study No. Report No.	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Numbers of Subjects	Healthy Subjects or Diagnosis of Patients	Study Status Type of Report	Location of Study Report
Phase I	BAY 38-9456 / 10021 PH-29915	Mechanistic study to investigate absorption in the oral cavity compared to absorption in the GIT (swallowed intake)	Randomized, non-blind, 2-fold crossover. Fasting intake. 1 week wash-out.	10 mg Vardenafil HCl solution 0.1 % single dose i. kept in the mouth for 15 min, then mouth was emptied and rinsed ii. swallowed with water	10 valid for safety and PK	Healthy male subjects aged 26-43 years	Completed Medical Research Report	Module 5.3.1.1.
Phase I	BAY 38-9456 / 12769 PH-35349	Compare PK of ODT to Levitra®; investigate effect of food and water, resp. on PK of ODT	Randomized, non-blind, 4-fold crossover. Single dose administration	10 mg ODT w/o water fasting w/o water fed with water fasting 10 mg Levitra®	16 valid for safety, 13 valid for PK	Healthy male subjects aged 27-49 years	Completed Medical Research Report	Module 5.3.3.1
Phase I	BAY 38-9456 / 13396 PH-35868	Compare PK of ODT to Levitra®; investigate multiple once-daily administration of ODT and effect of age on ODT.	Non-blind, age-stratified, group comparison Day 1: 10 mg Levitra® Day 4-13: 10 mg ODT	10 mg ODT w/o water, 10 x once-daily, fasting on PK profile days 10 mg Levitra® single dose	36 valid for safety. Valid for PK: 14 (18 to ≤45), 6 (>45 to <65), 7 (<70) and 7 (≥70)	ED patients stratified by age 18 to ≤45, >45 to <65, ≥65 to <70 and ≥70 years; overall range 26-80 years	Completed Medical Research Report	Module 5.3.3.2

Type of Study Clinical Phase	Study No. Report No.	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Numbers of Subjects	Healthy Subjects or Diagnosis of Patients	Study Status Type of Report	Location of Study Report
Phase III	BAY 38-9456 / 12093 (A44851)	Compare the efficacy and safety of vardenafil ODT 10 mg (PRN) after 12 weeks of treatment or LOCF with placebo in a general population of men with erectile dysfunction. In this study, 50% of the men on active treatment have to be 65 years-of-age or older (including a PK assessment in a subgroup of 24 patients)	Fixed dose, double blind, randomized, multicenter, placebo controlled	10mg vardenafil ODT or placebo ODT, on demand (PRN) but no more than one dose per day, oral treatment	358 valid for safety.	Male patients with erectile dysfunction	Completed Medical Research Report	Module 5.3.5.1
Phase III	BAY 38-9456 / 12094 (A45884)	Compare the efficacy and safety of vardenafil ODT 10 mg (PRN) after 12 weeks of treatment or LOCF with placebo in a general population of men with erectile dysfunction. In this study, 50% of the men on active treatment have to be 65 years-of-age or older	Fixed dose, double blind, randomized, multicenter, placebo controlled	10mg vardenafil ODT or placebo ODT, on demand (PRN) but no more than one dose per day, oral treatment	337 valid for safety.	Male patients with erectile dysfunction	Completed Medical Research Report	Module 5.3.5.1

Sponsor’s conclusions are briefly summarized:

Study 35349: Randomized, open-label, four-fold crossover study to investigate the effect of a high fat, high calorie breakfast and of water, respectively, on 10 mg vardenafil oral disintegrating tablet in comparison to one 10 mg commercial tablet in healthy, male subjects.

