CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200179Orig1s000

SUMMARY REVIEW

Deputy Division Director Summary Review for Regulatory Action

Date	June 17, 2010
From	George S. Benson, MD
Subject	Division Deputy Director Summary Review
NDA/BLA #	200179
Applicant Name	Bayer Healthcare, Inc.
Date of Submission	August 26, 2009
PDUFA Goal Date	June 26, 2010
Proprietary Name / Established Name	Staxyn/ Vardenafil hydrochloride
Dosage Forms / Strength	Oral dispersible tablet/ 10 mg
Proposed Indication(s)	Erectile dysfunction
Action	Approval

Medical Officer Review	Donald McNellis, MD
Statistical Review	Xin Fang, PhD Mahboob Sobhan, PhD
Pharmacology/toxicology Review	Yangmee Shin, PhD Lynnda Reid, PhD
CMC Review	Jean Salemme, PhD Donna Christner, PhD Moo Jhong Rhee, PhD
Biopharmaceutics Review	Sandra Suarez Sharp, PhD Angelica Dorantes, PhD Patrick Marroum, PhD
Clinical Pharmacology Review	Sandhya Apparaju, PhD Myong Jin Kim, PharmD Edward Bashaw, PharmD
CDTL Review	Suresh Kaul, MD
DDMAC	Emily Baker, PharmD Carrie Newcomer, PharmD
OSE/DRISK	Melissa Hulett, MSBA, BSN, RN Mary Willy, PhD
Project Management	Eufrecina Deguia Jennifer Mercier
DMEPA	Jibril Abdus-Samad, PharmD Todd Bridges, RPh

(b) (4)

9. Advisory Committee meeting
10. Pediatrics
11. Other relevant regulatory issues
12. Labeling
13. Decision/Action/Risk Benefit Assessment

1. Introduction

Vardenafil hydrochloride is a phosphodiesterase type-5 (PDE5) inhibitor which was approved for the treatment of erectile dysfunction in the United States on August 19, 2003. The drug is currently marketed by Bayer Healthcare, Inc. as Levitra (film-coated tablets in 2.5 mg, 5.0 mg, 10 mg and 20 mg dosage strengths). Bayer has developed a new vardenafil formulation, an orodispersible tablet (ODT) containing 10 mg vardenafil which dissolves rapidly in the mouth and is taken without water. The sponsor believes that this formulation provides a more convenient dosage form for some men. The Levitra film-coated tablets will continue to be marketed. Two other PDE5 inhibitors, sildenafil (Viagra) (approved March 27, 1998) and tadalafil (Cialis) (approved November 21, 2003) are also approved for the treatment of erectile dysfunction.

2. Background

An end of Phase 2 meeting was held on April 17, 2008. At this meeting, the design of the Sponsor's phase 3 studies for the evaluation of the ODT formulation of vardenafil was discussed. The Sponsor inquired concerning the likelihood of these studies supporting a recommended starting dose of a 10 mg ODT in the elderly. The current Levitra label states that a starting dose of 5 mg should be considered in patients ≥65 years of age. DRUP informed the Sponsor that further characterization of the pharmacokinetics of the ODT formulation was needed, as well as data concerning the clinical experience with this formulation in patients greater than 75 years of age.

The Sponsor subsequently requested a meeting to discuss their plans to submit a supplemental NDA and also to discuss a proposal to revise the Dosage and Administration and Geriatric sections of the Levitra label. This meeting was scheduled for October, 2008. The Sponsor submitted several questions concerning the proposed submission and also a package of information designed to support their proposed revision of the label to eliminate any discussion of a dosing adjustment for elderly patients. This package included an evaluation of vardenafil film-coated tablet and clinical trial adverse events analyzed by age group and vardenafil dose.

DRUP responded to the Sponsor's questions concerning the proposed submission. DRUP also responded that they did not believe that the information provided in the meeting package would support a label revision without extensive further review. In particular, DRUP noted that the data suggested increasing dizziness in elderly subjects receiving doses of 10 mg or 20 mg of the vardenafil film coated tablet (Levitra). The sponsor accepted the Division's written responses and the planned meeting was not held.

3. CMC/Device

The CMC reviewer concluded that "the information provided in this New Drug Application is sufficient to assure the identity, strength, purity, and quality of the drug product."

"Labeling issues have not yet been resolved, and no overall "Acceptable" recommendation from the Office of Compliance has been made as of the date of this review. Therefore, from a CMC perspective, this NDA is not recommended for approval until all pending issues are resolved."

An e-mail was received from the reviewer on May 18, 2010, stating that "An Acceptable recommendation is now in EES for NDA 200179."

