

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
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PHARMACOLOGY REVIEW(S)

**Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research**

Date: May 14, 2010

Reviewer: Lynnda Reid, Ph.D.
Supervisory Pharmacologist

NDA #/date: 200-179, August 26, 2009

Sponsor: Bayer HealthCare Pharmaceuticals

Drug Product: Vardenafil Orodispersible Tablet (10 mg)

Indication: Treatment of erectile dysfunction

Background: Vardenafil ODT is a new orodispersible 10 mg tablet formulation that offers the convenience of being taken without liquid. When placed on the tongue, the tablet dissolves with in ^(b)₍₄₎ seconds and provides systemic levels of vardenafil only slightly less than the approved Levitra® 20 mg vardenafil film coated tablet that must be swallowed.

Nonclinical data submitted to support the approval of Levitra® 20 mg vardenafil film coated tablet (NDA 21-400, 2003) was cross-referenced in this NDA to support 10 mg vardenafil ODT. No additional nonclinical data was submitted or requested.

Pharmacology: Vardenafil is a selective PDE5 inhibitor. Inhibition of PDE5 increases the level of cGMP during sexual stimulation, which enhances relaxation of smooth muscle, and induces penile erection.

Toxicology: Significant adverse effects in animals included testicular atrophy/degenerative, myocardio lesions, and arteritis. Similar effects have been observed in animals with other PDE5 inhibitors, but have not been observed in animals at clinically relevant exposures or reported in clinical trials. A NOAEL for any toxicity was considered to be 3 mg/kg/day in rats and dogs, which produces 2- 21 fold of exposure multiples compared to human exposures at 20 mg.

Testicular atrophy/degenerative, characterized by epididymal oligospermia/debris in dogs and testicular degeneration/tubular atrophy in rats, was observed in the 3 month repeat daily dose toxicology studies. Testicular toxicity was not progressive: the incidence was not seen in the 6-month rat study, and occurred in only one male at the mid- and high doses in the 1-year dog study. Exposure multiples were approximately 85-fold higher compared to clinical exposures with 20 mg Levitra®.

Arteritis was observed in rats and dogs and myocardial fibrosis and necrosis resulted in deaths at high exposure multiples. In dogs, subepicardial and pericardial edema in the atrium accompanied by an increase in minimal to mild subepicardial inflammatory infiltration was observed in the 1-month study. Mild to moderate periarteritis and arteritis occurred at high dose in the 1-, 3- and 12-month studies possibly secondary to the hypotensive effects of the drug. The periarteritis findings were not progressive in the 1-year chronic study. Exposure multiples were approximately >100-fold higher compared to clinical exposures with 20 mg Levitra®.

Adrenal vacuolation and hypertrophy of the pancreas, parotid/submandibular glands and thyroid gland were only observed in rats at exposure multiples of >12-fold. The acinar hypertrophy observed of the exocrine glands was considered an adaptive effect to PDE inhibition.

Genotoxicity: Vardenafil was not mutagenic or genotoxic under conditions tested in the standard genotoxicity battery: negative in the *in vitro* Ames test, chromosome aberration assay and induced forward mutation, and the *in vivo* mouse micronucleus assay.

Carcinogenicity: Vardenafil was not carcinogenic as tested in the two-year rat and mouse carcinogenicity studies. The highest doses used in the two-year studies resulted in systemic exposures approximately 400-fold higher in male rats and 21-fold higher in male mice than those observed clinically following use of 20 mg Levitra®.

Reproductive toxicology: Vardenafil had no significant effects on fertility or early embryonic development in rats at exposure multiples greater than 400-fold clinical exposures.

Administration of vardenafil to pregnant rats and rabbits during the period of early organogenesis resulted in severe maternal toxicity including mortalities. Delayed fetal skeletal development and reduced fetal/placental weights were observed in rats and increased post-implantation loss and delayed ossification were seen in rabbits as a consequence of maternal toxicity. Maternal toxicity was still evident in the pre- and post-natal study in rats, accompanied by reduced gestation index due to prenatal loss, increased stillborn pups/pup mortality (up to postpartum day 4), decreased neonate body weights, and delayed physical development in

offspring following weaning. These effects were only observed at high exposure multiples (>100-fold in rats and ~29-fold in rabbits) compared with clinical exposures. Potential adverse effects in a pregnant women exposed through semen are highly unlikely.

Vardenafil was secreted into the milk in lactating rats with an AUC for the milk at concentrations greater than 10 fold higher than found in maternal plasma. However, since circulating levels of vardenafil are unlikely to result from exposures through semen, any risk to infants through breast feeding is highly unlikely.

Summary: The toxicity profile for vardenafil is similar to that observed for other PDE5 inhibitors. The most concerning effects of testicular toxicity and arteritis occurred at high exposure multiples compared to clinical exposures and have not been reported in clinical studies.

It should be noted that the 10 mg vardenafil ODT is not equivalent to the LAVITRA® 10 mg vardenafil film coated tablet. There is a risk of overdose if men currently taking Levitra® 20 mg substitute two of the 10 mg vardenafil ODT tablets for a single dose of Levitra® 20 mg. This risk will be addressed in labeling and may be mitigated by marketing 10 mg vardenafil ODT under a new Tradename.

Outstanding nonclinical issues: None

Conclusions:

- I concur with the conclusions of the primary pharmacology/toxicology reviewer, Dr. Yangmee Shin, that the nonclinical data submitted to support LEVITRA® (vardenafil 20 mg film coated tablets) are adequate to support approval of 10 mg vardenafil orodispersible tablets.
- I concur with Dr. Shin's proposed labeling.

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

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/s/

LYNNDA L REID
05/14/2010

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 200-179
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Product: Vardenafil Orodispersible Tablet
Indication: Treatment of erectile dysfunction
Applicant: Bayer HealthCare Pharmaceuticals
Review Division: Division of Reproductive and Urologic Products
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1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

From a Pharmacology and Toxicology perspective, the previously submitted nonclinical data for approval of 2.5, 5, 10 and 20 mg LEVITRA[®] film-coated tablet support the approval of the newly proposed 10 mg vardenafil orodispersible tablet (ODT) formulation.

1.1.2 Additional Non Clinical Recommendations

None

1.1.3 Labeling

From a Pharmacology and Toxicology perspective, the sponsor's intention to use systemic exposure levels from the 20 mg LEVITRA[®] film-coated tablets for comparisons between animal and human exposures for labeling purposes is acceptable. The mean AUC and C_{max} values achieved from the proposed vardenafil ODT (AUC_{0-24h}~90 µg·hr/L, C_{max}~25 µg·hr/L) are within the ranges from the currently marketed LEVITRA[®] 20 mg tablet (AUC_{0-24h}~120 µg·hr/L, C_{max}~30 µg·hr/L).

