

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
200179Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 16th, 2010
From	Suresh Kaul, MD, MPH
Subject	Cross-Discipline Team Leader Review
NDA #	200,179
Applicant	Bayer Healthcare, Inc
Date of Submission	August 26th, 2009
PDUFA Goal Date	June 26th 2010
Early Action Date	June 18th, 2010
Proprietary Name / Established (USAN) names	Staxyn Vardenafil HCl
Dosage forms / Strength	Oral Dispersible Tablet, 10 mg As needed, not more than once in 24 hours
Proposed Indication(s)	Treatment of Erectile Dysfunction (ED) in adult males
Recommended:	<i>Approval</i>

Cross Discipline Team Leader Review

1. Introduction

I believe that **Staxyn** (vardenafil oral dispersible tablets) should receive an **approval action** for the indication of “treatment of erectile dysfunction” in adult males. Vardenafil Orally Dispersible Tablet (ODT) 10 mg has demonstrated “substantial evidence” of effectiveness in improving symptoms of erectile dysfunction in the target population and an acceptable safety profile.

Vardenafil hydrochloride is a selective phosphodiesterase type-5 (PDE5) inhibitor. Inhibition of PDE5 increases the level of cyclic guanosine monophosphate (cGMP) during sexual stimulation. This enhances relaxation of smooth muscle, and induces penile erection.

Vardenafil hydrochloride was approved in the United States on August 19, 2003 (NDA 21-400 Original Submission, September 24, 2001) as an oral tablet for the treatment of erectile dysfunction (ED). It is currently marketed, under the trade name LEVITRA®, as a film-coated tablet. These tablets contain the equivalent of 2.5 mg, 5 mg, 10 mg and 20 mg vardenafil.

Bayer Healthcare has developed a new vardenafil formulation, an orodispersible tablet (ODT) containing 10 mg of vardenafil. They believe that this formulation, which dissolves rapidly in the mouth and is taken without water, will provide a more convenient dosage form for many patients. They believe that it will complement the Levitra film-coated tablets, which they will continue to market.

The Primary Medical Reviewer, Dr. Don McNellis did not identify any issues during this review that would preclude approval of vardenafil 10 mg orodispersible tablet (ODT) for the treatment of erectile dysfunction in adult men.

2. Background

2.1 Drug Product

The proposed ODT formulation involves single dose strength of 10 mg, the recommended starting dose in ED. The objective of this development program was to supplement the current marketed Levitra film-coated tablets with a formulation that allows fast and discreet intake without water thus improving convenience to the patients. The ED patient places the Staxyn ODT tablet on the tongue, where it disintegrates in the available salivary fluid and the resulting solution is swallowed.

Staxyn 10 mg is presented as a white, round, biconvex, (b) (4) unmarked tablet. The tablet weight is 180 mg. Each tablet contains 11.85 mg of vardenafil HCl trihydrate (b) (4) corresponding to 10.0 mg vardenafil.

The **mechanism of action** of PDE5 inhibitors such as vardenafil is the inhibition of cGMP-specific PDE5, an enzyme responsible for the degradation of cGMP in the corpus cavernosum. Inhibition of this enzyme causes increased concentrations of cGMP, which in turn enhances smooth muscle relaxation and hence the erectile response.

Vardenafil ODT formulation will be made available as a single 10 mg tablet dose strength. The recommended dose in ED is one 10 mg ODT taken on-demand (prn) approximately 1 hour prior to sexual activity, not exceeding one dose over a 24-hour period. The tablet is intended for placement on the tongue where it disintegrates and dissolves in the salivary fluid, which is then swallowed. Vardenafil ODT should be taken without water and without regard to meals.

For patients requiring a low dose of vardenafil (2.5 mg or 5 mg for use in specific populations), the current IR formulation in these dose strengths should be used. The ODT formulation is not scored.

Since the Staxyn 10 mg ODT formulation is not bioequivalent to the 10 mg IR formulation, (ODT provides higher systemic exposure compared to same strength of the IR), two 10 mg ODT tablets should not be used in place of a 20 mg dose of Levitra. Patients needing a higher dose should use the approved Levitra film coated tablets.

2.2 Proposed indication and Currently Available Treatments

Vardenafil ODT formulation is indicated for use in the treatment of ED. ED is multifactorial in etiology and frequently involves interplay of both psychological and organic factors.

The currently approved PDE5 inhibitor medications for the treatment of Erectile Dysfunction are sildenafil (Viagra) oral tablet approved March 1998, vardenafil (Levitra) oral tablet approved August 2003 and tadalafil (Cialis) oral tablet, approved November 2003.

In addition, several formulations of alprostadil have been approved for intra-corporeal injection or use as a urethral suppository for the treatment of erectile dysfunction.

2.3 REGULATORY HISTORY

Vardenafil hydrochloride was approved in the United States on August 19, 2003 (NDA 21-400 Original Submission, September 24, 2001) as an oral tablet for the treatment of erectile dysfunction (ED). It is currently marketed, under the trade name LEVITRA®, as a film-coated tablet. These tablets contain the equivalent of 2.5 mg, 5 mg, 10 mg and 20 mg vardenafil.

The Sponsor and the Division of Reproductive and Urological Products (DRUP) at the end of Phase 2 meeting on April 17, 2008, discussed the design of the Sponsor's phase 3 studies for the evaluation of the ODT formulation of vardenafil. The Sponsor inquired about 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.

(b) (4)

3. CMC/Device

Dr. J. Salemme, the chemistry reviewer from Branch III, Division of Pre-Marketing assessment II, Office of NDQA has the following recommendation.

Recommendation and Conclusion on Approvability:

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

The Office of Compliance has recommended approval of the manufacturing sites. Labeling and carton labels have been corrected.

From a CMC perspective, the NDA is *recommended* for approval.

Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

Basis for Approvability Recommendation

The sponsor has provided sufficient information regarding raw material controls, manufacturing processes and process controls, and stability data that assure the quality of the drug product during the expiration dating period.

The drug substance, vardenafil hydrochloride, is identical to the drug substance approved for Levitra (vardenafil hydrochloride), NDA 21-400. Vardenafil hydrochloride is manufactured by Bayer Schering Pharma AG in Wuppertal, Germany, and is (b) (4) at the Bayer Schering Pharma AG site in Leverkusen, Germany.

A Letter of Authorization from Bayer to access NDA 21-400 for chemistry, manufacturing and controls are provided in this submission. Chemistry evaluations of the drug substance manufacturing and controls can be found in chemistry review #1 of NDA 21-400 by Dr. J. Boal and chemistry review #2 of NDA 21-400 by Dr. A. Fenselau.

Additionally, the information provided includes the approved drug substance specification, with tests, limits, and methods. The drug substance is controlled by the following tests: color, identity by HPLC, identity by IR, identity for chloride, particle size distribution, appearance of solution, sulfated ash, heavy metals, water content, residual solvents, impurities (specified, unspecified, and total), assay, and microbiological purity.