Labeling issues have been resolved. The Division of Medication Error and Prevention Analysis determined that the tradename Staxyn was acceptable on June 15, 2010.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology supervisor concurred with the primary pharmacology/toxicology reviewer 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." The pharmacology/toxicology portion of the label has been agreed upon.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The initial clinical pharmacology review concluded that the "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." No Phase 4 commitments are recommended.

Clinical Pharmacology and Biopharmaceutics findings included the following:

- 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 T1/2 values were comparable across treatments (~4 hours) and T_{max} (1.5 hours) was prolonged with the ODT formulation relative to IR. Once daily dosing of 10 mg ODT did not result in significant accumulation of vardenafil. T1/2 was unchanged with daily doses.

- Similar to the approved 10 mg IR formulation, elderly ED patients (≥ 65 years) had higher systemic exposure and longer T1/2 values of vardenafil and its metabolite M1 (activity 25 % that of vardenafil) compared to younger patients. 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 (18-45 years). 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.

- 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.

- 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 approximately 67% higher AUC of vardenafil; when comparing to younger patients receiving ODT, elderly on ODT may experience approximately 38% higher AUC; compared to elderly currently receiving 10 mg IR, elderly on 10 mg ODT may see approximately 20% higher exposure.

- In the two phase 3 clinical trials for TRADENAME, sponsor has prospectively enrolled approximately 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).

The clinical pharmacology team leader and Director of the Division of Clinical Pharmacology III subsequently concluded that a Post-Marketing trial should be required and an additional clinical pharmacology memorandum was written. The clinical pharmacology recommendation was that "this trial should be "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."

Additional clinical pharmacology 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 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.
- 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. However, the increase in dizziness with age was not seen in the vardenafil ODT studies.
- Cmax and AUC in the elderly were 21% and 38% higher, respectively, compared to the young males with ED.
- Given that vardenafil exposure is higher in the elderly men, the risk for orthostatic hypotension in the elderly men needs to be addressed.

Clinical Pharmacology Recommendation:

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

The sponsor has agreed to conduct the post-marketing clinical trial and proposed an acceptable timetable.

6. Clinical Microbiology

According to the CMC review, the microbial purity evaluation is "acceptable."

7. Clinical/Statistical-Efficacy

Primary phase 3 trials 12093 and 12094 provided the evidence for efficacy of vardenafil ODT for the treatment of erectile dysfunction. The design of the two clinical trials was identical, with the exception of the addition of a pharmacokinetic evaluation in a subset of patients following the completion of the efficacy portion of trial 12093. The trials were multi-center, randomized, double-blind trials evaluating the on demand use of a vardenafil 10 mg ODT as compared to the on demand use of a placebo ODT. Trial 12093 was carried out at 40 centers in Belgium, France, Germany, Spain, South Africa, and The Netherlands. Trial 12094 was carried out at 35 centers in the United States, Canada, Mexico and Australia.

Inclusion –exclusion criteria:

The main criteria for inclusion were men, 18 years-of-age or older with erectile dysfunction (defined according to the NIH Consensus Development Panel on Impotence) for more than 6 months. Because of the potential safety concern for increased exposure of vardenafil ODT in older men, the protocol specified that approximately 50% of the patients on treatment should be 65 years-of-age or older. Patients with diabetes were not excluded. Patients who had undergone a prostatectomy for prostate cancer were excluded.

Study design:

Subjects who met the criteria regarding attempts at intercourse and percentage of attempts that were unsuccessful (50%) during the four week untreated baseline period were then randomized to receive either vardenafil 10 mg ODT or a placebo ODT. The medication was to be taken, without water, as needed approximately one hour prior to intercourse, but not more than once in 24 hours. The placebo-controlled treatment period was 12 weeks. A Subject Diary was completed for each sexual encounter during this period.

Endpoints:

Three co-primary efficacy endpoints were evaluated:

- International Index of Erectile Function – Erectile Domain (IIEF-EF). The IIEF is a validated instrument for evaluating erectile function. The Erectile Domain score is the total of the scores for six questions (Q1, Q2, Q3, Q4, Q5, and Q15). The IIEF was administered at Visit 2 (baseline) and at Visit 4 (week 12). The change from baseline to week 12 was the endpoint evaluated.
- Sexual Encounter Profile Question 2 (SEP2) “Were you able to insert your penis into your partner’s vagina?” This question was answered in the Subject Diary for each sexual encounter during both the baseline period and the treatment period. The percentage of “Yes” responses was calculated for each period. The change in

"Yes" percentage from the baseline period to the treatment period was the endpoint evaluated.