The content of the proposed labeling pertaining to nonclinical studies is the same as in the previously approved LEVITRA[®] film-coated tablet. This is acceptable with the following exception of the recommended edits in the **Indications and Usage** section, **Pregnancy and Nursing Mothers** under **Use in Specific Populations** section, and **Animal Toxicology and/or Pharmacology** under **Nonclinical Toxicology** section.

The Division recommends that the contents under the **Animal Toxicology and/or Pharmacology** section be deleted, and moved to the appropriate sections (see below).

Recommended labeling is detailed as follows:

1 INDICATION AND USAGE

Sponsor's proposed label:

(b) (4)

Division's recommended label:

[TRADENAME] is a phosphodiesterase 5 inhibitor indicated for the treatment of erectile dysfunction.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Sponsor's proposed label:

(b) (4)

Division's recommended label:

Pregnancy Category B: [TRADENAME] is not indicated for use in women. There are no adequate and well controlled studies of [TRADENAME] use in pregnant women.

No evidence of specific potential for teratogenicity, embryotoxicity or fetotoxicity was observed in rats and rabbits that received vardenafil at up to 18 mg/kg/day during organogenesis. This dose is approximately 100 fold (rat) and 29 fold (rabbit) greater than the AUC values for unbound vardenafil and its major metabolite given the maximum recommended human dose (MRHD) of 20 mg.

In the rat pre-and postnatal development study, the no observed adverse effect level (NOAEL) for maternal toxicity was 8 mg/kg/day. Retarded physical development of pups in the absence of maternal effects was observed following maternal exposure to 1 and 8 mg/kg possibly due to vasodilatation and/or secretion of the drug into milk. The number of living pups born to rats exposed pre- and postnatally was reduced at 60 mg/kg/day. Based on the results of the pre- and postnatal study, the developmental NOAEL is less than 1 mg/kg/day. Based on plasma exposures in the rat developmental toxicity study, 1 mg/kg/day in the pregnant rat is estimated to produce total AUC values for unbound vardenafil and its major metabolite comparable to the human AUC at the MRHD of 20 mg.

8.3 Nursing Mothers

Sponsor's proposed label:

(b) (4)

Division's recommended label:

[TRADENAME] is not indicated for use in women. It is not known if vardenafil is excreted in human breast milk. Vardenafil was secreted into the milk of lactating rats at concentrations approximately 10-fold greater than found in the plasma. Following a single oral dose of 3 mg/kg, 3.3% of the administered dose was excreted into the milk within 24 hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Sponsor's proposed label:

Vardenafil was not carcinogenic in rats and mice when administered daily for 24 months. In these studies systemic drug exposures (AUCs) for unbound (free) vardenafil and its major metabolite were approximately 400- and 170-fold for male and female rats, respectively, and 21- and 37-fold for male and female mice, respectively, the exposures observed in human males given the Maximum Recommended Human Dose (MRHD) of 20 mg. (b) (4)

Division's recommended label:

This is acceptable.

13.2 Animal Toxicology and/or Pharmacology

Sponsor's proposed label:

(b) (4)

Division's recommended label:

This subsection may be deleted, and moved to **Pregnancy and Nursing Mothers** under **Use in Specific Populations** section (see above).

1.2 Brief Discussion of Nonclinical Findings

Vardenafil ODT is a new orodispersible tablet formulation that offers the convenience of being taken without liquid. The previously submitted nonclinical data to support LEVITRA[®] film-coated tablets appear adequate to support the new formulation with respect to systemic and local toxicity, considering the similar route of administration (oral vs orodispersible) and the AUC levels within the range of the approved LEVITRA[®] film-coated tablets (2.5, 5, 10 and 20 mg). However, vardenafil ODT is not bioequivalent to or interchangeable with the 10 mg LEVITRA[®] film-coated tablet. Vardenafil ODT had suprabioavailability (~50% higher AUC levels) over film-coated tablet with sustained C_{max} (1-3 hours) and delayed T_{max} (~0.75 hour) when compared to the same dose (10 mg) of LEVITRA[®] film-coated tablet. Based on the results from clinical studies with 10 mg vardenafil ODT, adverse event profiles were not significantly different in patient populations (e.g., young vs elderly). Considering that the clinical trials were not designed to report the time of the adverse events after the administration of study drug, as indicated by the sponsor, it is unknown whether the differences in PK profile (i.e., sustained C_{max} , increased residence time, delayed T_{max}) could lead to an altered time to onset, duration and/or the severity of the adverse effects.

The potential for local irritation of the vardenafil ODT formulation was not directly assessed in animals. However, previous toxicology studies conducted in animals given vardenafil via routes (oral gavage and drinking water) that would result in substantial exposure to the mouth and its adjacent tissues did not identify a cause for concern. In addition, local irritation/toxicity was assessed in clinical studies were conducted with the new formulation.

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number

224785-90-4 (vardenafil); 224785-91-5 (vardenafil hydrochloride)

2.1.2 Generic Name

Vardenafil hydrochloride

2.1.3 Code Name(s)

Bay 38-9456, (b) (4)

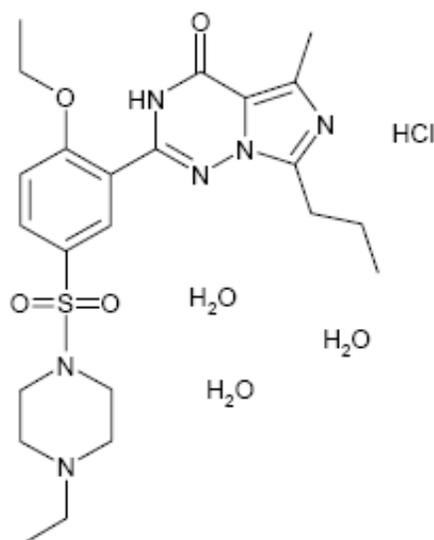
2.1.4 Chemical Name

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

2.1.5 Molecular Formula/Molecular Weight

 $C_{23}H_{32}N_6O_4S \cdot HCl \cdot 3H_2O$, 579.1 g/mole

2.1.6 Structure



2.1.7 Pharmacologic class

Phosphodiesterase (PDE) 5 inhibitor

2.2 Relevant IND/s, NDA/s, and DMF/s

IND 57,703; NDA 21-400

2.3 Clinical Formulation

(b) (4) vardenafil HCl trihydrate orodispersible tablet (ODT) 10 mg containing aspartame (sweetner), Pharmaburst B2 (b) (4), peppermint flavor and magnesium stearate (b) (4) as inactive ingredients

2.3.1 Drug Formulation

Orodispersible tablet

2.3.2 Comments on Novel Excipients

All inactive ingredients and excipients are found in previously approved drug products.

2.3.3 Comments on Impurities/Degradants of Concern

There are no impurities/degradants requiring qualification.

2.4 Proposed Clinical Population and Dosing Regimen

Vardenafil ODT (tradename is pending) was investigated for the treatment of adult men with erectile dysfunction (ED) at a single dose level of 10 mg taken orally without liquid approximately 60 minutes before sexual activity. The proposed maximum recommended dosing frequency is one tablet per day. Vardenafil ODT should be placed on the tongue where it will disintegrate rapidly. The sponsor proposes a single 10 mg dose for most patients including elderly men ≥ 65 years.