The **excipients**, Pharmaburst B2, aspartame, used as a sweetener, magnesium stearate, used as a (b) (4) and peppermint flavor comply with USP, NF, or Ph. Eur or other pharmacopoeial standards. Additionally, Pharmaburst B2 is manufactured according to DMF 40. A letter of authorization is provided. page

The **stability data** to 9 months/25C and to 6 months/40C indicate that the three batches in the proposed blister meet the acceptance criteria of the tests at all stability test points. However, the stability data provided up to 6 months/40C and up to 24 months/30C for the three validation batches of drug product in the non-US market blister show that little change has occurred in the drug product during stability studies. According to the ICH Q1E guidance, as little change occurs in the drug product during long-term or accelerated conditions, the 24 month data can be extended to 36 months. The data provided, therefore, support the requested expiration dating period of 36-months.

The **microbial purity** test according to the harmonized method of Ph. Eur/USP/Ph. Jap, is acceptable.

Dr. Salemm in her review, wrote that the information provided adequately supports the approval action of vardenafil hydrochloride ODT.

CTDL Comment:

I fully concur with the assessment of chemistry review team.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review team, Yangmee Shin, PhD and Lynnda Reid PhD, made the following recommendations in their final review dated May, 2010.

Recommendations

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.

Additional Non Clinical Recommendations

None

Dr. Shin in her review wrote that all inactive ingredients and excipients found in the orodispersible tablet are same as in previously approved drug products. There are no impurities/degradants that require further qualification.

CTDL Comment: I fully concur with Pharmacology/Toxicology review team's recommendation.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Reviewer, Dr, Sandhya Apparaju, made the following recommendation in her review dated/signed June 9, 2010:

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.

CTDL Comment:

I fully concur with Dr. Sandhya Apparaju's recommendation.

Phase IV Commitments

None

Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

- Vardenafil Hydrochloride (HCl) is a phosphodiesterase type-5 (PDE5) inhibitor drug approved as film-coated immediate release (IR) tablets for the treatment of Erectile Dysfunction (ED) [NDA 021400, Levitra; Approval: August 2003]. As approved, Levitra IR is available in 2.5 mg, 5 mg, 10 mg and 20 mg strengths. The starting dose for most ED patients is 10 mg, with an option to increase the dose to 20 mg or decrease it to 5 mg for effectiveness or safety reasons. The 2.5 mg strength is used when dosing with certain potent CYP3A4 inhibitor drugs.
- An orally disintegrating tablet (ODT) 10 mg formulation of Vardenafil has been developed by Bayer. The proposed recommended dose is one 10 mg ODT taken on-demand (p.r.n.) approximately 1 hour prior to sexual activity, not exceeding one dose over a 24-hour period. The tablet is intended for placement on the tongue where it disintegrates and dissolves in the salivary fluid, which is then swallowed. Dose should be taken without water.
- Three Clinical Pharmacology studies (#12769, #13396, #12093 (PK sub-study)) in healthy and ED populations evaluated single and multiple dose PK, food-effect, effect of concomitant water intake and age effect on systemic PK of vardenafil and its major metabolite M1. A mechanistic study 10021 evaluated the potential for absorption directly via the oral mucosa.
- The clinical and to-be-marketed formulations of Vardenafil ODT were identical.

- The development program included two phase 3 clinical trials (# 12093 and #12094) in ED patients to evaluate safety and efficacy of the 10 mg ODT formulation. The Bio-analytical methods used in the analyses of vardenafil and its metabolite M1 in the NDA were adequately validated.
- In healthy male volunteers (18-50 years), the C_{max} and AUC of vardenafil following a single dose administration of 10 mg ODT formulation was greater compared to Levitra 10 mg IR by 15 % and 44 %, respectively. In target ED patients 18-45 years of age, the C_{max} was somewhat lower (8 %) and AUC was greater by 29 % relative to IR. The T_{1/2} values were comparable across treatments (mean of ~4 hours) and T_{max} (median of 1.5 hours) was prolonged with the ODT formulation relative to IR (median of 0.75 hours). Once daily dosing of 10 mg ODT for ten days did not result in significant accumulation of vardenafil. T_{1/2} was unchanged with daily doses.
- Similar to the approved 10 mg IR formulation, elderly ED patients (≥ 65 years) had higher systemic exposure and longer T_{1/2} values of vardenafil and its metabolite M1 (activity 25 % that of vardenafil) compared to younger patients (18-45 years). For the 10 mg ODT formulation, the C_{max} and AUC estimates in the elderly were higher by 21 % and 38 % respectively, compared to the younger patients. For the metabolite M1, with the ODT formulation, the elderly patients had 40 % and 19 % increase respectively in C_{max} and AUC values following single dose administration, compared to younger patients.
- For the ODT formulation, food intake (high fat, high calorie) reduced the C_{max} of vardenafil by ~ 35 % while the AUC of vardenafil was not significantly affected. T_{max} was not altered with food. The major metabolite M1 had significantly lower C_{max} and AUC (~ 50 % and 32 % lower on average) in presence of food. In the phase 3 clinical trials of the ODT formulation, dosing was done on-demand without regard to food and thus ODT will be labeled for dosing irrespective of food intake.
- The systemic exposure (AUC) of vardenafil from the ODT formulation was decreased by 29 % when dose was swallowed with water. Clinical trials for the ODT formulation were conducted without water. Thus the labeling will indicate that the dose should be administered without water.
- Intrinsic and Extrinsic factors: Based on Clinical Pharmacology studies conducted for the approval of Levitra IR [NDA 21400] and the dose adjustments currently in place, sponsor recommends the following for Vardenafil ODT use which are acceptable per this reviewer's assessment:
 - Renal impairment: No dose adjustment for mild to severe renal impairment. Not recommended for use in renal dialysis.
 - Hepatic impairment: No dose adjustment for mild hepatic impairment. Not recommended for use in moderate to severe hepatic impairment.
 - Use with moderate to potent CYP3A4 inhibitors: not recommended
 - Nitrates: Use of Staxyn is contraindicated.
- Dosing in geriatric patients (≥ 65 years): Sponsor proposes that the ODT formulation (Staxyn) is safe for use in elderly and that no dosage adjustment is needed. The current labeling for Levitra IR notes that due to a potential for higher systemic exposure, a lower starting dose of 5 mg should be 'considered' in the elderly. Due to supra-bioavailability of the ODT relative to 10 mg IR (29 % in ED patients) and due to

higher exposure potential with age (38 % higher AUC in ≥ 65 year old patients), it is estimated that compared to younger patients receiving the 10 mg approved IR formulation, elderly patients receiving 10 mg ODT formulation may have ~ 67 % higher AUC of vardenafil; when comparing to younger patients receiving ODT, elderly on ODT may experience ~ 38 % higher AUC; compared to elderly currently receiving 10 mg IR, elderly on 10 mg ODT may see ~ 20 % higher exposure.