- Sexual Encounter Profile Question 3 (SEP3) "Did your erection last long enough for you to have successful intercourse?" This question was answered in the Subject Diary for each sexual encounter during both the baseline period and the treatment period. The percentage of "Yes" responses was calculated for each period. The change in "Yes" percentage from the baseline period to the treatment period was the endpoint evaluated.

The three co-primary endpoints were evaluated simultaneously and it was pre-specified that all three must show a change from the baseline to week 12 that is significant at the p=0.05 level for an overall finding of efficacy.

Demographics – Trial 12093

The average age of all subjects was approximately 62 years. As specified in the Protocol, approximately 50% of the subjects had to be greater than 65 years of age. The average age in the younger patient stratum was approximately 53 years, while elderly subjects had an average age of approximately 70 years. The age at entry into the study ranged from 21 to 84 years. Twenty-six subjects (7.3%) were 75 years-of-age and older. Demographic characteristics are shown in Table 1 and the co-existing diseases occurring in this population in study 12093 are shown in Table 2.

Table 1. Demographic Characteristics – Study 12093

Parameter		Vardenafil 10 mg ODT		Placebo	
		<65 years	≥65 years	<65 years	≥65 years
N		87	97 (13>75)	81	93 (13>75)
Race	White	55 (63%)	68 (70%)	53 (65%)	64 (69%)
N (% rounded)	Black	3 (3%)	4 (4%)	2 (2.5%	5 (5%)
	Asian	6 (7%)	3 (3%)	2 (2.5%)	2 (2%)
	Missing	23 (27%)	22 (23%)	24 (25%)	22 (24%)
Age (years)	Mean ± SD	52.8 ± 9.0	69.7 ± 4.2	52.7 ± 8.5	69.8 ± 4.9
Weight (kg)	Mean ± SD	87.1 ± 11.7	81.6 ± 11.4	88.0 ± 15.0	82.6 ± 11.9
BMI (kg/m^2)	Mean ± SD	27.5 ± 3.5	26.9 ± 3.2	27.9 ± 4.3	27.1 ± 3.6

Source: NDA 200179, Module 5.3.5.1, Report of Study 12093, Table 11-2.

Subjects are appropriately distributed between the two age groups, <65 years and >65 years. The "Missing" racial data is secondary to the study sites in France not being allowed to report this information. Twenty six patients were elderly males >75 years of age.

Table 2. Co-existing Diseases – Study 12093

MedDRA (%) Higher Level Term	Vardenafil 10 mg ODT		Placebo	
	<65 years	≥65 years	<65 years	≥65 years
Ischemic coronary artery disorders	3 (3%)	11 (11%)	9 (11%)	11 (12%)
Diabetes mellitus	23 (26%)	33 (34%)	22 (27%)	30 (32%)
Elevated cholesterol	17 (20%)	28 (29%)	13 (16%)	18 (19%)
Purine metabolism NEC	1 (1%)	4 (4%)	8 (10%)	8 (9%)
Hyperlipidemia	5 (6%)	5 (5%)	6 (7%)	4 (4%)
Lipid metabolism and deposit disorders NEC	4 (5%)	6 (6%)	7 (9%)	3 (3%)
Bronchospam and obstruction	2 (2%)	6 (6%)	6 (7%)	6 (7%)
Prostatic neoplasms and BPH	13 (15%)	29(30%)	12 (15%)	22(24%)
Large intestine therapeutic procedures	5 (6%)	7 (7%)	2 (3%)	5 (5%)
Vascular hypertensive disorders	23 (26%)	45 (46%)	34 (42%)	46 (50%)

Source: NDA 200179, Module 5.3.5.1, Report of Study 12093, Table 11-4.

Approximately 30% of the study population had diabetes and 26-50% had hypertension. Of the patients >65 years of age in the vardenafil treatment group, 45 (46%) had "vascular hypertensive disorders."

Demographics – Study 12094

The average age was approximately 62 years. As in study 12093, this is due to the protocol requirement that approximately 50% of the subjects be greater than 65 years of age. The average age in the younger patient stratum was approximately 53 years, while elderly subjects had an average age of approximately 70 years. The age at entry into the study ranged from 22 to 88 years. Thirty-four subjects (10%) were 75 years-of-age and older. Demographic characteristics of the safety population are shown in Table 3 and the co-existing diseases occurring in this population are shown in Table 4.

Table 3. Demographic Characteristics – Study 12094

Parameter		Vardenafil 10 mg ODT		Placebo	
		<65 years	≥65 years	<65 years	≥65 years
N		86	85 (16>75)	84	82 (18>75)
Race	White	53 (62%)	65 (77%)	54 (64%)	60 (73%)
N (% rounded)	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

Source: NDA 200179, Module 5.3.5.1, Report of Study 12094, Table 11-2.