2.5 Regulatory Background

The original LEVITRA[®] film-coated tablet was approved in the US in 2003 for the treatment of ED. The recommended dose for the marketed tablet form of vardenafil is 10 mg, taken orally with liquid approximately 60 minutes before sexual activity, and may be increased to 20 mg or decreased to 5 mg based on efficacy and side effects.

To support the new vardenafil ODT formulation, the sponsor submitted two 12-week placebo-controlled studies in young (<65 years) and elderly (≥ 65 years) men with ED (340 placebo and 355 vardenafil ODT) (see Clinical review for details).

3 Studies Submitted

3.1 Studies Reviewed

There were no new nonclinical studies performed to support vardenafil ODT. A full nonclinical program for vardenafil to support the original NDA approval for the ED indication was previously reviewed (see NDA 21-400 review). The nonclinical program included general and safety pharmacology, PK/ADME, acute and chronic toxicology, genotoxicity, carcinogenicity, and reproductive and developmental toxicology studies.

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

NDA 21-400; IND 57,703

4 Pharmacology

The following brief summary is based on the previously submitted data to support LEVITRA[®] film-coated tablet under NDA 21-400.

4.1 Primary Pharmacology

Vardenafil is a selective PDE5 inhibitor based on the IC₅₀ values on various recombinant and tissue-derived PDEs in vitro with selectivity ratios of >15-fold relative to PDE6, >130-fold relative to PDE1, >300-fold relative to PDE11, and >1000-fold relative to PDE2, 3, 4, 7, 8, 9 and 10. Inhibition of PDE5 increases the level of cGMP during sexual stimulation, which enhances relaxation of smooth muscle, and induces penile erection.

Vardenafil increased concentrations of cGMP and induced relaxation in unstimulated and stimulated corpus cavernosal tissues in human and rabbits. Both vardenafil (BAY 38-9456) and its major metabolite M-1 (BAY 44-5576) induced erections either after oral (vardenafil 1-30 mg/kg) or intravenous (vardenafil 0.3-1 mg/kg, M-1 1-3 mg/kg) administration in a conscious rabbit model. M-1 was approximately 10-fold less potent than vardenafil.

4.2 Secondary Pharmacology

See Safety Pharmacology section below

4.3 Safety Pharmacology

Neurological effects: In rats, vardenafil had no significant effect on the central nervous system (CNS) for nociception, traction ability, balance ability, seizure threshold and behavior at the highest oral dose (10 mg/kg) tested.

Cardiovascular effects: Vardenafil exhibited a dose-dependent decrease in total peripheral resistance (TPR) and systolic blood pressure (SBP) accompanied by increases in heart rate (HR), cardiac contractility and cardiac output in anesthetized male dogs after single intraduodenal administration at 0.3-10 mg/kg. Oral vardenafil alone (0.1-3.0 mg/kg) or in combination with oral glyceroltrinitrate (0.5 mg/kg) produced a more pronounced reduction of BP and increased HR with prolonged duration than oral sildenafil (0.07-2.1 mg/kg) in conscious dogs. Vardenafil given at oral doses of 3- to 30 mg/kg and sildenafil at 10- to 30 mg/kg equipotently produced a dose-dependent decrease in mean blood pressure and an increase in HR in female conscious spontaneously hypertensive rats (SHR). QT and/or QTc intervals were rather shortened dose-dependently both in conscious and anesthetized dogs. In vitro hERG channel

activity was blocked by vardenafil and sildenafil similar to class III antiarrhythmics with higher potency for vardenafil (IC_{50} =30 μ M at +20 mV, 84 μ M at -20 mV, 32 μ M at +40 mV) than sildenafil (IC_{50} =47 μ M at +20 mV, 111 μ M at -20 mV, 56 μ M at +40 mV). The threshold (1 μ M) and the IC_{50} (30 μ M) concentrations at +20 mV are approximately 29- and 880-fold higher, respectively, than the mean peak plasma level in humans at the MRHD of 20 mg LEVITRA[®] film-coated tablet (~16.6 μ g/L, 34 nM).

Pulmonary effects: Vardenafil had no significant effect on respiratory parameters in male rats at up to the highest dose tested (10 mg/kg).

Renal effects: Vardenafil had no significant effect on diuresis and hematological parameters in male rats at up to 10 mg/kg, the highest dose tested.

Gastrointestinal effects: Vardenafil had no significant effect on intestinal motility and gastric tolerability test in male rats at up to 10 mg/kg, the highest dose tested.

Abuse liability: Not provided

Other:

- In the presence of the NO donor SNP, concentration-dependent enhancement of the antiaggregatory effects of SNP was observed with ≥ 0.01 μ M vardenafil when tested in the presence of agonist-induced platelet aggregation. However, vardenafil alone did not inhibit platelet aggregation at up to 10 μ M in vitro.
- A statistically significant increase (~10%) in blood glucose was noted 30 minutes following a dose of 10 mg/kg in fed male rats, but not in fasted rats.
- A dose-dependent decrease in hemoglobin, erythrocytes and hematocrit up to 11%, with statistical significance at ≥ 3 mg/kg, was observed in male rats.

5 Pharmacokinetics/ADME/Toxicokinetics

The following brief summary on animal PK/ADME/Toxicokinetics is based on the previously submitted data to support LEVITRA[®] film-coated tablet. Human PK studies were conducted with vardenafil ODT. See Clinical Pharmacology review for details in human PK profile of vardenafil ODT.

5.1 PK/ADME

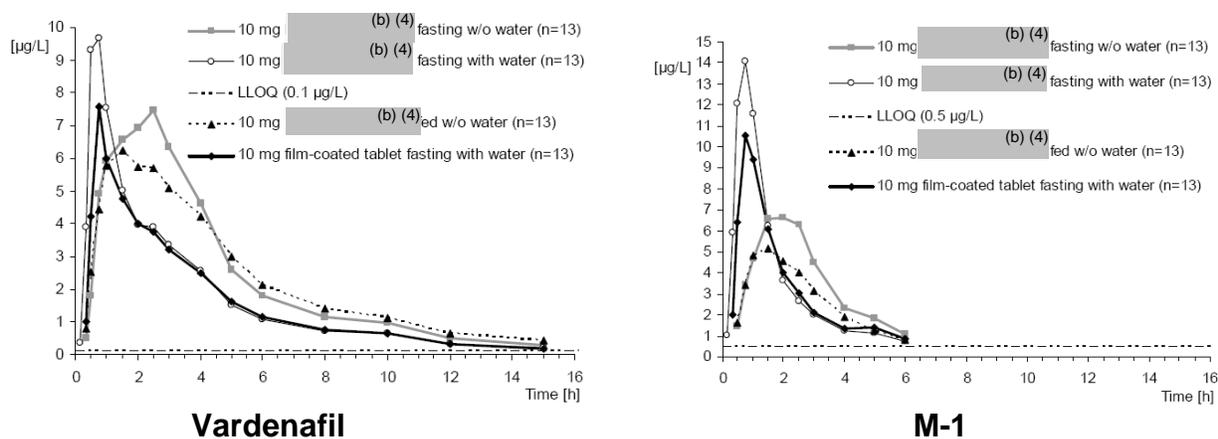
Absorption: Vardenafil is rapidly absorbed with an absolute oral bioavailability of 7.4-28.6 % in Wistar rats, 27-33 % in Beagle dogs and 14.5 % in man. Volume of distribution at steady state is 2.0 L/kg in the rat, 2.5 L/kg in man and 5.2 L/kg in the dog, indicative of moderate distribution into organs and tissues.