- *10 mg vardenafil as ODT administered fasting and without water had a 44% increased bioavailability in comparison to Levitra (administered fasting with water). Cmax was increased by 15% with prolongation of tmax by 45 minutes.*
- *No effect of food was observed on the AUC of vardenafil after ODT administration. Cmax was decreased by 35% after administration with food.*
- *Intake of 10 mg vardenafil ODT with water decreased the bioavailability of vardenafil by 29% compared to intake of ODT without water and resulted in similar exposure as 10 mg Levitra (3% and 10% higher Cmax and AUC, respectively, of 10 mg ODT with water compared to 10 mg Levitra).*

Open-label, age-stratified group-comparison study to investigate the pharmacokinetics, safety and tolerability of multiple once daily doses of 10 mg vardenafil orodispersible tablet preceded by one single dose of 10 mg commercial tablet in young and elderly male patients with erectile dysfunction (BAY 38-9456/13396)

- *The 10 mg vardenafil ODT demonstrated an increase in AUC by 21 – 29 % paralleled by a decrease in Cmax by 8 – 19 % compared to the 10 mg IR tablet in male ED subjects.*

- Age has similar effects on the systemic vardenafil exposure of 10 mg ODT and marketed IR tablet. Following the first 10 mg ODT dose vardenafil AUC and C_{max} were increased by 39 % and 21 %, respectively, in subjects aged ≥65 years compared to subjects aged ≤45 years.
- On the last day of the multiple-dose regimen, vardenafil AUC_{τ,ss} and C_{max,ss} were greater by 31 % and 16 %, respectively, in subjects aged ≥65 years. These effects of age on systemic drug exposure of the 10 mg ODT formulation were numerically smaller compared to the 10 mg vardenafil IR tablet where AUC and C_{max} were increased by 48 % and 39 %, respectively, in subjects aged ≥65 years. In numerical terms the increases in vardenafil AUC and C_{max} with age were smaller with 10 mg ODT compared to IR tablet.
- The pharmacokinetics of 10 mg ODT are time-linear and there is no relevant accumulation in plasma following multiple once-daily doses.

Bioanalytical aspects: Concentrations of vardenafil were determined after automated solid phase extraction by HPLC coupled with a tandem mass spectrometer (HPLC/MS/MS). Bioanalytical study methodology, assay validations and study reports have been identified for all but one of the studies (PK sub-study in phase 3 trial 12093). Information will be requested.

PLR version of proposed labeling has been submitted in both annotated and final formats.

Clinical vs. TBM: The clinical and to-be-marketed formulations are identical.

Composition of the proposed ODT formulation is shown:

dose strength	10 mg
development number	(b) (4)
Vardenafil hydrochloride 3H ₂ O	11.85
Aspartame	(b) (4)
Flavor peppermint	
Magnesium stearate	
Pharmaburst B2	
tablet mass	180.00

The following comments should be communicated to the sponsor in the 74-day filing letter:

- Information request: The bioanalytical method validation report and study sample analysis report for the PK sub-study 12093 couldn't be located in the NDA. Submit this information or if already submitted, indicate its location in the NDA.
- Review issue: Your proposal to revise the starting dose recommendation in elderly patients to 10 mg will be a review issue.

Recommendation: The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 find that the Human Pharmacokinetics and Bioavailability section for NDA 200179 is fileable.

Sandhya Apparaju, Ph.D.

Date

Myong Jin Kim, Pharm.D., Team Leader

Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANDHYA K APPARAJU
10/20/2009