Elderly black men (>65 years) appear to be somewhat under represented as compared to younger black men. In the white group the opposite is true, with the elderly being represented in larger numbers as compared to the younger subjects. Thirty-four patients were elderly males >75 years of age.

Table 4. Co-existing Diseases – Study 12094

MedDRA (%) Higher Level Term	Vardenafil 10 mg ODT		Placebo	
	<65 years	≥65 years	<65 years	≥65 years
Hearing losses	1 (1%)	6 (7%)	3 (4%)	10 (12%)
Refractive accommodative disorder	6 (7%)	8 (9%)	4 (5%)	5 (6%)
Cataract conditions	2 (2%)	12 (14%)	1 (1%)	5 (6%)
GI atonic and hypomotility disorders	12 (14%)	20 (24%)	10(12%)	19 (23%)
Atopic disorders	9 (11%)	6 (7%)	5 (6%)	6 (7%)
Allergies to foods, drugs etc.	5 (6%)	8 (9%)	4 (5%)	8 (10%)
Respiratory tract infections	2 (2%)	9 (11%)	7 (8%)	12 (15%)
Diabetes mellitus	16 (19%)	25 (29%)	17 (20%)	12 (15%)
Elevated cholesterol	12 (14%)	9 (11%)	5 (6%)	15 (18%)
Purine metabolism NEC	3 (4%)	4 (5%)	6 (7%)	4 (5%)
Hyperlipidemia NEC	13 (15%)	20 (24%)	6 (7%)	13 (16%)
Lipid metabolism and deposit disorders NEC	1 (1%)	4 (5%)	3 (4%)	1 (1%)
Bronchospam and obstruction	11 (13%)	8 (9%)	3 (4%)	4 (5%)
Musculoskeletal and connective tissue signs and symptoms	12 (14%)	10 (12%)	10 (12%)	8 (10%)
Osteoarthropathies	5 (6%)	13 (15%)	3 (4%)	10 (12%)
Arthropathies NEC	4 (5%)	8 (9%)	1 (1%)	9 (11%)
Skin neoplasms	0 (0%)	4 (5%)	5 (6%)	5 (6%)
Depressive disorders	11 (13%)	3 (4%)	10 (12%)	7 (9%)
Prostatic neoplasms and BPH	7 (8%)	11(13%)	5 (6%)	17(21%)
Joint therapeutic procedures	5 (6%)	9 (11%)	6 (7%)	4 (5%)
Hernia repairs	5 (6%)	10 (12%)	0 (0%)	5 (6%)
Male genital tract therapeutic procedures	6 (7%)	3 (4%)	7 (8%)	2 (2%)
Arterial therapeutic procedures	3 (4%)	7 (8%)	0 (0%)	7 (9%)
Vascular hypertensive disorders	28 (33%)	44 (52%)	29 (35%)	41 (50%)

Source: NDA 200179, Module 5.3.5.1, Report of Study 12094, Table 11-4.

Approximately 20% of the subjects had diabetes and 33-50% had hypertension. Of the patients >65 years of age in the vardenafil treatment group, 44 (52%) had "vascular hypertensive disorders."

Study results – primary end points for Study 12093 (Table 5) and Study 12094 (Table 6):

Table 5. Study 12093, Change from baseline (ITT) - Primary Endpoints

	IIEF-EF		SEP 2		SEP 3	
	Vardenafil 10 mg ODT Mean ± SD	Placebo Mean ± SD	Vardenafil 10 mg ODT Mean ± SD	Placebo Mean ± SD	Vardenafil 10 mg ODT Mean ± SD	Placebo Mean ± SD
Subjects (N)	181	172	179	169	178	164
Baseline Value	12.8 (4.85)	12.85 (5.14)	39.4 (35.48)	37.5 (36.04)	13.2 (20.56)	14.5 (20.86)
Week 12 Value	21.48 (8.12)	14.2 (7.59)	74.9 (32.26)	44.7 (38.38)	65.0 (36.57)	25.8 (32.11)
Change from Baseline	8.6 (7.40)	1.4 (6.86)	35.5 (35.93)	7.2 (35.79)	51.7 (35.18)	11.3 (28.67)
Treatment LS-mean difference	-7.1 (-8.6 - -5.7)		-27.04 (-33.7 - -20.4)		-38.19 (-45.0 - -31.4)	
p (F-Test) 'Treatment'	<0.0001		<0.0001		<0.0001	

Source: Module 5.3.5.1, Report of Study 12093, Tables 11-5 ,11-6, 11-7, 11-8, 11-9 and 11-10.