PK studies with the new formulation were conducted in healthy and ED subjects. PK profile of the 10 mg vardenafil ODT appears different from that of the 10 mg LEVITRA[®] film-coated tablet. Following administration of 10 mg vardenafil ODT without water,

median T_{max} was somewhat delayed (~1.5 hours) compared to LEVITRA[®] film-coated tablet (~0.75 hour). Plasma concentrations reached a plateau between 1-3 hours. Increased bioavailability (~50% higher than vardenafil AUC) was also observed. Mean residence time was increased with vardenafil ODT by 0.6–0.7 hour. C_{max} was lower with the ODT (8% and 19%; ≤ 45 years and ≥ 65 years) compared to the film-coated tablet. These suggest that sublingual and buccal absorption may have occurred through permeation of the oral mucosa in the absence of first-pass metabolism. There was no significant accumulation of vardenafil and M-1 in plasma in all age groups of ED patients following once daily dosing for 10 days.

The sponsor's figures below illustrate the effect of food and water on bioavailability of vardenafil or M-1 following a single dose of 10 mg vardenafil ODT or 10 mg LEVITRA[®] film-coated tablet in healthy young males with 20-49 years of age (Study 12769).

Figure 1. Effect of Food and Water on Plasma Concentrations ($\mu\text{g/L}$) of Vardenafil or M-1 After a Single Dose of 10 mg Vardenafil ODT or 10 mg LEVITRA[®] Film-Coated Tablet (calculated as free base)



Distribution: Oral administration of [¹⁴C]-vardenafil to male rats was rapidly distributed to organs and tissues with the highest concentrations in the liver followed by adrenal, kidney, lung, testis, skin, plasma, blood, heart and brain with the longest terminal $t_{1/2}$ of 71 hours for kidneys. The majority of the radioactivity was eliminated within 24 hours except for the GI tract with the remaining residues mainly located in the liver. Pigmented rats had radioactivity detected in the eye and pigmented skin with the terminal elimination $t_{1/2}$ of 14 days and 5 days, respectively, indicating a potential for affinity to melanin. Oral administration of [¹⁴C]-vardenafil to pregnant Wistar rats on gestation day 19 was also rapidly and thoroughly distributed to maternal organs and tissues except to brain and cartilage with the highest exposure in amnion, maternal liver, spleen and thyroid and mammary glands. Maximum fetal concentrations were found in the GI tract, liver, lung, heart, adrenal cortex, eye wall, skin and the cartilage. The AUC in fetal brain was approximately 2-fold higher than that in the maternal brain. Within 24 hrs, 3.3% of

the radioactivity was excreted into milk in lactating rats, in which the AUC was more than 10-fold higher than in the plasma.

Metabolism: Vardenafil was extensively metabolized via N-deethylation, oxidation, and degradation of the piperazine ring and hydroxylation of the arylmethyl group or the propyl group in all species tested with numerous metabolites found in bile or feces. In human liver microsomes, CYP3A5 (11%), CYP2C8 (6%), CYP2C9 (6%) and CYP2C19 (2%) play a considerable role as high-affinity components in the N-desethylation, whereas CYP3A4 predominates (80%) as a low-affinity component at higher concentrations. BAY 44-5576 (M-1) formed by N-deethylation was the major metabolite in the plasma of animals and humans. In human plasma, but not in animal species, a thermally unstable N-glucuronide of M-1 was also identified at similar concentrations as M-1. Metabolic profiles and pathways were qualitatively similar in the rat, dog and mouse compared with man.

Excretion: [¹⁴C]-Vardenafil-related radioactivity was mainly excreted via the bile and feces, renal excretion being in the range from 4-6% in all species tested including humans.

Pharmacokinetic drug interactions: Inhibitors of CYP3A4, CYP3A5 and CYP2C9 are expected to reduce vardenafil clearance, given that vardenafil is metabolized primarily by CYP3A4 and CYP3A5, and to a lesser degree by CYP2C9. Therefore, concomitant use with CYP3A4 inhibitors results in significant increases in plasma levels of vardenafil. In vitro studies did not reveal significant drug-drug interaction potential for the recombinant CYP1A2, CYP2A6 and CYP2E1 with K_i values of vardenafil and its metabolites M-1 and M-4 $>100 \mu\text{M}$. Weak inhibitory effects toward CYP1A2 ($K_i=126 \mu\text{M}$), CYP2C8 ($K_i=67.5 \mu\text{M}$) and CYP2C19 ($73.2 \mu\text{M}$) were identified. Calculation of a K_i value for vardenafil on CYP3A4 was not possible due to inhibitory effects caused by metabolites M-1 and M-4, which are simultaneously formed by this enzyme. The K_i values for M-1 and M-4 on CYP3A4 were determined to be $1.4 \mu\text{M}$ and $20.6 \mu\text{M}$, respectively. K_i values of M-1 were approximately $45 \mu\text{M}$ for both CYP2C9 and 2D6, and $9.8 \mu\text{M}$ for CYP2C19.

Other Pharmacokinetic Studies: Vardenafil and its metabolite M-1 were highly bound to plasma proteins with mean free fractions of 5.22-7.88% in rats, 6.39-9.55% in mice, 3.39-10.57% in rabbits, 12.58-15.17% in dogs, and 4.82-5.42% in humans in vitro similar to ex vivo data determined at 20 minutes after oral administration. The major binding protein fraction in humans was albumin, and to a lower extent, α -globulins, β -globulins and LDL. The unbound fraction of [¹⁴C]-vardenafil to dog plasma proteins ex vivo declined to 3-5% at 24 hours, reflecting the altered binding characteristics of metabolites found in plasma.

5.2 Toxicokinetics

Toxicokinetic parameters were assessed in rats, mice, dogs and rabbits. AUC generally increased supra-proportionally with dose. Accumulation was observed following repeat-

dosing in rats and dogs. Greater exposure towards vardenafil was noted in the female than in the male rats, probably due to a sexual dimorphism in CYP450 enzymes. In mice, a decrease in plasma concentrations was found following repeated dosing.