MYONG JIN KIM
10/20/2009

BIOPHARMACEUTICS REVIEW			
Office of New Drugs Quality Assessment			
Application No.:	NDA 200-179 (000)	Reviewer: Sandra Suarez Sharp, Ph.D	
Division:	DRUP		
Sponsor:	Bayer Healthcare Pharmaceuticals	Team Leader: Angelica Dorantes, Ph.D	
Trade Name:	(b) (4)	Supervisor: Patrick J. Marroum, Ph.D	
Generic Name:	Vardenafil Hydrochloride Rapid Dissolve	Date Assigned:	Sep 15, 2009
Indication:	Erectile dysfunction (ED)	Date of Review:	Oct 7, 2009
Formulation	(b) (4) Tablets		
Route of Administration	Oral		
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	CDER Stamp Date	Date of informal/Formal Consult	DUE DATE
Aug 26, 2009	Aug 26, 2009	Sep 15, 2009	Nov 13, 2009
Type of Submission:	Original NDA		
Type of Consult:	Disintegration method and specifications--- FILING REVIEW		
REVIEW SUMMARY:			
<p>LEVITRA[®] (vardenafil hydrochloride) 2.5, 5, 10 and 20 mg film-coated tablets were approved by the Agency on Aug 19, 2003 as an oral treatment for ED.</p> <p>The sponsor is proposing a new formulation for vardenafil hydrochloride consisting of an orally disintegrating tablet (orodisperse) for the treatment of ED. This new formulation, (b) (4), contains the equivalent to 10 mg vardenafil and it has been formulated to rapidly disintegrate in the mouth. The development program for this new product consists of two identical Phase 3 clinical trials, and additional clinical pharmacology studies aiming to evaluate the effect of age, food and water of the bioavailability of vardenafil.</p> <p>Disintegration testing is being proposed in lieu of dissolution as the quality control test of the orodisperse tablets. This review summarizes the data supporting this proposal and makes conclusions and recommendations about the value of in vitro disintegration testing and its applicability for assessing the product's quality in lieu of dissolution testing.</p> <p>The use of disintegration as a surrogate for dissolution testing is feasible under certain circumstances as delineated by the ICH Q6A guidelines (e.g. high solubility, rapidly dissolving drug product). However, vardenafil hydrochloride does not appear to be classified as a highly soluble compound. In addition, information about dissolution of (b) (4) was not provided. The sponsor claims that the disintegration method for (b) (4) is more discriminating than dissolution testing. However, the data provided to support this claim is insufficient. Therefore, the sponsor is requested to develop a discriminating dissolution method for (b) (4). This dissolution method should be in addition to the proposed disintegration method which ensures that the proposed product meets the claim of a "rapidly</p>			

dissolved" product.

RECOMMENDATION:

The ONDQA/biopharmaceutics team has reviewed NDA 200-179 (000) for filing purposes. We found this NDA filable from biopharmaceutics perspective. The sponsor's proposal to use disintegration as a quality control test in lieu of dissolution testing for (b) (4) is not acceptable. The following comments should be conveyed to the sponsor as part of the 74-day letter:

1. Your proposal of using disintegration testing as a quality control test in lieu of dissolution is not acceptable for the following reasons:
 - o Vardenafil hydrochloride does not appear to be a highly soluble substance. The ICH Q6A guidance outlines that disintegration may be substituted for dissolution if a product contains a drug which is highly soluble throughout the physiological range (dose/solubility volume < 250 mL from pH 1.2 to 6.8).
 - o Information on (b) (4) dissolution throughout the physiological pH was not been provided. Disintegration may be used in lieu of dissolution if the drug product is rapidly dissolving (dissolution >80% in 15 minutes at pH 1.2, 4.0 and 6.8).
 - o The relationship between dissolution and disintegration has not been established.
2. Your claim in terms of (b) (4) disintegration method being more discriminating than the dissolution method is inconclusive due to a lack of sufficient information (e.g. dissolution method development report and validation).
3. Based on the statements delineated in points 1 and 2, in addition to your proposed disintegration method, you are requested to develop a more discriminating dissolution method which will serve as a quality control test.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: NDA 200-179 (000), JDavis, ADorantes, JSalemme, DChristner

INTRODUCTION

LEVITRA[®] (vardenafil hydrochloride) 2.5, 5, 10 and 20 mg film-coated tablets are approved in the United States as an oral treatment for erectile dysfunction (ED). The tablets contain the equivalent of 2.5 mg, 5 mg, 10 mg and 20 mg vardenafil. Vardenafil is a potent and selective phosphodiesterase type-5 (PDE5) inhibitor.

The sponsor is proposing a new formulation for vardenafil hydrochloride, (b) (4), consisting of an orally disintegrating tablet (orodisperse) for the treatment of ED. This new formulation contains the equivalent to 10 mg vardenafil and it has been formulated to rapidly disintegrate in the mouth. The median time to reach Cmax (Tmax)

in patients receiving 10 mg (b) (4) in the fasted state varied between 45 to 90 minutes. After administration of 10 mg (b) (4) to patients mean vardenafil AUC was increased by 21 to 29 % while mean Cmax was 8 to 19 % lower in comparison to 10 mg LEVITRA film coated tablet. A high fat meal had no effect on vardenafil AUC and Tmax in healthy volunteers and reduced Cmax by 35%. Based on these results (b) (4) can be taken before or after food. If (b) (4) is taken with liquid, the AUC is reduced by 29 % and median Tmax is shortened by 60 minutes while Cmax is not affected. (b) (4) should be taken without liquid.