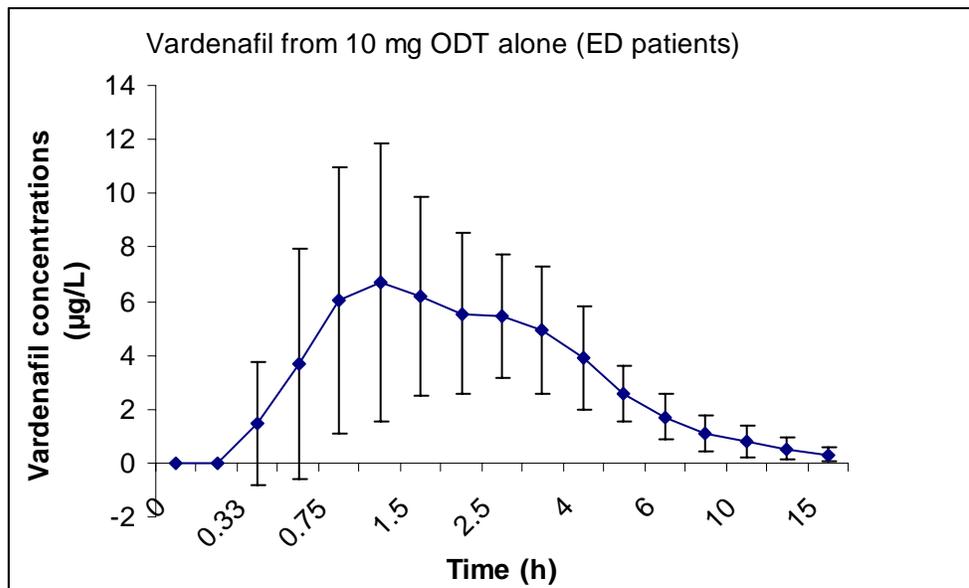
- In the two phase 3 clinical trials for Staxyn, sponsor prospectively enrolled ~ 52 % elderly patients (43 % patients ≥ 65 to < 75 years and 9 % patients ≥ 75 years) in order to obtain adequate safety and efficacy information for this population. In these studies elderly patients did not experience a greater frequency of adverse events with the ODT formulation use. Clinical Pharmacology 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).

CDTL Comment:

Thus based on available safety information for the ODT formulation in the elderly population, it is reasonable to allow 10 mg ODT to be used as a starting dose in elderly (≥ 65 years).

Graph 1: PK profile of Vardenafil ODT

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



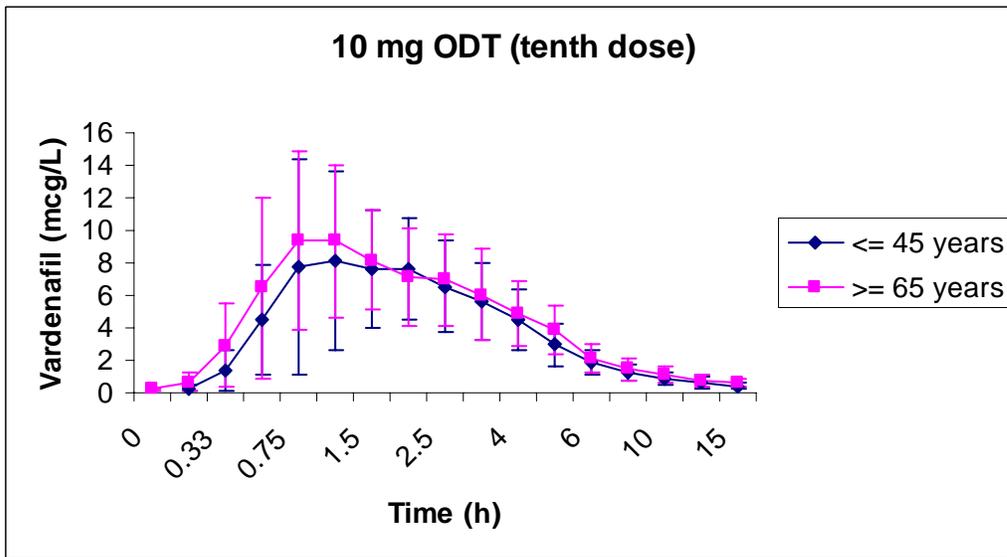
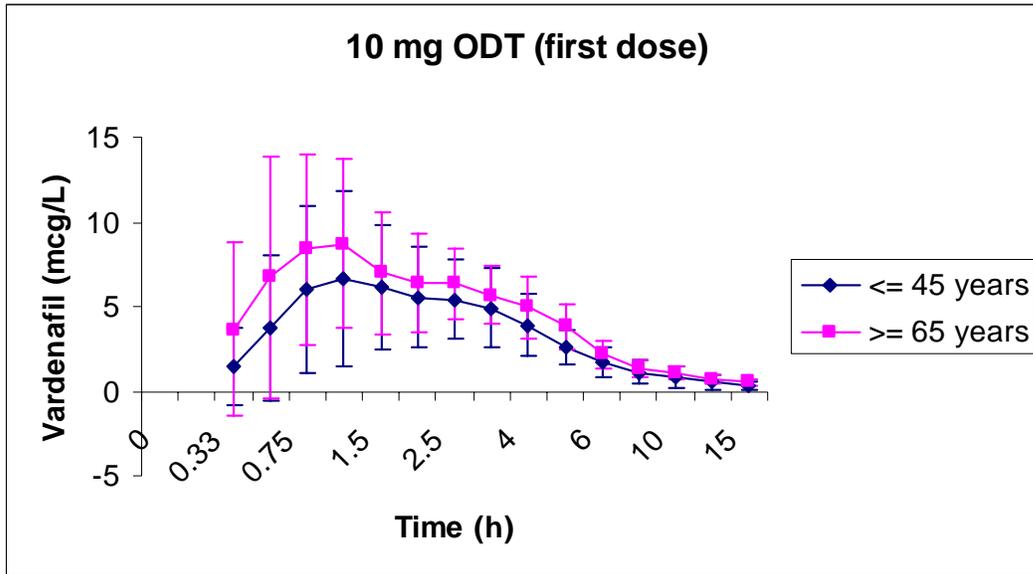
Plasma vardenafil concentrations following a single dose of Vardenafil 10 mg ODT in ED males of study 13396 (18-45 years).

Table 1: Study 13396
Single dose PK of vardenafil and M1 metabolite from the
ODT formulation in young ED patients (18- 45 years).

Single dose PK for 10 mg ODT		
Mean ± SD (% CV)		
Parameter (Units)	Vardenafil	Metabolite M1
C _{max} (µg/L)	8.4 ± 4.4 (52)	4.47 ± 2.99 (67)
T _{max} (h)	1.5 [0.75 – 2.5]	1.5 [0.75 – 2.5]
AUC (µg.h/L)	34.58 ± 19.5 (56)	13.93 ± 9.21 (66)
AUC _{0-t_n} (µg.h/L)	32.9 ± 18.6 (56)	9.06 ± 7.55 (83)
AUC ₂₄ (µg.h/L)	33.6 ± 18.3 (55)	13.85 ± 9.25 (66)
T _{1/2} (h)	4.6 ± 2.4 (52)	2.85 ± 0.93 (32)

- Vardenafil: In ED patients, following a single dose administration of 10 mg ODT formulation, vardenafil concentrations were below lower limit of quantitation (LLOQ) for up to 20 minutes post-dose. Vardenafil concentrations then peaked at a median T_{max} of 1.5 hours to a peak concentration of 8.4 µg/L on average. The concentrations declined from plasma with a mean T_{1/2} value of 4.6 hours. Concentrations were detectable throughout the sampling duration.
- M1 metabolite: In ED patients, following a single 10 mg ODT formulation, M1 concentrations were below detection limit for approximately 45 minutes post dose. Metabolite concentrations then peaked to 4.47 µg/L at a median T_{max} of 1.5 h. Concentrations declined with an average T_{1/2} of 2.9 hours. Metabolite exposure was approximately 40 -50 % of parent vardenafil in this study. Metabolite exposure was generally below LLOQ at ~ 6-8 hours post-dose.