6 General Toxicology

The following brief summary is based on the previously submitted data to support LEVITRA[®] film-coated tablet under NDA 21-400. Unless otherwise noted, calculations comparing systemic exposures in toxicology studies to human exposures are based on the mean AUC_{0-24h} of 90 ng·hr/mL for the parent and M-1 following administration of 10 mg vardenafil ODT reported in Clinical Study 12093.

6.1 Single-Dose Toxicity

Acute toxicity studies were conducted in rats and mice following oral and intravenous administration of vardenafil. Mortality was noted at oral doses of 2000 and 125 mg/kg in mice and rats, respectively, and intravenous doses of 100 mg/kg in both species. Treatment-related clinical signs observed prior to mortality consisted of decreased motility, uncoordinated/staggering gait, abdominal/lateral position, tremor, tonic-clonic convulsions, labored breathing, narrowed palpebral fissure, hunched posture, vocalization, gasping, and/or chromodacryorrhea.

6.2 Repeat-Dose Toxicity

Repeat-dose toxicology studies were conducted at up to 2 years via oral gavage, drinking water and/or intravenous administration in mice, rats and dogs. The major target organs and tissues included the following:

- cardiovascular system: myocardial fibrosis/degeneration and mononuclear cell infiltration in rats; periarteritis/arteritis and/or periarterial edema in mice, rats and dogs; flushing, decreased BP and increased HR in dogs
- reproductive system: testicular tubule degeneration in both rats and dogs; epididymal sperm retention and oligospermia in dogs; stromal hyperplasia in ovaries/cervix in rats
- lung: foreign body granuloma in rats
- adrenal gland: zona glomerulosa vacuolation and hypertrophy in rats
- submandibular/parotid gland: acinar hypertrophy in rats; increased salivation in dogs
- pancreas: acinar hypertrophy, mononuclear cell infiltration and interstitial fibrosis in rats and/or dogs
- eye: retinal atrophy and degeneration of optic nerve in rats; reddened eye and lens vacuolization in dogs
- liver: hepatocytic hypertrophy in rats; mononuclear cell infiltration and cytoplasmic inclusions in dogs

- kidney: basophilic cortical tubules and mineralization in rats; karyomegaly and mononuclear cell infiltration in dogs
- mesenteric lymph node: hemorrhage in dogs
- thyroid: follicular cell hypertrophy and colloid alteration in rats

The histopathological findings in target organs and tissues were often associated with altered clinical pathology parameters (e.g., increased liver enzymes, increased renal markers, bloody urine) and/or organ weights (e.g., adrenal, liver, kidney, testis, heart).

Mortality was observed in rats at high oral doses (125 mg/kg in males, 75 mg/kg in females) secondary to myocardial damage in repeat-dose studies. The deteriorating clinical signs of CNS toxicity observed in acute-dose studies of mice and rats that led to deaths of animals were not noted in repeat-dose studies conducted at lower doses. Furthermore, some of the findings seen in short-term studies (e.g., ocular, hepatic and renal effects) were no longer evident in long-term studies at comparable doses.

Myocardial fibrosis/necrosis and/or vascular inflammation were noted in all species tested. In rats, increased incidences of myocardial fibrosis were observed in females at 100 mg/kg at 1 month; in females at ≥ 25 mg/kg and in males at 100 mg/kg at 3 months; in females at 75 mg/kg at 6 months. The cardiac lesions did not progress markedly over a 2-year exposure period. In mice, there was a trend for increased incidences of arteritis/periarteritis and myocardial fibrosis in males at ≥ 40 ppm (≥ 7 mg/kg) in a 2-year study although the toxicological significance is not clear. In dogs, myocardial fibrosis/necrosis and subepicardial changes in the cardiac atrium included subepicardial/pericardial edema, partly accompanied by an increase in minimal to mild subepicardial inflammatory infiltration. Increased incidence and severity of subepicardial edema occurred in males at ≥ 10 mg/kg and in females at ≥ 3 mg/kg at 1 month. Minimal to mild edema of the adventitial layer of the arteries from 10 mg/kg, combined with subepicardial inflammatory cell infiltration was found in males at high dose of 30 mg/kg. Slight arteritis/periarteritis in the right ventricle was noted in one of each male and female dog at 30 mg/kg. Myocardial fibrosis/necrosis in the left ventricle was seen in females at 30 mg/kg. In a 3-month study, minimal to moderate periarteritis/arteritis was observed in multiple cardiac lesions at 30 mg/kg (3/6M, 1/6F), and intramural edema in the right atrium was seen at ≥ 3 mg/kg in females and ≥ 30 mg/kg in males. In a 1-year study, minimal to slight periarterial edema was found in one of each male and female dogs at 30 mg/kg. These sporadic incidences following prolonged administration of vardenafil indicate that the vascular inflammation was not aggravated over time. In addition, these findings were noted in the presence of hemodynamic changes, suggesting that the myocardial findings may be secondary to the vasodilatory property of the drug. Systemic exposures at the NOAEL for the parent and M-1 for the cardiac findings in the longest-term studies are approximately 240-510 fold in rats ($AUC_{0-24h} \sim 22000-46000$ ng·hr/mL) and 70-fold in dogs ($AUC_{0-24h} \sim 7100-7500$ ng·hr/mL) compared to the human exposure at the proposed 10 mg vardenafil ODT (see Table 1).

Testicular/epididymal findings manifested as histopathological lesions of bilateral multifocal degeneration of the germinal epithelium in the testes with subsequent

increase in oligospermia and/or spermatic debris in the epididymes were observed in the 3-month studies in rats (≥ 25 mg/kg) and dogs (≥ 10 mg/kg). In dogs, sperm retention in the epididymides and tubular degeneration in testes were observed at ≥ 10 mg/kg at 1 year. In rats, increased incidence of Leydig cell hyperplasia and mononuclear cell infiltration in testes were noted in all treated male groups, and a sporadic incidence of granuloma inflammation in epididymides at ≥ 15 mg/kg in a 2-year study. However, reduced incidence rates of testicular effects (e.g., tubular atrophy, Leydig cell atrophy, tubular mineralization) or epididymal (aspermia, epithelial vacuolation, inflammation) were noted in mice with statistical significance at 1000 ppm (~ 150 mg/kg) in a 2-year study. In a fertility study, decreased fertility was observed in male rats at 100 mg/kg. Systemic exposures at the NOAEL for the parent and M-1 for these findings in the chronic dosing studies are approximately 10-fold in rats ($AUC_{0-24h} \sim 970$ ng·hr/mL) and 12-fold in dogs ($AUC_{0-24h} \sim 1100$ ng·hr/mL) greater than the human exposure at the 10 mg vardenafil ODT (see Table 1).