Table 6. Study 12094, Change from baseline (ITT) - Primary Endpoints

	IIEF-EF		SEP 2		SEP 3	
	Vardenafil 10 mg ODT Mean ± SD	Placebo Mean ± SD	Vardenafil 10 mg ODT Mean ± SD	Placebo Mean ± SD	Vardenafil 10 mg ODT Mean ± SD	Placebo Mean ± SD
Subjects (N)	167	160	168	161	168	160
Baseline Value	11.8 (5.72)	12.9 (5.75)	37.2 (36.2)	39.2 (35.10)	12.9 (18.89)	15.5 (20.94)
Week 12 Value	20.4 (9.11)	14.3 (7.71)	67.5 (37.59)	43.0 (38.35)	58.8 (39.01)	27.5 (32.48)
Change from Baseline	8.5 (8.11)	1.4 (6.14)	30.2 (35.40)	3.8 (33.63)	46.0 (36.47)	12.0 (29.44)
Treatment LS-mean difference	-6.92 (-8.4 - -5.4)		-25.97 (-32.7- -19.3)		-33.43 (-40.4 - -26.4)	
p (F-Test) 'Treatment'	<0.0001		<0.0001		<0.0001	

Source: Module 5.3.5.1, Report of Study 12094, Tables 11-5 ,11-6, 11-7, 11-8, 11-9 and 11-10.

Study 12093 and Study 12094 each showed that the three co-primary endpoints improve from their baseline level more with vardenafil ODT treatment than with placebo treatment. The difference between vardenafil treatment and placebo treatment is significant at the $p < 0.0001$ level for each endpoint in each study.

Analyses of subpopulations demonstrate that vardenafil is significantly more effective than placebo in improving IIEF-EF score in both the <65 and >65 year old age groups.

Statistical review: The statistical reviewer concluded that "from a statistical perspective, this application provided adequate data to support the efficacy of VODT10 in the treatment of ED patients."

Efficacy summary: Two adequately controlled trials using accepted endpoints have demonstrated that vardenafil ODT is effective in the treatment of erectile dysfunction. The results from both trials are consistently highly statistically significant.

8. Safety

Two phase 1 PK studies (13396; n=36 and 12769; n=16) and two phase 3 trials (12093; n=358 and 12094; n=337) form the safety database for vardenafil ODT. The two phase three trials were 12 weeks in duration and the patients were nearly evenly divided between drug and placebo groups. Safety data from the two phase 3 studies were pooled and form the primary basis for the safety analysis.

A secondary review of the safety experience of patients <65 years of age as compared to those ≥65 years of age was also performed. Also discussed in this section is the safety experience of patients in 58 trials of vardenafil film-coated tablets. This analysis is targeted at evaluating the safety experience of subjects ≥65 years of age as compared to that of subjects <65 years of age. These age-targeted analyses were done to provide information to base dosing recommendations for elderly patients.

In the two phase 3 trials, the average exposure time was 72 days for patients receiving placebo and 76 days for patients receiving vardenafil. Details of treatment duration are shown in Table 7. This calculated treatment duration covers the time from date of first study medication to date of last study medication. Since this was a 'prn' medication the treatment duration is not identical with the individual study duration, which is calculated via the visit dates.

Table 7. Treatment Duration (Days)

	Placebo			Vardenafil ODT			Overall
	<65 years	≥65 years	Total	<65 years	≥65 years	Total	Total*
Number of Patients	160	173	333	168	180	348	681
Mean	70.6	72.6	71.7	77.5	74.0	75.7	73.7
Minimum	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Median	78.5	78.0	78.0	82.0	80.0	81.0	80.0
Maximum	111.0	104.0	111	117.0	116.0	117	117

Source: NDA 200179, Module 5.3.5.3, Integrated Summary of Safety, Table 5-1.
*The overall safety population consists of 695 patients.

The average number of doses per subject-week was slightly higher in subjects treated with vardenafil (2.7 tablets/week) compared to subjects treated with placebo (2.0 tablets/week).

The demographic characteristics of the phase 3 trials (Studies 12093 and 12094 combined) are shown in Table 8.

