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APPLICATION NUMBER:
200179Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type NDA
Application Number 200179
Priority or Standard Standard

Submit Date August 26, 2009
Received Date August 26, 2009
PDUFA Goal Date June 26, 2010
Early Action Date June 18, 2010
Division / Office Division of Reproductive and
Urologic Products/ ODEIII

Reviewer Name Donald McNellis, M.D.
Review Completion Date June 16, 2010

Established Name Vardenafil HCL
(Proposed) Trade Name STAXYN
Therapeutic Class Phosphodiesterase Type 5
Inhibitor
Applicant Bayer Healthcare
Pharmaceuticals, Inc.

Formulation Oral Dispersible Tablet, 10mg
Dosing Regimen As needed, not more than
once in 24 hours
Indication Erectile Dysfunction
Intended Population Males greater than 18 years of
age with erectile dysfunction

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, Vardenafil Orally Dispersible Tablet (ODT) 10 mg should be approved for the indication of “treatment of erectile dysfunction” in adult males.

This recommendation is based on the demonstration of “substantial evidence” of effectiveness in improving symptoms of erectile dysfunction in the target population and an acceptable safety profile.

1.2 Risk Benefit Assessment

This submission has provided substantial evidence from adequate and well-controlled studies that vardenafil ODT will have the effect claimed in labeling. This claim is that vardenafil ODT 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.

The two phase 3 efficacy studies, 12093 and 12094, were identical in study design. They were double-blind, placebo-controlled, randomized studies evaluating the effect of 12 weeks of vardenafil ODT treatment as compared to placebo on three primary endpoints.

The three primary endpoints were 1) The change in IIEF erectile function domain score from baseline, 2) The change in percentage of sexual episodes during the treated period in which the subject answered “Yes” to SEP question #2 as compared to the percentage during the baseline period, and 3) The change in percentage of sexual episodes during the treated period in which the subject answered “Yes” to SEP question #3 as compared to the percentage during the baseline period. The endpoints were evaluated simultaneously, and all three were required to show significance for an overall finding of significant efficacy.

Vardenafil ODT 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.

Pharmacokinetic evaluation of vardenafil ODT has shown that it provides increased AUC as compared to a 10 mg vardenafil film-coated tablet. Also, as with vardenafil film-coated tablets, the AUC and C_{max} are greater in subjects greater than 65 years of age as compared to those less than 65 years of age. For this reason, the phase three trials were enriched with elderly subjects. The safety data from these phase three trials do not reveal any increased risk, including risks related to vasodilation, in elderly patients as compared to younger patients.

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.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No post marketing risk evaluation and mitigation strategies are warranted at this time based on a clinical review of the submission.

1.4 Recommendations for Postmarket Requirements and Commitments

No post marketing requirements and commitments are recommended based on a clinical review of the submission.

The primary Clinical Pharmacology reviewer believed that no Phase IV commitments were needed. 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:

A drug interaction study to assess the potential for orthostatic hypotension in elderly men (age 65 – 80) with erectile dysfunction on vardenafil hydrochloride ODT, 10 mg, whose hypertension is under control with a vasodilator and 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 has submitted a timeline for submitting the study protocol and completing the study.

2 Introduction and Regulatory Background

2.1 Product Information

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.

2.2 Tables of Currently Available Treatments for Proposed Indications

The following is a summary of currently approved oral medications for the treatment of erectile dysfunction:

Table 1. Summary of Currently Approved PDE5 Inhibitor Medications for the Treatment of Erectile Dysfunction

	Trade Name	Sponsor	Route of Administration	NDA Number	Date of Approval
Sildenafil	Viagra	Pfizer	Oral Tablet	20,895	March 27, 1998
Vardenafil	Levitra	Bayer Healthcare	Oral Tablet	21,400	August 19, 2003
Tadalafil	Cialis	Eli Lilly	Oral Tablet	21,368	November 21, 2003

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

Table 2. Currently Approved Intracorporeal or Intraurethral Medications for the Treatment of Erectile Dysfunction

	Trade Name	Sponsor	Route of Administration	NDA Number	Date of Approval
Alprostadil	Caverject	Pharmacia	Intracorporeal Injection	20,379	July 6, 1995
Alprostadil	MUSE	Vivus	Intraurethral Suppository	20,700	November 19, 1996
Alprostadil	EDEX	Schwarz	Intracorporeal Injection	20,649	June 12, 1996
Alprostadil	---	Bedford	Intracorporeal Injection	74,815	January 20, 1998
Alprostadil	---	Teva	Intracorporeal Injection	75,196	April 30, 1999

2.3 Availability of Proposed Active Ingredient in the United States

Vardenafil is currently available in the United States only as Levitra film-coated tablets. It is available in 2.5 mg, 5 mg, 10 mg, and 20 mg strengths.