Follicular cell hypertrophy in the thyroid was observed in male and female rats in the 1- and 3-month studies at high doses (100/125 mg/kg), but was more pronounced in females. In a 2-year study, the increased incidence was statistically significant at the highest dose (75 mg/kg) in both sexes. These findings were often associated with altered T3/T4 or TSH levels, and were reversible during the 4-week recovery period assessed in a 3-month study. An in vitro mechanistic study showed no indication that vardenafil interfered with thyroid enzymes, suggesting that the thyroidal changes may be an adaptive response secondary to increased hepatic thyroxin elimination rather than a direct effect on the thyroid or on the pituitary. Systemic exposures at the NOAEL ($AUC_{0-24h} \sim 7500-8100$ ng·hr/mL) for the parent and M-1 for the thyroid findings in the 2-year study are approximately 80-fold greater than the human exposure at the proposed dose of 10 mg vardenafil ODT.

Acinar hypertrophy was seen in exocrine/endocrine glands including the adrenal, pancreas and/or salivary glands mostly in rats. Increased incidence and/or severity of the salivary gland hypertrophy were observed in males at 100/125 mg/kg and in females at ≥ 25 mg/kg in a 3 month study; in both sexes at 75 mg/kg in a 6-month study; and in males at ≥ 3 mg/kg and in females at ≥ 10 mg/kg in a 2-year study. In mice, sporadic incidence of hypertrophy were seen in males at 1000 ppm (~ 150 mg/kg), but not in females at up to 1000 ppm (~ 190 mg/kg) in a 2-year study. In dogs, inflammatory response was noted in submandibular gland at 30 mg/kg at 3 months, but not at 1 year. Increased salivation was noted on almost a daily basis at ≥ 10 mg/kg in the 1-year study although a relevance of the finding is not clear. Systemic exposures for the parent and M-1 at the NOAEL for the findings in 2-year studies are approximately 28-fold in male mice ($AUC_{0-24h} \sim 2500$ ng·hr/mL), 48-fold in female mice ($AUC_{0-24h} \sim 4300$ ng·hr/mL) and 10-14 fold in rats ($AUC_{0-24h} \sim 970-1300$ ng·hr/mL) above the exposure at the proposed human dose of 10 mg vardenafil ODT (see Table 1).

7 Genetic Toxicology

The following is based on the previously submitted data to support LEVITRA[®] film-coated tablet under NDA 21-400.

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Negative

7.2 *In Vitro* Chromosomal Aberration Assays in Mammalian Cells

Negative

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Negative

7.4 Other Genetic Toxicity Studies

Negative in V79 forward mutation assay

8 Carcinogenicity

The following brief summary is based on the previously submitted data to support LEVITRA[®] film-coated tablet under NDA 21-400.

Two-year carcinogenicity bioassays were conducted in rats by oral gavage and in mice via drinking water. A statistical significance was observed in carcinomas of the pars distalis of the pituitary gland with a negative trend (2/3/1/0) and in benign thymomas with a positive trend (0/0/2/3) in female rats. The increased incidence of thymomas was not considered to be biologically significant, given the incidence within the historical control data. In mice, histiocytic sarcomas were slightly higher in high-dose females (4/4/3/7), but were reduced in males (2/2/0/0) with a negative trend. Overall, it was concluded that the studies are negative at up to 1000 ppm (~150 mg/kg for males, ~190 mg/kg for females) in both sexes of mice ($AUC_{0-24h} \sim 2500-4300$ ng·hr/mL), 75 mg/kg in male rats ($AUC_{0-24h} \sim 46000$ ng·hr/mL), and 25 mg/kg in female rats ($AUC_{0-24h} \sim 22000$ ng·hr/mL) tested, producing approximately 27-47 fold exposure multiples for mice and 240-510 fold exposure multiples for rats above the anticipated human exposure at the proposed clinical dose of 10 mg vardenafil ODT.

9 Reproductive and Developmental Toxicology

The following brief summary is based on the previously submitted data to support LEVITRA[®] film-coated tablet under NDA 21-400.

9.1 Fertility and Early Embryonic Development

Reduced fertility index was seen in high-dose male rats (100 mg/kg), but the values were within the historical control range. The NOAEL of 25 mg/kg in a corresponding 1-month rat study (PH-28163) corresponded to an exposure ($AUC_{0-24h} \sim 1500$ ng·hr/mL) for the parent drug approximately 30-fold greater than the clinical exposure at 10 mg vardenafil ODT ($AUC_{0-24h} \sim 50$ ng·hr/mL, Study 12093) in humans given 10 mg (see Table 1).

9.2 Embryonic Fetal Development

In a developmental toxicity study in rats, severe maternal toxicity including mortality, clinical signs (piloerection, sunken flanks, disturbance of gait, hypoactivity), decreased food intake, increased water intake/urination, body weight loss, and pathological findings in the stomach (filled with bedding material, reddish brown spots in gastric mucosa) and heart (myocardial fibrosis, edema, necrosis, diffuse inflammatory infiltration) was observed in rats at the highest dose of 100 mg/kg. Gestation rates were reduced based on one case of total (early) resorption in each of the dose groups at ≥ 18 mg/kg. Increased incidence of post-implantation loss (above historical control range) and concomitant reduction in litter size were observed in the remaining females at 100 mg/kg. Reduced placental and fetal weights associated with retarded skeletal development (delayed ossification of phalanges of digits, toes, metacarpals/metatarsals, sternebrae, vertebral arches/bodies, enlargement of frontanelles, increased asymmetric 4th sternebrae variation) were found at the high dose.

In a rabbit developmental toxicity study, dams had reddening of the ears/hypoactivity at high dose (90 mg/kg), and decreased food intake/feces/urine at ≥ 18 mg/kg. Gestation rate was decreased at the high dose due to total resorption of fetuses in one female rabbit. Dose-related increase in postimplantation loss was observed with a concomitant decrease in live fetuses at ≥ 18 mg/kg. Retarded ossification of single locations was noted in high-dose fetuses.

The increased incidence and the type of external and skeletal malformations associated with low fetal weights (3 fetuses out of 2 litters with malformation of craniofacial bones including cleft palate/alteration of os palatinum and os exoccipitale or combined with sternal, vertebral and rib findings) in rats were regarded as secondary to the vasodilatory property of the test substance based on the severe maternal toxicity. The NOAEL of 18 mg/kg for developmental toxicity in rats ($AUC_{0-24h} \sim 12000$ ng·hr/mL) and rabbits ($AUC_{0-24h} \sim 1100$ ng·hr/mL) for vardenafil and M-1 is approximately 130- and 10-fold greater, respectively, than the humans dose of 10 mg vardenafil ODT based on AUC values. The NOAEL for maternal toxicity was established at 18 mg/kg in rats ($AUC_{0-24h} \sim 12600$ ng·hr/mL) and 3 mg/kg in rabbits ($AUC_{0-24h} \sim 50$ ng·hr/mL), corresponding to approximately 130- and 0.5-fold the total drug exposure (parent+M-1) in humans given 10 mg vardenafil ODT (see Table 1).