Table 8. Demographic Characteristics of the Phase 3 Safety Population

	Placebo (N=340)	Vardenafil ODT (N=355)
Age stratum, n (%)		
<65 years	165 (48.5%)	173 (48.7%)
≥65 years	175 (51.5%)	182 (51.3%)
Age group, n (%)		
<45 years	28 (8.2%)	27 (7.6%)
45 - <65 years	137 (40.3%)	146 (41.1%)
65 - <75 years	144 (42.4%)	153 (43.1%)
≥75 years	31 (9.1%)	29 (8.2%)
Age (y), mean (range)	61.9 (21-88)	61.5 (22-83)
Race, n (%)		
White	231 (67.9%)	241 (67.9%)
Black	18 (5.3%)	16 (4.5%)
Asian	14 (4.1%)	24 (6.8%)
Hispanic	39 (11.5%)	35 (9.9%)
Missing/other	38 (11.2%)	39 (11.0%)
Any medical history finding, n (%)	310 (91.2%)	317 (89.3%)
Hx of cardiac disorder	62 (18.2%)	58 (16.3%)
Hx of arteriosclerosis	21 (6.2%)	19 (5.4%)
Hx of myocardial infarction	18 (5.3%)	15 (4.2%)
Hx of CNS bleed or CVA	12 (3.5%)	9 (2.5%)
Hx of diabetes mellitus	86 (25.3%)	102 (28.7%)
Hx of dyslipidemia	109 (32.1%)	139 (39.2%)
Hx of hypertension	150 (44.1%)	141 (39.7%)
Antihypertensive Treatment		
None (despite dx of hypertension)	14 (4.1%)	11 (3.1%)
1 Antihypertensive	55 (16.2%)	44 (12.4%)
2 Antihypertensives	42 (12.4%)	58 (16.3%)
3 or more Antihypertensives	39 (11.5%)	28 (7.9%)
Hx of renal impairment		
Mild	86 (25.3%)	95 (26.8%)
Moderate	10 (2.9%)	11 (3.1%)
Hx of hepatic impairment	5 (1.5%)	4 (1.1%)

Source: NDA 200179, Module 5.3.5.3, ISS, Table 5-8.

Deaths:

There were no deaths in either the phase 1 studies or the two phase 3 studies.

Serious Adverse Events:

In the phase 1 studies, there was one serious adverse event. A subject was hospitalized as a result of a motorcycle accident. The accident occurred two days after exposure to vardenafil ODT and was determined as not related to the study drug exposure by the investigator.

The phase 3 analysis includes serious adverse events that occurred within 7 days of the last exposure to study medication. In these studies there were seven serious adverse events (SAE's) that occurred in six patients receiving vardenafil and there were two serious adverse events that occurred in two patients receiving placebo. SAE's in the two phase 3 trials combined are shown in Table 9.

Table 9. Serious Adverse Events in Phase 3 Studies

Subject Number	Primary SOC(PT)	Placebo <65 years N = 165	Placebo ≥65 years N = 175	Vardenafil ODT <65 years N = 173	Vardenafil ODT ≥65 years N = 182
	Any Event (events/subjects)	1/1	1/1	3/2	4/4
12093-10010-0006	Cardiac Disorders (Acute Coronary Syndrome)	0	0	0	1 (0.5%)
12093-16006-0007	Femoral Artery Stenosis (Femoral Artery Stenosis)				1 (0.5%)
12093-37005-0005	Gastrointestinal Disorders (GI Hemorrhage)	0	0	0	1 (0.5%)
12093-37007-0003	Nervous System Disorders (Syncope)	0	0	0	1 (0.5%)
12093-37007-0009	Ear and Labyrinth Disorders (Deafness Neurosensory)	0	1 (0.6%)	0	0
12094-14011-0008	Neoplasms (Prostate Cancer)	1 (0.6%)	0	0	0
12094-14013-0009	Vascular Disorders (Hypertension)	0	0	1 (0.6%)	0
12094-14016-0008	General Disorders (Chest Pain)	0	0	1 (0.6%)	0
12094-14017-0008	Arrhythmia (Arrhythmia)	0	0	1 (0.6%)	0

Source: NDA 200179, Report of Study 12093, Table 12-7 and Report of Study 12094, Table 12-7. Subject 12094-14013-0009 added based on MO analysis of Drug/Event timing.

Case narratives of the patients experiencing SAE's appear on pages 45 to 48 of the primary medical officer's review. Patient 0006 had a significant history of cardiovascular disease including cardiomyopathy and patient 0003 had "inner ear disease" which may have contributed to his syncopal episode. Drug causality could not be reasonably determined for any of the serious adverse events.

Study Discontinuation:

Two patients in the placebo group and 5 patients in the vardenafil group withdrew prematurely from the phase 3 trials because of adverse events (Table 10).

Table 10. Patients Withdrawing Prematurely from the Phase 3 Studies due to Adverse Events

		Placebo		Vardenafil ODT	
Subject Number	Primary SOC(PT)	<65 years	≥65 years	<65 years	≥65 years
12093 10010-0006	Acute Coronary Syndrome	0	0	0	1
12093 30001-0003	ALT Increased	0	0	1	0
12093 37007-0009	Sensorineural hearing loss	0	1	0	0
12094 14013-0009	Chest Pain , Blurry vision	0	0	1	0
12094 14022-0011	Lightheadedness, Headache, Swallowing difficulty	0	0	0	1
12094 40002-0016	Anxiety attacks	0	1	0	0
12094 40004-0008	Muscle spasms, dizziness, flushing	0	0	1	0

Source: NDA 200179, Report of Study 12093, page 126 and Report of Study 12094, Table 12-9.