2.4 Important Safety Issues with Consideration to Related Drug Class

PDE5 inhibitors are contraindicated in combination with nitrates because of potential hypotensive events. PDE5 inhibitors should also be used with caution when they are co-administered with alpha-blocker medications. Both classes are vasodilators with potential blood pressure lowering effects. When vardenafil is used in combination with these classes of medication, there is the potential for an additive effect on blood pressure.

There have been rare post-marketing reports of the occurrence of non-arteritic anterior ischemic optic neuropathy (NAION) and hearing loss in patients receiving PDE5 inhibitor medications.

There have also been rare reports of priapism in patients receiving PDE5 inhibitor medications.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

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) had an end of Phase 2 meeting 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.



3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Sponsor has in place standard operating procedures that are consistent with ICH Good Clinical Practice. These include archiving of source data, data validation of CRF data, internal audits, and documentation of qualifications of investigators.

As part of this review, an assessment of the datasets and Case Report Forms (CRF) of Studies 10293 and 10294 was done and did not reveal miscoding or discrepancies between the data recorded on the CRFs and the datasets.

3.2 Compliance with Good Clinical Practices

According to the Applicant, all clinical trials submitted to the NDA were conducted in accordance with Good Clinical Practice (GCP) and the Declaration of Helsinki. In support of this, the Applicant submitted samples of informed consent, documents of IRB approval, and required case report forms.

3.3 Financial Disclosures

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 categories of compensation potentially affected by the outcome of the covered studies. There is no evidence that any investigator has a financial conflict of interest.

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

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

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.

4.2 Clinical Microbiology

There were no microbiology issues.

4.3 Preclinical Pharmacology/Toxicology

The Toxicology reviewer has indicated that, 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.

4.4 Clinical Pharmacology

The Primary Reviewer for the Division of Clinical Pharmacology III, Office of Clinical Pharmacology found the Clinical Pharmacology and Biopharmaceutics information submitted in NDA 200179 [Vardenafil Orally Disintegrating Tablet 10 mg] to be acceptable. They also found the relevant product labeling to be acceptable.

Based on available safety information for the ODT formulation in the elderly population, the reviewer also believes that it is reasonable to allow 10 mg ODT to be used as a starting dose in elderly (≥ 65 years) men.

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:

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

The Sponsor has agreed to conduct this study as a Post Marketing Requirement and has submitted a timeline for submitting the study protocol and completing the study.

4.4.1 Mechanism of Action

Penile erection is a hemodynamic process initiated by the relaxation of smooth muscle in the corpus cavernosum and its associated arterioles. During sexual stimulation, nitric oxide is released from nerve endings and endothelial cells in the corpus cavernosum. Nitric oxide activates the enzyme guanylate cyclase resulting in increased synthesis of cyclic guanosine monophosphate (cGMP) in the smooth muscle cells of the corpus cavernosum. The cGMP in turn triggers smooth muscle relaxation, allowing increased blood flow into the penis, resulting in erection. The tissue concentration of cGMP is regulated by both the rates of synthesis and degradation via phosphodiesterases (PDEs). The most abundant PDE in the human corpus cavernosum is the cGMP-specific phosphodiesterase type 5 (PDE5); therefore, the inhibition of PDE5 enhances erectile function by increasing the amount of cGMP. Because sexual stimulation is required to initiate the local release of nitric oxide, the inhibition of PDE5 has no effect in the absence of sexual stimulation.

In vitro studies have shown that vardenafil is a selective inhibitor of PDE5. The inhibitory effect of vardenafil is more selective on PDE5 than for other known phosphodiesterases (>15-fold relative to PDE6, >130-fold relative to PDE1, >300-fold relative to PDE11, and >1,000-fold relative to PDE2, 3, 4, 7, 8, 9, and 10).

4.4.2 Pharmacodynamics

Blood Pressure

The effect of vardenafil on blood pressure has previously been evaluated in a study of patients with erectile dysfunction. Single doses of vardenafil 20 mg (film-coated tablet) caused a mean maximum decrease in supine blood pressure of 7 mmHg systolic and 8 mmHg diastolic (compared to placebo), accompanied by a mean maximum increase of heart rate of 4 beats per minute. The maximum decrease in blood pressure occurred between 1 and 4 hours after dosing. Following multiple dosing for 31 days, similar blood pressure responses were observed on Day 31 as on Day 1. Vardenafil may add to the blood pressure lowering effects of antihypertensive agents.

The effect of vardenafil on blood pressure and heart rate when used in combination with nitrates and with alpha-blockers has also been studied. In each case, additive effects on blood pressure and heart rate were seen. Because the disease state of patients requiring nitrate therapy is anticipated to increase the likelihood of hypotension, the use of vardenafil by patients on nitrate therapy or on nitric oxide donors is contraindicated. Patients taking alpha-blockers should initiate vardenafil therapy at the lowest recommended starting dose. In the case of vardenafil, the lowest starting dose is only available in film-coated tablets. Therefore, patients on alpha-blocker therapy should not begin vardenafil therapy using vardenafil ODT.