Table 2:



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). The 90 % CI surrounding the point estimate (ratio) was outside the 0.8-1.25 range. On the last day of the multiple-dosing, vardenafil $C_{max,ss}$ and $AUC_{\tau,ss}$ [$AUC(288-312)_{ss}$] were greater by 16 % and 31 %, respectively, in subjects aged ≥ 65 years.

Clinical-Pharmacology Reviewer recommendations for Specific Populations:

Renal Impairment:

Sponsor proposes that Staxyn ODT is not recommended in patients on renal dialysis. No dosing recommendations are proposed for other renal impairment populations.

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

Hepatic Impairment:

Sponsor proposes that patients with moderate or severe hepatic impairment should not use Staxyn ODT.

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

Geriatrics:

(b) (4)

In young ED patients, vardenafil 10 mg ODT formulation provides a 29 % higher AUC of the parent drug compared to Levitra 10 mg IR. [The magnitude of increase with the ODT relative to IR was higher (by 44 %) in healthy young volunteers for reasons unknown]. Elderly patients (≥ 65 years) also demonstrate ~ 21 % and 38 % higher C_{max} and AUC of vardenafil compared to younger patients (≤ 45 years) with the ODT formulation.

Compared to young ED patients, elderly patient receiving the ODT may experience ~ 67 % increase in AUC and a modest increase in C_{max}. This estimated increase is similar to the observed absolute increases of ~ 60 % on average in study 13396 when comparing the AUC values of young ED males (18-45 years; 28.3 $\mu\text{g}\cdot\text{h/L}$) receiving Levitra IR 10 mg to that of the AUC values in elderly ED males (≥ 65 years; 45.35 $\mu\text{g}\cdot\text{h/L}$) receiving ODT 10 mg; C_{max} values were comparable.

With ODT use in younger patients, the increase in metabolite AUC was ~ 9 % relative to Levitra IR use. In elderly patients, there was a further increase of ~ 20 % with age. Therefore, compared to younger ED patients, elderly patients receiving the ODT formulation may experience ~ 29 % higher AUC of metabolite and a modestly higher C_{max}. When the absolute increases in AUC were compared for younger (18-45 years) ED males receiving Levitra IR vs. older (≥ 65 years) ED males receiving 10 mg ODT in study 13396, there was a 40 % overall increase in metabolite AUC [14.04 $\mu\text{g}\cdot\text{h/L}$ vs. 19.7 $\mu\text{g}\cdot\text{h/L}$]. The increase

in C_{max} was modest (9 %).

In an elderly patient currently receiving Levitra 10 mg IR, switching to the Staxyn 10 mg formulation will potentially result in ~ 20 % increase in systemic exposure [based on relative bioavailability estimates in study 13396 for elderly ED patients receiving both treatments after adequate wash-out].

For an elderly patient currently on a 5 mg dose of Levitra IR, it is anticipated that the net increase in AUC would be more than doubled when switched to the 10 mg ODT formulation, due to the supra-bioavailability of the ODT relative to IR.

Clinical Pharmacology Reviewer's Comment:

Since the safety of the ~ 70 % higher systemic exposures of vardenafil in the elderly (age range 65- 88 years) has been adequately assessed and found to be unremarkable in the two phase 3 clinical trials that included 50 % elderly (of which ~ 10 % were above the age of 75 years), it is this reviewer's opinion that the ODT(Staxyn)10 mg can be administered to elderly ED patients as the starting dose.

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

CDTL comment:

I fully concur with Clinical Pharmacology Reviewer's recommendation.

COMMENTS from Clinical Pharmacology Team Leader (TL Memo dated June 14th, 2010)

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

elderly men needs to be addressed.

RECOMMENDATION From Clinical Pharmacology Team Leader and the Director of the Division of Clinical Pharmacology III:

NDA 200179 is acceptable from a Clinical Pharmacology perspective with the following Post-Marketing Requirement.(PMR).

POST-MARKETING REQUIREMENT:

A drug interaction study to assess the potential for orthostatic hypotension in elderly men (age 65 – 80) with erectile dysfunction on Staxyn 10 mg ODT, whose hypertension is under control with a vasodilator, who have been on a stable dose for at least four weeks.

The Sponsor has agreed to perform this study as a Post Marketing Requirement and submitted a timeline for study protocol submission and completing the study:

Final Protocol Submission: within 6 months of NDA approval date

Study Completion Date: within 20 months of NDA approval date

Final Report Submission: within 26 months of NDA approval date

6. Microbiology

The **microbial purity** test according to the harmonized method of Ph. Eur/USP/Ph. Jap, is acceptable as per Dr Salemme's review of vardenafil hydrochloride ODT.

7. Clinical/Statistical- Efficacy

Clinical Program for Efficacy

7.1 Design, Primary Objective and Efficacy Assessment

The Sponsor conducted two clinical trials (**12093 & 12094**) evaluating the efficacy of their 10 mg vardenafil ODT. These trials were adequately designed to evaluate meaningful endpoints. Each trial has shown that this medication has significant efficacy for the treatment of erectile dysfunction. The trials also established that vardenafil 10 mg ODT is effective in both men <65 years of age and men ≥65 years of age

Design: The design of clinical trials **12093 and 12094** were 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.

Trial 12093

409 male subjects were screened and 362 subjects were randomized to treatment. 186 subjects were randomized to vardenafil 10 mg ODT, and 176 subjects were randomized to placebo. Four subjects, two in the placebo group and two in the vardenafil group, did not take any medication and are not included in the efficacy or safety analysis groups. An additional three subjects, two in the placebo group and one in the vardenafil group, did not record any efficacy information in their diaries and were excluded from the efficacy analysis group but included in the safety analysis group.

The average age of all safety 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%) of the safety population were 75 years-of-age and older.

Trial 12094

473 male subjects were screened and 339 subjects were randomized to treatment. 172 subjects were randomized to vardenafil 10 mg ODT, and 167 subjects were randomized to placebo.

Two subjects, one in the placebo group and one in the vardenafil group, did not take any medication and are not included in the efficacy or safety analysis groups. An additional six subjects, four in the placebo group and two in the vardenafil group, did not record any efficacy information in their diaries and were excluded from the efficacy analysis group but included in the safety analysis group.

The average age of all safety subjects 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%) of the safety population were 75 years-of-age and older.

Patients who met the inclusion criteria and had no excluding factors (for a detailed list of IC and EC, see MO Review) entered a four week untreated baseline period. Subjects completed a diary entry for each sexual episode during the baseline period as well as during the treatment period.

Subjects needed to make at least four attempts at sexual intercourse on four separate days during the untreated four week baseline period. An attempt at intercourse was judged to have occurred if the answer “Yes” was recorded for the following question in the Subject Diary: “Was sexual activity initiated with the intention of intercourse?”