9.3 Prenatal and Postnatal Development

In a pre- and postnatal developmental toxicity study in rats, similar treatment-related effects seen in the embryonic fetal developmental toxicity study were noted at doses between 1 and 60 mg/kg. Maternal effects at high dose (60 mg/kg) included piloerection, reddish discolored pinnae, sunken flanks and high stepping gait around the time of parturition, transiently increased water consumption, intermittently light colored feces and reduced food intake from start of treatment up to postpartum day 14 and minimal to mild myocardial fibrosis (11 out of 25 dams). At the high dose, the gestation index was affected by a prenatal loss of a complete litter. Increased numbers of stillborn pups and mortality of F1 pups up to postpartum day 4 resulted in decreased live birth index, litter size at birth/rearing period, and rearing index. Body weight of F1 pups was decreased at high dose from birth to the end of the study, and was more pronounced during the rearing period and in males. Reduced lactation behavior at high dose was assumed, given a few pups with no milk spots. Retarded physical development of pups (eruption of incisors, development of normal gait, preputial separation) in the absence of maternal effects was observed following maternal exposure to 1 and 8 mg/kg. Delayed development of fur became evident from 8 mg/kg, and delay of pinnae detachment and eye opening were noted at high dose. Decreased vertical activity occurred in all treated male groups and high-dose females on postpartum Day 22. F1 generation had reduced body weight with decreased food intake in females at high dose. The numbers of pregnant females that delivered and litter size were reduced in high-dose F1 rats. Decreased fertility index was also seen in high-dose F1 females. These findings in F1 animals at 8 and 60 mg/kg are considered to be treatment-related, given the systemic effects noted at these dose levels. The NOAEL for maternal effects and fertility of the F1 generation was identified as 8 mg/kg. The NOAEL for pre- and postnatal development and motor activity of the F1 generation was considered to be <1 mg/kg. Based on plasma exposures in the rat developmental toxicity study, 1 mg/kg/day in the pregnant rat is estimated to produce total AUC values for vardenafil and M-1 comparable to the human AUC at 10 mg vardenafil ODT (see Table 1).

10 Special Toxicology Studies

The following brief summary is based on the previously submitted data to support LEVITRA[®] film-coated tablet under NDA 21-400.

In vitro interaction study of the synthesis of thyroidal hormones and the regulation of the hypothalamic-pituitary-thyroidal axis was investigated using thyroid peroxidase (TPO), iodothyronine deiodinase type I and iodothyronine deiodinase type II. Vardenafil neither affected TPO-catalyzed guaiacol oxidation and iodine formation nor inhibited iodothyronine deiodinase I- and II at maximally employable concentration, suggesting that the compound did not interfere with the key enzymes of thyroidal hormone synthesis and regulation.

Vardenafil (free base) did not produce skin irritation in rabbits (n=3) at 1, 24, 48 and 72 hours after patch removal following the 4-hour exposure period at a single dose of 500

mg. A single application of 100 mg vardenafil into a conjunctival sac of the right eye of rabbits caused conjunctival redness (grade 1) and conjunctival chemosis (grade 1) one hour post-dosing.

11 Integrated Summary and Safety Evaluation

The following table summarizes exposure multiples of vardenafil ODT at the NOAEL for potential toxicity observed in pivotal toxicology studies in animals compared to humans.

Table 1. Summary of Exposure Multiples at the NOAEL for the Major Findings Observed in Pivotal Toxicology Studies in Animals Compared to Humans Based on AUC

Study Type	Species	Target Organ Toxicity	NOAEL (mg/kg)	Exposure Multiple
General toxicity	Dog	↓QT, ↑HR/SBP/DBP	Dog; 3	12
	Dog, Rat, Mouse	Myocardial fibrosis/necrosis, periarteritis/arteritis	Dog; 10 Rat; 75 (M), 25 (F)	Dog: 70 Rat: 510 (M), 240 (F)
	Dog, Rat	Testicular degeneration, Leydig cell hyperplasia, oligospermia, sperm retention	Dog: 3 Rat: 3	Dog: 12 Rat: 10
	Rat, Mouse	Salivary gland acinar hypertrophy	Rat: 3 Mouse: 150 (M), 190 (F)	Rat: 10-14 Mouse: 28 (M), 48 (F)
Reproductive & Developmental toxicity	Rat	↓Fertility	Rat; 25	30
	Rat, Rabbit	Embryonic/fetal development	Rat: 18 Rabbit: 18	Rat: 130 Rabbit: 10
	Rat	Prenatal/postnatal development	Rat; <1	Rat: <1

Mean AUC_{0-24h} value of 90 ng·hr/mL/day for parent and M-1 based on Study 12093 in humans was used to estimate exposure multiples except for the fertility study (AUC_{0-24h}~50 ng·hr/mL/day for parent only).

LEVITRA[®] (vardenafil HCl) 2.5, 5, 10 and 20 mg film-coated tablets are approved in the United States as an oral treatment for ED. The dose should be adjusted based on efficacy and side effects. Vardenafil ODT is a newly proposed oral disintegrating tablet (orodispersible) formulation containing vardenafil HCl 10 mg. Vardenafil ODT is formulated to rapidly disintegrate in the mouth and allows administration without liquid. In this submission, the sponsor also proposes that no dosage adjustment is required in elderly patients based on the results from the completed clinical studies for 10 mg vardenafil ODT and post-marketing database for LEVITRA[®] film-coated tablets. In the completed clinical trials for vardenafil ODT, elderly patients did not experience a greater incidence of adverse events despite the higher AUC (~50%) compared to younger patients. However, it is not clear to this reviewer that the potential age-related changes in the CNS, cardiovascular, hepatic or renal function, and preexisting disease or concomitant drug therapy are taken into account for dose selection in elderly patients (see Clinical and Clinical Pharmacology Reviews for details).

The majority of the adverse effects seen in animals (central nervous system, cardiovascular system, eye, pancreas, salivary gland, thyroid, testis, *etc*) with vardenafil are considered to be related to its exaggerated pharmacological activities due to PDE5 inhibition.

The toxicity profile for vardenafil is similar to that of other phosphodiesterase 5 (PDE5) inhibitors. PDE5 is found in various parts of the body including the penis, lung, platelet, heart, pancreas, visceral/vascular/skeletal smooth muscle, liver, eye and the brain regions. The wide distribution of PDE5 and the corresponding versatile effects of PDE5 inhibitors may be associated with the undesirable effects of vardenafil in off-target systems as well as for the beneficial effects in on-target systems. Numerous published studies implicate the nitric oxide (NO)-cGMP pathway in PDE5 inhibitor-induced toxicity, given that the PDE5 inhibitors enhance NO-mediated response by elevating cGMP. In particular, NO is a potent biological mediator that displays a duality of function as an antioxidant and a prooxidant in a number of physiologic processes including neurotransmission, immune function, carcinogenesis and cardiovascular modulation depending on the concentration, duration, type, localization and exposure condition. Overstimulation of the NO-cGMP pathway in tissues and organs other than target sites may result in unwanted effects.