CHEMISTRY

Drug Substance

According to the sponsor, (b) (4). It appears as vardenafil *mono* hydrochloride trihydrate (HCL 3H2O) is stable over a wide range of environmental humidity and is not hygroscopic under typical production conditions. In solid form it shows acceptable temperature, hydrolytic and photolytic stability.

(b) (4) Solubility is, however, pH dependent and decreases significantly at neutral pH.

Formulation

(b) (4) is a white, round orodispersible tablet with no debossing. The components and composition of the product are summarized in Table 1.

Table 1. Components and composition for (b) (4) tablets, 10 mg

Composition	Reference to standard	Function	Amount [mg]
Drug substance			
Vardenafil hydrochloride trihydrate (b) (4)	specification	drug substance	11.85 ^a
Excipients			
Aspartame	Ph. Eur., NF	(b) (4)	(b) (4)
Flavor peppermint	specification ^b		
Magnesium stearate	Ph. Eur., NF, Ph. Jap.		
Pharmaburst B2 ^c	specification		
consisting of:			
Crospovidone	Ph. Eur., NF		- ^c
Mannitol	Ph. Eur., USP		- ^c
Silica colloidal hydrated	Ph. Eur., NF	- ^c	
Sorbitol	Ph. Eur., NF	- ^c	
Weight			180.00

^a corresponding to 10.0 mg vardenafil

^b components of flavor peppermint are Ph. Eur., FCC and BP quality

^c exact specification of the commercially available blend Pharmaburst™ B2 is stated in the composition of (b) (4)

Disintegration Method

The sponsor is proposing disintegration as a surrogate for dissolution testing. The following method and specifications are being proposed:

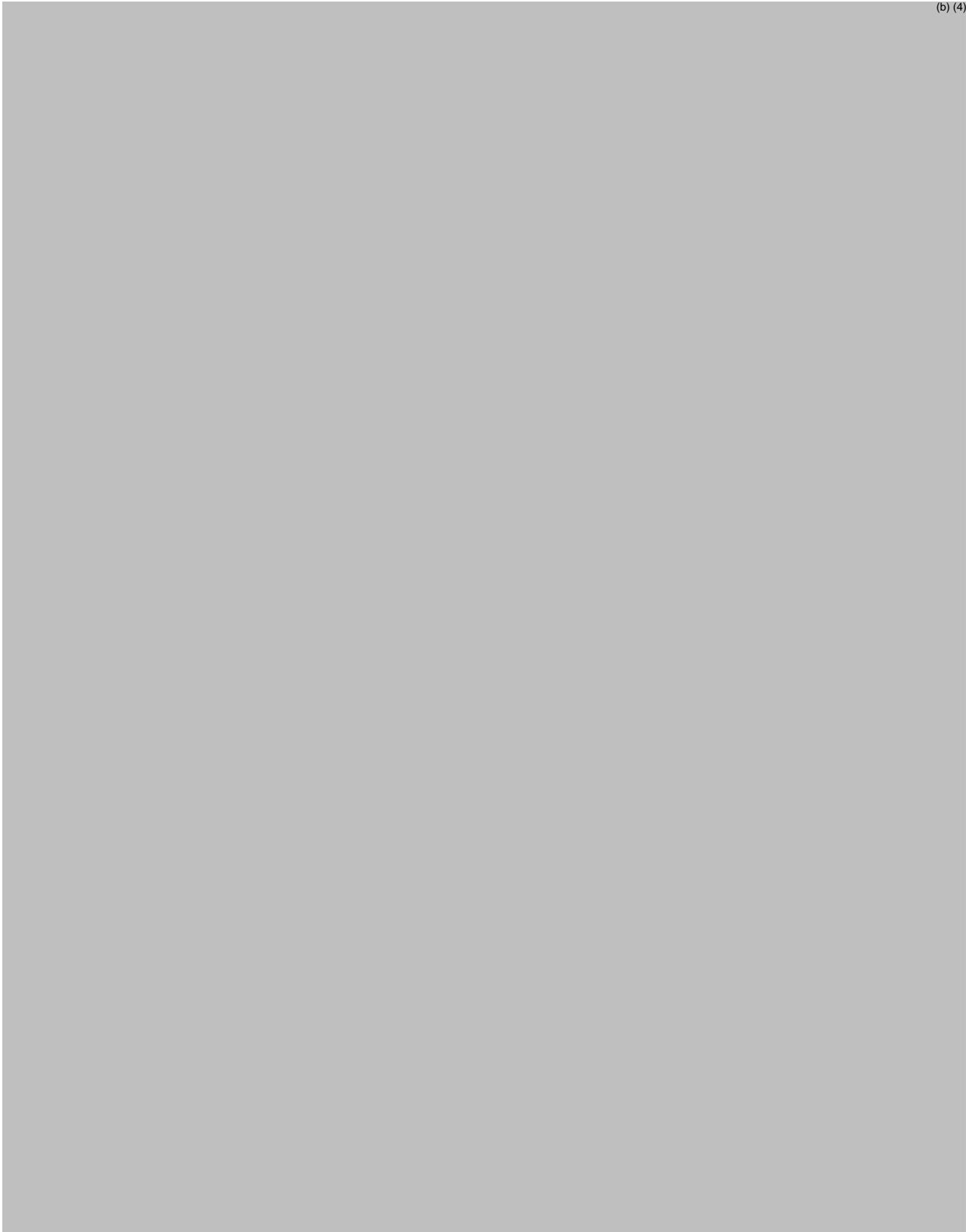
(b) (4)