At least 50% of attempts at sexual intercourse during the untreated baseline period needed to be unsuccessful. An attempt was judged to be unsuccessful if at least one of the following questions in the Subject Diary was answered with a “No”: (a) “Were you able to achieve at least some erection (some enlargement of the penis)?” (b) “Were you able to insert your penis in your partner’s vagina?” (c) “Did your erection last long enough for you to have successful intercourse?”

Subject Diaries were evaluated during a clinic visit (Visit 2) at the completion of the baseline period.

Subjects who met the criteria regarding attempts at intercourse and percentage of attempts that were unsuccessful 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 treatment period was 12 weeks. A Subject Diary was completed for each sexual encounter during this period.

Analysis of Primary Endpoint(s)

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.

The **following secondary efficacy endpoints** were also evaluated:

- Percentage of subjects achieving “back to normal” erectile function (IIEFEF ≥ 26) at Visit 4 (Week 12) or LOCF
- All diary questions other than SEP 2 and 3 that concerned erectile function that were assessed over the entire treatment period
- Number of sexual attempts under medication till first successful attempt (SEP 3)
- The Treatment Satisfaction Scale (TSS); baseline versus endpoint
- A Global Assessment Question (GAQ) to be administered at the final visit only (or at Premature Discontinuation).

Analysis of Primary Endpoints:

Table 3: 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 (- 8.56 - - 5.66)		-27.04(- 33.66 - - 20.43)		-38.19 (- 45.02 - - 31.37)	
p (F-Test) 'Treatment'	<0.0001		<0.0001		<0.0001	

Table 4: 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 (- 8.45 - - 5.38)		-25.97(- 32.69 - - 19.26)		-33.43 (- 40.44 - - 26.43)	
p (F-Test)	<0.0001		<0.0001		<0.0001	

CTDL Comment:

For both Study 12093 and Study 12094, each of the three co-primary endpoints (IIEF-EF, SEP-2 and SEP-3) show a difference (i.e. change from baseline) between the vardenafil-treated group and the placebo-treated group that is both clinically meaningful and statistically significant at the $p = 0.0001$ level. Therefore, it is reasonable to conclude that vardenafil 10 mg ODT has significant efficacy for the treatment of erectile dysfunction (ED).

Analysis of Secondary Endpoints(s)

1. Responder analysis of Subjects reporting normal erectile function at week 12. IIEF-EF scores in the range of 26 – 30 are considered to represent “normal” erectile function. The Sponsor has evaluated the proportion of subjects having IIEF-EF scores >25 at week 12. Vardenafil showed a response of 40% and 46% in studies 12093 and 12094 respectively.
2. SEP Diary Questions other than 2 and 3. The rate at which questions 1, 4, 5, and 6 (Enlargement, Hardness, Overall satisfaction and Ejaculation) of the Sexual Encounter Profile were answered “Yes” during the treatment period was compared to the rate during the baseline period. Vardenafil response of “Yes” in both studies was clinically meaningful and statistically significant.
3. Number of sexual attempts till first successful (SEP 3) attempt. This was seen as a “Yes” response to SEP 3
4. Treatment Satisfaction Scale: The TSS is a self-report measure of subject’s satisfaction with various aspects of erectile function and treatment. It was administered at the baseline visit and at the week 12 visit. TSS included Ease of Erection, Erectile function Satisfaction, Pleasure of Sexual activity, Satisfaction with Orgasim, Confidence for completion, Satisfaction with Medication. All these attributes of TSS were statistically significant.
5. Global Assessment Question: At the week 12 visit, subjects were asked “Has the treatment you have been taking over the past four weeks improved your erection?” 72% men in study 12093 and 67% men in study 12094 responded “Yes” compared to 26% and 24% in studies 12093 and 12094 respectively.

CTDL Comment:

The key secondary endpoints showed a clinically meaningful and statistically significant difference that supports the conclusion that vardenafil 10mg ODT is an effective treatment for erectile dysfunction (ED).

Efficacy in Subpopulations:

The Sponsor also evaluated the efficacy of vardenafil 10 mg ODT in subjects <65 years of age and those ≥65 years of age.

Table: 5

IIEF-EF: Study 12093

Study 12094

	Vardenafil 10 mg ODT Mean ± SD		Placebo Mean ± SD		Vardenafil 10 mg ODT Mean ± SD		Placebo Mean ± SD	
	<65 years	≥65 years	<65 years	≥65 years	<65 years	≥65 years	<65 years	≥65 years
N	85	96	80	92	83	84	80	80
Baseline	13.4 ± 4.78	12.2 ± 4.87	13.4 ± 4.74	12.3 ± 5.44	12.6 ± 5.57	11.1 ± 5.79	13.3 ± 5.08	12.5 ± 6.35
Week 12 (LOCF)	23.0 ± 6.95	19.9 ± 8.81	15.4 ± 7.64	13.2 ± 7.42	22.9 ± 8.43	17.8 ± 9.08	15.0 ± 7.58	13.6 ± 7.82
Change from baseline	9.6 ± 6.28	7.7 ± 8.19	2.1 ± 7.33	0.9 ± 6.42	10.3 ± 7.78	6.7 ± 8.06	1.7 ± 6.28	1.1 ± 6.01

Table: 6

Significance Levels for Age-related IIEF-EF Pair Comparisons

Comparison of Change From Baseline to Week 12 In Group	Study 12093 (p=)	Study 12094 (p=)
<65 Vardenafil vs <65 Placebo	<0.0001	<0.0001
≥65 Vardenafil vs ≥65 Placebo	<0.0001	<0.0001

Table: 7

SEP 2 Scores by Age – Study 12093

Study 12094

	Vardenafil 10 mg ODT Mean ± SD		Placebo Mean ± SD		Vardenafil 10 mg ODT Mean ± SD		Placebo Mean ± SD	
	<65 years	≥65 years	<65 years	≥65 years	<65 years	≥65 years	<65 years	≥65 years
N	85	94	79	90	84	84	81	80
Baseline	44.7 ± 36.68	34.6 ± 33.85	43.1±36.86	32.5±34.77	42.9±35.61	31.6±36.11	44.2±33.53	34.1±36.11
Treatment Period	80.5 ± 26.84	69.8 ± 35.87	48.6±39.55	41.2±37.22	76.1 ± 33.85	58.9±39.33	48.8±38.83	37.1±37.18
Change from baseline	35.8 ± 33.63	35.2 ± 38.06	5.5 ± 42.82	8.7 ± 28.41	33.2 ± 33.27	27.3 ± 37.39	4.6 ± 34.12	3.0 ± 33.33

Table 8: Significance Levels for Age-related SEP 2 Pair Comparisons

Comparison of Change From Baseline to Week 12 In Group	Study 12093 (p=)	Study 12094 (p=)
<65 Vardenafil vs <65 Placebo	<0.0001	<0.0001
≥65 Vardenafil vs ≥65 Placebo	<0.0001	<0.0001