As expected from the drug's vasodilatory property, the cardiovascular system was one of the major targets. Vardenafil altered hemodynamic and ECG parameters in vitro and in vivo: inhibition of hERG current, reduced blood pressure and vascular resistance, tachycardia, increased heart rate, cardiac contractility and cardiac output, and shortened PQ and QT intervals. Cardiac lesions (myocardial fibrosis/necrosis and/or vascular inflammation) were also noted in multiple species at approximately 2-30 fold clinical exposures in short-term studies. However, the vascular inflammation was not evident following prolonged administration of vardenafil.

Recent evidence suggests potentially serious adverse effects associated with the use of PDE5 inhibitors although a casual relationship to drug exposure has not been established. These include neurological (seizure, amnesia), sudden cardiac death, cerebrovascular/cardiovascular (myocardial infarction, cerebrovascular hemorrhage, ischemic attack), ocular (non-arteritic anterior ischemic optic neuropathy, increased intraocular pressure, retinal vascular disease or bleeding, vitreous detachment/traction) and auditory (hearing loss) effects.

The CNS effects caused by PDE5 inhibitors are considered to be due to the NO-cGMP mediated modulation of seizure threshold. NO functions as both an anticonvulsant and a proconvulsant depending on the type of seizure, source of NO and the type of neurotransmitters involved (Eur J Pharmacol 587:129, 2008; Br J Pharmacol 147:935, 2006; Neurosci Lett 376:116, 2005). A recent study showing EEG abnormalities in ED patient taking tadalafil suggests perturbations of cerebrovascular vasoconstrictive response by PDE5 inhibitors (Neurol Res 31:313, 2009). Similarly, increased NO production has been demonstrated in animals with hearing loss, suggesting that excess NO is toxic to auditory organs (Biol Pharm Bull 31:1981, 2008; Hear Res 145:149, 2000; Ann NY Acad Sci 884:171, 1999) administered in doses comparable and/or higher than the MRHD of 20 mg. The PDE5 inhibitor-induced ocular effects could also be due to the NO-cGMP mediated vasodilatation (Drug Safety 32:1, 2009; Br J Ophthalmol 92:469, 2008; Invest Ophthalmol Vis Sci 49:720, 2008; Eye 22:144, 2008; Br J Ophthalmol 91:1551, 2007; Ophthalmology 109:584, 2002). These data suggest that the adverse

effects of PDE5 inhibitors seen in off-target organs may result from an overstimulation of the NO-cGMP pathway by PDE5 inhibition.

Vardenafil caused testicular/epididymal effects and reduced fertility in rats and/or dogs. The effects of PDE5 inhibitors in the male reproductive system are controversial. Studies reported no or positive or negative effect of PDE5 inhibitors on semen parameters in vivo or in vitro (see *Curr Pharm Des* 15:3506, 2009; *Int J Impot Res* 20:530, 2008; *Asian J Androl* 10:115, 2008 for detailed reviews). PDE5 inhibitors also enhanced progressive sperm motility and hyperactivation, and acrosome-reacted sperm (*Fertil Steril* 87:1064, 2007; *Am J Obstet Gynecol* 182:1013, 2000), suggesting a role of PDE5 inhibitors on sperm acrosome reaction and capacitation process. In a clinical study conducted in collaboration with the sponsor (*J Urol* 179:1060, 2008), there was no significant effect on sperm motility or morphology after single or 6-month oral doses in healthy volunteers given 20 mg vardenafil.

Effects (hypertrophy, hyperplasia) in the exocrine and endocrine glands (pancreas, salivary glands, thyroid and adrenal glands) were more significant with vardenafil compared with other PDE5 inhibitors. Acinar hypertrophy was observed in salivary glands (parotid and submandibular glands) administered via oral gavage or drinking water. These findings in general occurred at low doses in longer-term studies, suggesting that the incidence and/or severity may be increased following prolonged administration of the drug. It is not clear whether a combination of hypertrophy and hyperplasia occurred simultaneously with vardenafil as observed with repeated administration of drugs such as β -adrenergic receptor agonists or PDE inhibitors (*Toxicol Pathol* 19:214, 1991; *Biochem Pharmacol* 34:4229, 1985; *Am J Physiol* 212:1293, 1967). However, the lesions without evidence of progression to neoplasia in vardenafil-treated animals in 2-year studies suggest the lack of cellular proliferation over a 2-year period. Although the physiological significance and the clinical relevance of the findings are unknown, the hypertrophy could reflect a pathological consequence to an overactivation of the salivary glands by the ODT formulation, in which there is a potential for increased oral cavity permeation and accumulation. In humans, excessive stimulation of the glands may be manifested as dry mouth resulting from changes in secretory activity of the glands that may ultimately lead to impaired salivary function. NO is known to play an important role in regulation of salivary secretion, and chronically elevated NO production may act as a mediator of dry mouth (*Rheumatology* 48:727, 2009; *Arthritis Rheum* 40:875, 1997). If this is the case, the adverse effect of dry mouth seen in the clinical studies may be due to changes in secretory activity of the salivary glands that may ultimately lead to salivary gland dysfunction caused by PDE5 inhibition, given the expression of PDE5 in the salivary glands (*Arch Oral Biol* 47:567, 2002; *Odontology* 90:7, 2002). The potential in patients with certain medical conditions or other medications (e.g., diabetes, alcoholism, anticholinergics, antidepressants, antihypertensives, dehydration) that may exacerbate adverse salivary gland function is unknown. Elderly patients with diminished salivary output may have a higher potential for oral irritation possibly due to accumulation of the drug in salivary glands, considering any age-related alterations in normal salivary gland performance.

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/

YANGMEE SHIN
05/14/2010

LYNNDA L REID
05/14/2010
I concur.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 200-179

Applicant: Bayer HealthCare
Pharmaceuticals

Stamp Date: August 26, 2009

Drug Name: (b) (4)
(b) (4)

NDA/BLA Type: Original

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		Based on the original NDA 21-400 No new nonclinical studies provided (reformulated to an orodispersible tablet)
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	x		Based on the original NDA 21-400
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	x		Based on the original NDA 21-400
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		A right of reference letter to the original NDA 21-400 included
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	x		<ul style="list-style-type: none"> • Comparative single-dose PK studies in humans provided for the newly proposed orodispersible tablet and the approved film-coated tablet • Steady-state PK following multiple doses of the new formulation requested
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	x		Toxicology studies via oral gavage and in drinking water provided in the original NDA 21-400
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	x		Based on the original NDA 21-400
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x		Based on the original NDA 21-400

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	x		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	x		
11	Has the applicant addressed any abuse potential issues in the submission?			Not applicable
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Yangmee Shin, Ph.D. 10/1/09

 Reviewing Pharmacologist/Toxicologist Date

Lynnda Reid, Ph.D. 10/1/09

 Team Leader/Supervisor Date

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

/s/

YANGMEE SHIN
10/19/2009

LYNNDA L REID
10/19/2009