Patient 0006 had a long history of ischemic cardiomyopathy. Patient 0003 had elevated LFT's at baseline and a "greater than usual" alcohol intake during the study. In patient 0009, the mild chest pain resolved and the relationship of the chest pain to the medication is difficult to assess from the available information. An association of patient 0011's and 0008's symptoms to study medication could not be excluded.

Common Adverse Events:

Adverse Events occurring in >1% of subjects in either treatment group are shown in Table 11.

Table 11. Treatment Emergent Adverse Events Occurring in ≥1% of Subjects

Preferred Term	Placebo N = 340	Vardenafil ODT N=355
Headache	6 (1.8%)	51 (14.4%)
Flushing	2 (0.6%)	27 (7.6%)
Nasal congestion	1 (0.3%)	11 (3.1%)
Dyspepsia	0 (0.0%)	10 (2.8%)
Dizziness	0 (0.0%)	8 (2.3%)
Back pain	1 (0.3%)	7 (2.0%)
Diarrhea	3 (0.9%)	6 (1.7%)
Supraventricular extrasystoles	3 (0.9%)	4 (1.1%)
Dysgeusia	4 (1.2%)	4 (1.1%)
Muscle spasms	2 (0.6%)	4 (1.1%)

Source: NDA 200179, Module 5.3.5.3, ISS, Table 5-23.

These adverse event incidences are similar to those seen in previously conducted trials of vardenafil film-coated tablets. The labeled adverse events for the Levitra film coated tablet in fixed and flexible dose controlled trials include headache 15%, flushing 11%, "rhinitis" 9%, dyspepsia 4%, and dizziness 2%. In the vardenafil ODT trials, of the 8 patients with dizziness, 5 patients were <65 years of age and 3 were >65 years of age. There were no patients >75 years of age with the adverse event of dizziness. Orthostatic hypotension was reported in 2 (0.6%) of the patients in the placebo group and 2(0.6%) of the patients in the vardenafil ODT group.

Laboratory findings:

The primary medical officer did not find any significant effect on hematology parameters, liver function tests, or renal function tests which could be ascribed to vardenafil.

Vital signs:

With respect to standing systolic/diastolic blood pressure, there was a mean decrease from baseline of 1.3/0.6 mm Hg in the vardenafil treated subjects as compared to an increase of 1.7/1.2 mm Hg in the placebo treated subjects. The mean change from baseline in pulse rate was -0.6 bpm in the placebo group and -0.7 bpm in the vardenafil group.

Safety summary:

No new safety concerns were identified with the vardenafil ODT formulation when compared to the adverse event profile of vardenafil film-coated tablets (Levitra). The adverse events were qualitatively and quantitatively similar to those seen with both vardenafil film-coated tablets and also to those of other drugs in its class. The most

common adverse events (seen in >2% of subjects and more frequently than seen in placebo) were headache, flushing, nasal congestion, dyspepsia, dizziness and back pain.

The adverse events of sudden visual loss and sudden hearing loss are labeled for all of the PDE5 inhibitors. There were no events of this nature in the vardenafil ODT treated subjects, although one episode of sudden hearing loss occurred in a subject receiving placebo. Oral irritation events were also examined because the medication is designed to be dissolved in the mouth and there was no evidence of increased oral adverse events in patients taking this medication. In patients taking Levitra film coated tablets, the Levitra label states that "a starting dose of 5 mg Levitra should be considered in patients >65 years old." This labeling was based on the fact that vardenafil exposure is higher in patients >65 years of age compared to patients <65 years of age. In the vardenafil ODT primary efficacy and safety trials, no increase in adverse events in the older population (who comprised >50% of the total study population) was seen. I believe that patients >65 years of age can initiate therapy with 10 mg vardenafil ODT.

9. Advisory Committee Meeting

No Advisory Committee was convened for this NDA submission. Vardenafil is an approved product (Levitra film coated tablets). No new safety concerns were identified with this new vardenafil formulation.

10. Pediatrics

The Sponsor requested a full waiver of the requirement to conduct assessments of varenafil orodisposible tablets in pediatric patients.

The Division recommended a full waiver because studies would be highly impracticable to conduct and because the disease/condition does not exist in normal children.

The Pediatric Review Committee (PeRC) agreed with the Division that "PREA does not apply" and to grant a full pediatric waiver for this product.