Table: 9

SEP 3: Scores by Age – Study 12093

Study 12094

	Vardenafil 10 mg ODT Mean ± SD		Placebo Mean ± SD		Vardenafil 10 mg ODT Mean ± SD		Placebo Mean ± SD	
	<65 years	≥65 years	<65 years	≥65 years	<65 years	≥65 years	<65 years	≥65 years
N	85	93	78	86	84	84	81	79
Baseline	16.3 ± 21.95	10.4 ± 18.89	14.5±2 1.63	14.5±2 0.27	16.4± 18.71	9.3± 18.5	15.5± 19.68	15.5±22.29
Treatment Period	70.8 ± 33.33	59.6 ± 38.71	29.7±3 5.05	22.3±2 8.94	69.6 ± 35.27	48.1± 39.81	30.7± 33.33	24.3±31.47
Change from baseline	54.5 ± 32.72	49.2 ± 37.28	15.2 ± 31.3	7.7 ± 25.72	53.2 ± 33.22	38.8 ± 38.32	15.2± 29.55	8.7 ± 29.15

Table 10:

Significance Levels for Age-related SEP 3 Pair Comparisons

Comparison of Change From Baseline to Week 12 In Group	Study 12093 (p=)	Study 12094 (p=)
<65 Vardenafil vs <65 Placebo	<0.0001	<0.0001
≥65 Vardenafil vs ≥65 Placebo	<0.0001	<0.0001

CTDL Comment:

Clinical reviewer, Dr. Don McNellis in his review writes that Vardenafil is significantly more effective than placebo, in improving the IEF-EF, SEP 2 and SEP 3 scores, in both groups <65 and ≥65 age as is clearly shown in Tables 5-10. I fully concur with the clinical reviewer’s conclusion.

Overall, these data show that vardenafil is effective in treating erectile dysfunction in subjects <65 years of age and also in subjects that are ≥65 years of age. It is noteworthy that greater than 50% of the patient population enrolled in these two trials were >65 years of age and about 10% of the total population were >75 years of age. In my opinion that is a fair representation of that age group.

Other Subpopulations Evaluated:

The Sponsor has performed an analysis of the efficacy of vardenafil 10 mg ODT versus placebo in the subpopulations having diabetes mellitus, hypertension and dyslipidemia. This analysis according to the clinical reviewer Dr. McNellis showed that the medication has significant efficacy in each of these subpopulations.

Subject Disposition

Study 12093

Altogether 409 subjects were enrolled. Of these, 362 (89%) were randomized to receive vardenafil 10 mg ODT or placebo treatment. A total of 186 subjects received vardenafil and 176 subjects received placebo treatment. Four of these patients, 2 in the vardenafil group and 2 in the placebo group, were not included in the safety population because there was no evidence that these subjects took study medication. The safety population therefore comprises of 358 subjects, 98.9% of all randomized subjects.

Three additional subjects, one in the vardenafil group and 2 in the placebo group, did not meet the intention-to-treat (ITT) criteria because they had no post-baseline efficacy assessment in any of the clinical variables. The ITT population therefore corresponds to 355 subjects or approximately 98% of all randomized subjects.

Thirty-two subjects, 13 in the vardenafil group and 19 in the placebo group, prematurely left the study. The majority of subjects that discontinued prematurely withdrew their consent. There were very few subjects that discontinued prematurely because of an adverse event.

Table 11: Premature Termination – Study 12093

Reason	Vardenafil 10 mg ODT			Placebo		
	Total	<65 years	≥65 years	Total	<65 years	≥65 years
Randomized	186	88	98	176	82	94
Premature Termination Total	13(7%)	8 (9%)	5 (5%)	19(11%)	7 (9%)	12(13%)
Adverse Event	3 (2%)	1 (1%)	2 (2%)	1 (1%)	0 (0%)	1 (1%)
Consent Withdrawn	5 (3%)	4 (5%)	1 (1%)	7 (4%)	4 (5%)	3 (3%)
Insufficient Therapeutic Effect	2 (1%)	1 (1%)	1 (1%)	8 (5%)	2 (2%)	6 (6%)
Lost to follow-up	2 (1%)	2 (2%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Non-compliant with medication	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)
Protocol violation	1 (1%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)	1 (1%)

Study 12094

Altogether 473 subjects were enrolled. Of these, 339 (72%) were randomized to receive vardenafil 10 mg ODT or placebo treatment. A total of 171 subjects received vardenafil and 166 subjects received placebo treatment.

Two of these patients, 1 in the vardenafil group and 1 in the placebo group, were not included in the safety population because there was no evidence that these subjects took study

medication. The safety population therefore comprised of 337 subjects or 99% of all randomized subjects.

Six additional subjects, two in the vardenafil group and four in the placebo group, did not meet the intention-to-treat (ITT) criteria because they had no post-baseline efficacy assessment in any of the clinical variables. The ITT population therefore corresponds to 331 subjects or approximately 98% of all randomized subjects.

Forty-four subjects, 21 in the vardenafil group and 23 in the placebo group, prematurely discontinued from the study. The reasons for premature discontinuation were withdrawal of consent and lost to follow up. There were very few subjects who withdrew because of an adverse event.

Table 12: Premature Termination – Study 12094

Reason	Vardenafil 10 mg ODT			Placebo		
	Total	<65 years	≥65 years	Total	<65 years	≥65 years
Randomized	172	86	86	167	85	82
Premature Termination Total	21(12%)	11 (13%)	10(12%)	23(14%)	13(15%)	10(12%)
Adverse Event	4 (2%)	3 (3%)	1 (1%)	1 (1%)	0 (0%)	1 (1%)
Consent Withdrawn	6 (3%)	3 (3%)	3 (3%)	4 (2%)	3 (4%)	1 (1%)
Insufficient Therapeutic Effect	2 (1%)	2 (2%)	0 (0%)	12 (7%)	5 (6%)	7 (9%)
Lost to follow-up	4 (2%)	2 (2%)	2 (2%)	3 (2%)	2 (2%)	1 (1%)
Protocol violation	5 (3%)	1(1%)	4 (5%)	3 (2%)	3 (4%)	0 (0%)

CTDL Comment:

The percentage of patients who withdrew from the studies 12093 and 12094 as a result of an adverse event is relatively very low.

7.4 Statistical Review:

The statistical review team Xin Fang and Mahboob Sobhan from the Division of Biometrics III concluded that the efficacy data from the two phase-3 studies showed that the vardenafil orodispersible tablet 10 mg (VODT10) statistically significantly increased the IIEF-EF score, the overall success rates of SEP-2 (penetration), and the overall success rates of SEP-3 (maintenance) at Week 12.

From the statistical perspective, this application provided adequate data to support the efficacy of VODT10 in the treatment of ED patients.

Dr. XIN Fang in his review wrote that both the studies (12093 and 12094) appear to be adequate. The increase in IIEF-EF scores, the overall success rates of the SEP 2 and the SEP 3 were statistically significant in the VODT 10 group compared to the placebo group in both studies. However, in the region of South Africa, a high placebo effect in terms of SEP-2 and SEP-3 scores was observed. The efficacy of the VODT10 in South African men with ED was not confirmed.

CTDL Comment:

I concur with the assessment of Xing Fang and Mahboob Sobhan from the Division of Biometrics III.

8. Safety

The Sponsor has conducted two phase 3 clinical trials evaluating vardenafil 10 mg ODT and two phase 1 trials of vardenafil 10 mg ODT. Review of adverse events, vital signs, EKGs, hematology and chemistry data indicate that this medication is safe for use as a treatment of erectile dysfunction in appropriately selected men greater than 18 years of age.