**Rationale for the Use of Disintegration as a Surrogate for Dissolution
Disintegration Method Discriminatory Power**

(b) (4)

Dissolution Method Discriminatory Power

In order to check the discriminatory capability of dissolution tests the same modified tablet batches as used for assessing the disintegration test (Table 1) were evaluated using the same dissolution test method as for the market product Levitra® (dissolution medium 0.1 M HCl, 50 rpm, 900mL). Additional altered manufacturing conditions were also tested for two experimental batches as shown in Table 2. The results of the dissolution testing under these conditions are shown in Figure 1. A complete drug substance release already after about (b) (4) was found for all tested batches, regardless the respective variations of the manufacturing process.



Based on these findings the sponsor concludes that due to its insufficient time resolution the dissolution test system is inappropriate, especially in view of the very rapid tablet disintegration. Consequently, the disintegration test is regarded as superior to dissolution as quality parameter for this drug product and dissolution testing is therefore not included in the list of specified quality control tests.

Reviewer's Remarks

The sponsor's proposal to use disintegration as a quality control test with no dissolution testing is not acceptable. The ICH Q6A guidance¹ outlines that disintegration may be substituted for dissolution if:

- a product contains a drug which is highly soluble throughout the physiological range (dose/solubility volume < 250 mL from pH 1.2 to 6.8)
- the drug product is rapidly dissolving (dissolution >80% in 15 minutes at pH 1.2, 4.0 and 6.8)
- a relationship to dissolution has been established or
- disintegration is shown to be more discriminating than dissolution

Vardenafil hydrochloride does not appear to be a highly soluble substance and information on dissolution throughout the physiological pH has not been provided. The sponsor made an attempt to show that disintegration is not discriminating than dissolution. However, the data presented is insufficient to reach a conclusion in terms of the discriminatory power of disintegration vs. dissolution testing. Therefore, the sponsor will be requested to developed a discriminating dissolution method for [REDACTED]^{(b) (4)}
[REDACTED].

¹ Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug products : Chemical Substances (The tripartite harmonized ICH guideline, finalized (Step 4) in October 1999).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200179	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	VARDENAFIL HCL

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/s/

SANDRA SUAREZ
10/20/2009

PATRICK J MARROUM
10/20/2009