11. Other Relevant Regulatory Issues

Division of Scientific Investigations:

There were no clinical site inspections requested for this vardenafil ODT drug development program.

Financial Disclosure:

The Sponsor has provided information concerning the financial disclosures of all investigators involved in the clinical trials for this product. All of the principal investigators and sub-investigators from all sites of studies had no disclosures in the [redacted] (b) (4) studies.

In summary, adequate information was submitted to demonstrate compliance with financial disclosure requirements.

The Division of Risk Management (DRISK) reviewed the Patient Package Insert and their recommendations were considered and incorporated into the labeling.

The Division of Drug Marketing, Advertising and Communications (DDMAC) reviewed the label and their recommendations were considered and incorporated into the labeling.

The Division of Medication Error Prevention and Analysis reviewed several tradenames. The Sponsor's proposals have all been rejected and, at the time of writing this review, no tradename has been approved. DMEPA also made recommendations concerning the label and these recommendations were incorporated into the label.

Addendum: On June 15, 2020, DMEPA found the tradename "Staxyn" acceptable.

12. Labeling

Labeling negotiations with the Sponsor have been completed.

Because the 10 mg vardenafil ODT is not bioequivalent to the 10 mg vardenafil film-coated tablet (Levitra), the orodispensible tablet will have a separate tradename and a separate label.

The Dosage and Administration section of the Highlights states:

"TRADEMARK is not interchangeable with vardenafil 10 mg film-coated tablets (Levitra). TRADEMARK provides higher systemic exposure compared to vardenafil 10 mg film-coated tablets (Levitra)."

As with other PDE5 inhibitors, the use of vardenafil ODT with nitrates or nitric oxide donors is contraindicated because of the risk of hypotension.

Because vardenafil ODT is only available in the 10 mg dose form, the Warnings and Precautions Section states that "Do not use TRADEMARK in patients taking potent or moderate CYP3A4 inhibitors."

As with other PDE5 inhibitors, the Warnings and Precautions Section also contains warnings concerning non-arteritic anterior ischemic optic neuropathy and sudden hearing loss.

Use of vardenafil ODT and alpha blockers concomitantly is also described in the Warnings and Precautions section of the label.

Patients over the age of 65 years may initiate the 10 mg vardenafil ODT dose.

13. Decision/Action/Risk Benefit Assessment

Decision:

The primary medical officer, the cross-discipline team leader, and the CMC, clinical pharmacology, statistical, and pharmacology/toxicology review teams all believe that NDA 200179 should be approved. I agree.

Risk/Benefit Determination:

Two adequately controlled trials using accepted endpoints have demonstrated that vardenafil ODT is effective in the treatment of erectile dysfunction. The results from both trials are consistently highly statistically significant, and efficacy has been demonstrated.

No new safety concerns were identified with the vardenafil ODT formulation when compared to the adverse event profile of vardenafil film-coated tablets (Levitra). The adverse events were qualitatively and quantitatively similar to those seen with both vardenafil film-coated tablets and also to those of other drugs in its class (PDE5 inhibitors). The most common adverse events (seen in >2% of subjects and more frequently than seen in placebo) were headache, flushing, nasal congestion, dyspepsia, dizziness and back pain.

The adverse events of sudden visual loss and sudden hearing loss are labeled for all of the PDE5 inhibitors. None of these events occurred in the vardenafil ODT treated subjects, although one episode of sudden hearing loss occurred in a subject receiving placebo. Oral irritation events were also examined because the medication is designed to be dissolved in the mouth and there was no evidence of increased oral adverse events in patients taking this medication. In patients taking Levitra film coated tablets, the Levitra label states that "a starting dose of 5 mg Levitra should be considered in patients >65 years old." This labeling was based on the fact that vardenafil exposure is higher in patients >65 years of age compared to patients <65 years of age. In the vardenafil ODT primary efficacy and safety trials, no increase in adverse events in the older population (who comprised >50% of the total study population) was seen. I believe that patients >65 years of age can initiate therapy with 10 mg vardenafil ODT.

The risk/benefit assessment of vardenafil ODT favors approval of vardenafil ODT for the treatment of erectile dysfunction.

Recommendations for Risk Evaluation and Mitigation Strategies (REMS)/Post Marketing Requirement (PMR):

Because of higher vardenafil exposure seen in elderly patients, the clinical pharmacology review team recommended that a PMR be performed. This trial should be "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."

The sponsor agreed to perform this PMR and proposed an acceptable timetable.

Addendum: On June 15, 2010, DMEPA found the tradename Staxyn to be acceptable.

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/

GEORGE S BENSON
06/17/2010