The trials also established that vardenafil 10 mg ODT is safe in men <65 years of age and in men ≥65 years of age. The trials do not indicate a different safety profile in the older men as compared to the younger men.

8.1 Safety Populations and Overall Exposure

The overall exposure and safety assessments were adequate to characterize the safety profile of vardenafil 10 mg ODT.

In two **Phase I studies (13396 and 12769)** healthy males received vardenafil 10 mg ODT. In study 13396, 36 healthy subjects received a single dose of vardenafil ODT and in study 12769, 16 healthy subjects received 3 doses of vardenafil 10 mg ODT.

In two **Phase 3 studies (12093 and 12094)** 168 males < 65 years with erectile dysfunction and 180 males >65 years with erectile dysfunction received treatment medication for 12 weeks. In the two phase 3 trials, the average exposure time was 72 days for patients receiving placebo and 76 days for patients receiving vardenafil. 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.

8.2 Demographics

Table 13: Demographics of the Phase 1 Safety Population

	Study 12769 N = 16	Study 13369 N = 36
Age, mean (range)	37.6 (27 - 49)	54.5 (26 – 80)
Race		
White, n (%)	16 (100%)	35 (97%)
Black, n (%)	0 (0%)	1 (3%)
Weight (kg), mean	81.3	85.5

Table 14: Demographics 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%)

CDTL Comment:

I concur with the primary reviewer's assessment. From the table 14, it is very clear that all age groups are fairly represented.

8.3 Discontinuation due to Adverse Events

The patients who withdrew prematurely from study 12093 and study 12094 are shown in Table 15. In study 12093, four patients discontinued the study because of adverse events, while in study 12094 five patients withdrew because of adverse events. On further evaluation of the subject Case Report Forms, the Sponsor concluded that one patient in Study 12093 and one subject in Study 12094 had been misclassified as withdrawing early. Table 15 further shows the seven subjects, who truly withdrew from the studies because of adverse events.

Table 15: Phase 3 Studies due to Adverse Events

Subject Number	Primary SOC(PT)	Placebo 0 <65 years	Placebo 0 ≥65 years	Vardenafil ODT <65 years	Vardenafil ODT ≥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

CTDL Comment:

Dr. McNellis in his review about the premature discontinuation due to adverse events wrote that in majority of patients who withdrew due to an adverse event, an association with the study medication could not be established.

For example, in the case (0003) with increased transaminase level, alcohol may have played a role. In the case of patient (0009), vision changes are possibly related to the medication. In another patient (0011), mild lightheadedness and headache could not be ruled out as being associated with the study medication.

*Dr. McNellis further reinforces that the adverse events with a plausible relationship to vardenafil are consistent with the established profile of vardenafil. There were no **new** adverse events seen in these trials. The incidence and types of AEs leading to permanent drug discontinuation did not appear to differ significantly from those observed in earlier studies of vardenafil.*

I fully concur with the clinical reviewer’s assessment.

8.4 Deaths

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

8.5 Table 16: Common Adverse Events seen with phosphodiesterase type 5 inhibitor medications

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%)

CDTL Comment:

The adverse events as shown in Table 16 are very similar to those seen in the approved vardenafil film coated tablet (Levitra).

8.6 Adverse Events of Special Interest seen with PDE5 inhibitors

The following adverse events are of special interest for phosphodiesterase type 5 inhibitor medications: myalgia, cardiac arrhythmia, hypersensitivity reactions, vasodilatation and dizziness, hearing loss, and visual loss. In addition, because of the product formulation, oral irritation was also evaluated as an event of special interest.

Table 16: Adverse Events of Special Interest

Event of Special Interest	Preferred Term	Placebo (N=340)	Vardenafil ODT (N=355)
Muscular Adverse Events			
	Back pain	1 (0.3%)	7 (2.0%)
	Myalgia	0 (0.0%)	3 (0.8%)
	Muscle Spasms	2 (0.6%)	4 (1.1%)
Cardiac Arrhythmia/Conduction Abnormality			
	Heart rate increased	0	1 (0.3%)
	Supraventricular extrasystoles	3(0.9%)	4 (1.1%)
	Bundle branch block	0	1 (0.3%)
	Palpitations	1 (0.3)	1 (0.3%)
	Tachycardia	1 (0.3%)	0
	Bundle branch block left	1 (0.3%)	1 (0.3%)
	Ventricular extrasystoles	2 (0.6%)	3 (0.8%)
	Bundle branch block right	4 (1.2%)	0
Immediate Hypersensitivity			
	Dyspnea	1(0.3%)	2 (0.6%)
	Erythema	0	1 (0.3%)
	Flushing	2(0.6%)	27 (7.6%)
	Nasal Congestion	1(0.3%)	11 (3.1%)
	Pruritis	0	1 (0.3%)
	Rash	2(0.6%)	3 (0.8%)
	Syncope	0	1 (0.3%)
	Wheezing	0	1 (0.3%)
Vasodilation Events			
	Flushing	2(0.6%)	27 (7.6%)
	Feeling Hot	0	3 (0.8%)
	Dizziness	0	8 (2.3%)
	Vertigo	0	2 (0.6%)
	Syncope	0	1 (0.3%)
	Orthostatic hypotension	2(0.6%)	2 (0.6%)

Event of Special Interest	Preferred Term	Placebo (N=340)	Vardenafil ODT (N=355)
Hearing Loss			
	Deafness neurosensory	1 (0.3%)	0
Visual Loss			
	Vision blurred	2 (0.6%)	1 (0.3%)
Oral irritation			
	Dry Mouth	1 (0.3%)	2 (0.6%)
	Tongue Induration	0 (0.0%)	1 (0.3%)
	Dysgeusia	4 (1.2%)	4 (1.1%)

CDTL Comment:

Dr. McNellis in his review commented as follows: There appears to be a trend toward increased muscle-related adverse events (myalgia, back pain, and muscle spasm). This has been seen in previous studies of vardenafil.

There does not appear to be any signal regarding cardiac arrhythmias or conduction abnormalities in these data.

Immediate hypersensitivity reactions occurred more frequently with vardenafil as opposed to placebo. Episodes of flushing accounted for the major portion of hypersensitivity..

Vasodilation-related adverse events and dizziness occurred more frequently in the vardenafil treated subjects as compared to the placebo treated patients. Flushing accounts for the major portion of the difference in vasodilation events.

Dizziness was seen in eight patients receiving vardenafil ODT (Staxyn). Five subjects who experienced dizziness, were in the age group <65 years (range from 54 to 62 years), and 3 subjects were in the age group ≥65 years (range from 65 to 68 years). The severity of dizziness was mild and resolved without any further medical intervention. All subjects who experienced dizziness had a history of hypertension and some had stroke or cardiovascular conditions, hypercholesterolemia as well. All patients were on concomitant medications to treat these existing conditions. There were no patients >75 years, who experienced an episode of dizziness. The total number of subjects >75 years of age enrolled in studies 12093 & 12094, who received the study drug were 29 (i.e. 10% of total patient population).

Flushing and muscle spasms were seen as additional adverse reactions contributing to the subsequent withdrawal from treatment.

There were no events suggestive of NAION and no hearing loss episodes.

One case of induration of the tongue in a vardenafil treated subject was seen. Review of the CRF and the narrative description of the event indicated that the episode began after one

exposure to the medication. The condition was treated with amoxicillin, acetaminophen and prednisone and resolved after approximately 10 days. The subject continued daily doses of vardenafil ODT during the treatment of the induration and completed the 12 week study with no additional episodes. I believe that the episode is unlikely to be related to the vardenafil treatment.

Dysgeusia (change in taste) was recorded in four subjects receiving vardenafil and in four subjects receiving placebo. All eight cases were seen at the same study site. This adverse event was recorded in eight of eleven subjects at this site and in no other subjects at any other site. The investigator was recording the subject's subjective taste sensation as the treatment dissolved in the mouth. It was mistakenly recorded as an adverse event if the taste sensation was sour or bitter. It is reasonable to consider these events as not being true adverse events, and there is no evidence to suggest that the treatment with vardenafil adversely affected the taste.

Additionally, there were no subjects in either study who reported either inflammation or an ulceration in the mouth secondary to the use of vardenafil ODT.

Overall, the data from these studies do not reveal any new safety signals, but do confirm the common adverse events known to occur with vardenafil.

I fully concur with the clinical reviewer's assessment.

Safety Issues of Particular Interest

Dizziness was seen among eight subjects receiving vardenafil in phase 3 clinical trials (12093 and 12094). Five subjects experiencing dizziness were in the age group <65 years (range from 54 to 62 years), and 3 subjects were in the age group ≥65 years (range from 65 to 68 years). The severity of dizziness was mild and resolved without any further medical intervention in 6 of 8 cases. Individual case narratives for cases of dizziness are described in Dr. McNellis's review. The review of vardenafil ODT Phase 3 clinical studies indicate that dizziness is basically a tolerability issue that did not require any further medical intervention. There were no subjects >75 years old, who reported dizziness in these two phase 3 trials, although about 10% (29 patients) of study population were above age >75.

Only one patient who experienced dizziness had PK data and this information did not suggest any marked differences compared to average PK data from the remaining subjects [370100004; Tmax: 1.5 h; Cmax: 10 ug/L; AUC: 47.2 ug.h/L].

Syncope was experienced by only one patient while on vardenafil. The syncopal attack was very brief and did not involve fainting. This patient was 73 years of age and did not require any further medical intervention.

Orthostatic Hypotension: Four subjects were reported to have orthostatic hypotension. Two of these subjects were in the placebo treated group and two in the vardenafil ODT treated group. There was one patient >65 years of age and other <65 years of age, who supposedly

experienced mild orthostatic hypotension. However, in both the cases it was transient and did not require any further medical intervention.

Special Safety Studies

A drug interaction study with Nifedipine (calcium channel blocker) and vardenafil 20 mg in hypertensive patients was previously conducted and reviewed by clinical pharmacology team. This study did not show any significant potential for drug interaction (i.e. no significant potentiation in lowering of blood pressure was observed when the two drugs were co-administered), and therefore a dose recommendation was not required for vardenafil film coated tablets.

9. Advisory Committee Meeting

No Advisory Committee meeting was held for this new application. Vardenafil Hydrochloride is an approved drug with no new safety concerns.

10. Pediatrics

The Applicant requested a full waiver of the requirement to conduct assessments of PDE5 inhibitor in pediatric patients.

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

The Pediatric Review Committee (PeRC)/PREA Subcommittee agreed with the Division that PREA does not apply to this application. This was communicated to the Project Manager, Freshnie Deguia from George Greeley of PeRC on June 1st, 2010.

11. Other Relevant Regulatory Issues

Division of Scientific Investigation (DSI)

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

Division of Medication Errors and Prevention (DMEPA)

The review team from DMEPA made the following recommendation for the proprietary name **Staxyn**.

The proposed proprietary name, **Staxyn** (Vardenafil Hydrochloride) orally disintegrating tablets (ODT), is acceptable from a look-alike and sound-alike perspective. In addition, our evaluation did not identify any other factors that render the name unacceptable at this time.

Our decision is based upon the information submitted by the Applicant, DDMAC's promotional evaluation, DRUP's initial comments and DMEPA's safety evaluation. The DMEPA review team informed the sponsor about the acceptability of name Staxyn on June 15th, 2010.

The review team from DMEPA also made few recommendations for the label. All the changes were incorporated into the label before a substantially complete draft label was sent to the sponsor on June 10th, 2010 and again on June 16th, 2010.

Division of Drug Advertising, Marketing and Communication (DDMAC)

Each of the DDMAC comments as made by Carrie Newcomer, were considered individually and discussed within the clinical review team and the recommendations were incorporated into the negotiated label.

Labeling

A substantially complete draft label was sent to the sponsor on May 24th, 2010, June 10th, 2010 and again on June 16th, 2010. Discussions were held with the sponsor to reach an agreement towards a final label.

Key issues/labeling changes:

Safety:

Highlights of PI:

Dosage and Administration

Staxyn is not interchangeable with vardenafil 10mg film coated tablets.

Warnings and Precautions: Do not use Staxyn in patients taking potent and moderate CYP3A4 inhibitors. Caution is advised when PDE5 inhibitors are co-administered with alpha-blockers.

Drug-Drug Interactions:

Do not use Staxyn with moderate or potent CYP3A4 inhibitors.

Use in Specific Populations:

Do not use Staxyn in patients with moderate or severe hepatic impairment.

Do not use Staxyn in patients on renal dialysis.

12. Recommendations

12.1 Recommended Regulatory Action

In my opinion, the sponsor has provided sufficient evidence for efficacy and safety in support of this NDA (200179). Therefore, an approval action should be granted for Staxyn 10 mg ODT.

12.2 Risk Benefit Assessment

This submission has provided substantial evidence from two well-controlled studies that vardenafil ODT (Staxyn) is an effective treatment for men with erectile dysfunction. Vardenafil ODT was efficacious in achieving both primary and secondary efficacy endpoints. No significant safety issues were detected. Vardenafil ODT (Staxyn) has been shown to be generally safe for its intended use as recommended in the label by all tests reasonably applicable to assessment of safety. The pattern of adverse events is similar to those seen with 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, specific for this drug class, were examined. There were no events of this nature in the 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. There did not appear to be any suggestion of increased oral events in subjects using this medication.

The overall risk/benefit profile for vardenafil ODT was assessed and determined to be favorable. In summary, the data that have been submitted by the Sponsor are adequate to allow the reasonable conclusion that vardenafil ODT is an **effective and safe** treatment for men with erectile dysfunction. The data also provide an adequate basis for labeling the product so that it can be used in a safe and effective manner.

12.3 Recommendation for Post marketing Requirement

No post marketing requirement was requested by the primary Medical Officer and/or by the primary Clinical Pharmacology reviewer. However, the Clinical Pharmacology Team Leader and the Director of the Division of Clinical Pharmacology III, subsequently concluded that the following Post-Marketing trial should be required:

The Division of Clinical Pharmacology III requested a PMR, that would involve conducting a drug interaction study in ED patients 65 – 80 years old, who are stable on anti-hypertensive medication and will receive Staxyn 10 mg ODT.

The Sponsor has agreed to conduct this study.

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/

SURESH KAUL
06/17/2010

GEORGE S BENSON
06/17/2010