Cardiac Electrophysiology

The effect of 10 mg and 80 mg vardenafil, administered as film-coated tablets, on QT interval was evaluated in a single-dose, double-blind, randomized, placebo- and active-controlled (moxifloxacin 400 mg) crossover study in 59 healthy males (81% White, 12% Black, 7% Hispanic) aged 45-60 years. The QT interval was measured at one hour post dose because this time point approximates the average time of peak vardenafil concentration. The 80 mg dose of vardenafil (four times the highest recommended dose of the film-coated tablets) was chosen because this dose yields plasma concentrations covering those observed upon co-administration of a low-dose of vardenafil (5 mg) and 600 mg BID of ritonavir. Of the CYP3A4 inhibitors that have been studied, ritonavir causes the most significant drug-drug interaction with vardenafil. Table 6 summarizes the effect on mean uncorrected QT and mean corrected QT interval (QTc) with different methods of correction (Frederica and a linear individual correction method) at one hour post-dose. No single correction method is known to be more valid than the other. In this study, the mean increase in heart rate associated with a 10 mg dose of vardenafil, administered as a film-coated tablet, compared to placebo was 5 beats/minute and with an 80 mg dose of vardenafil the mean increase was 6 beats/minute.

Therapeutic and supra-therapeutic doses of vardenafil and the active control moxifloxacin produced similar increases in QTc interval. This study, however, was not designed to make direct statistical comparisons between the drug/or the dose levels. The clinical impact of these QTc changes is unknown.

Effects on the Eye

Single oral doses of phosphodiesterase inhibitors have demonstrated transient dose-related impairment of color discrimination (blue/green) using the Farnsworth-Munsell 100-hue test and reductions in electroretinogram (ERG) b-wave amplitudes, with peak effects near the time of peak plasma levels. These findings are consistent with the inhibition of PDE6 in rods and cones, which is involved in phototransduction in the retina. The findings were most evident one hour after administration, diminishing but still present 6 hours after administration. In a single dose study in 25 normal males, vardenafil (film-coated tablets) 40 mg, twice the maximum daily recommended dose, did not alter visual acuity, intraocular pressure, fundoscopic and slit lamp findings.

In another double-blind, placebo controlled clinical trial, at least 15 doses of 20 mg vardenafil were administered over 8 weeks versus placebo to 52 males. Thirty-two (32) males (62%) of the patients completed the trial. Retinal function was measured by ERG and FM-100 test 2, 6 and 24 hours after dosing. The trial was designed to detect changes in retinal function that might occur in more than 10% of patients. Vardenafil did not produce clinically significant ERG or FM-100 effects in healthy men compared to placebo. Two patients on vardenafil in the trial reported episodes of transient cyanopsia (objects appear blue).

Effects on Semen

A study has shown that daily doses of vardenafil (20 mg administered as film-coated tablets) for six months has no detrimental effect on semen characteristics in men with normal baseline levels.

4.4.3 Pharmacokinetics

The pharmacokinetics of vardenafil have been evaluated in healthy male volunteers (18-50 years) and in young (18-45 years) and elderly (≥ 65 years) ED patients. Studies have shown that vardenafil 10 mg orally disintegrating tablets provide higher systemic exposure of vardenafil compared to vardenafil 10 mg film-coated tablets.

The median time to reach C_{max} (T_{max}) in patients receiving 10 mg vardenafil ODT in the fasted state was 1.5 h [range: 0.75 – 2.5 h]. After administration of 10 mg vardenafil ODT to elderly (≥ 65 years) and young (18 – 45 years) ED patients, mean vardenafil AUC was increased by 21 to 29 %, respectively while mean C_{max} was lower by 19 % and 8 % in comparison to 10 mg vardenafil (film coated tablets). In a study of healthy male volunteers (18-50 years), the mean C_{max} and AUC of vardenafil from vardenafil ODT were higher by 15 % and 44 %, respectively compared to 10 mg vardenafil film-coated tablets.

5 Sources of Clinical Data

This submission included reports of two phase 3 trials (12093 and 12094). These reports formed the basis for the review of efficacy of vardenafil ODT. These two phase 3 trial reports as well as two phase 1 trial reports (12769 and 13396) provided the data for safety evaluation of vardenafil ODT. In addition, the Sponsor provided data for and analyses of 58 additional studies that were performed using Levitra film-coated tablets. These study reports provided supportive information for a safety review.

5.1 Tables of Studies/Clinical Trials

Table 3. Phase 1 Trials of Vardenafil ODT

Study No.	Study objective/ population	Number Of Subjects	Dosing	Primary Endpoints
12769	To investigate the effect of a high-fat, high-calorie breakfast and of water, respectively, on the pharmacokinetics of 10 mg vardenafil oral disintegrating tablet (ODT).	16 healthy males	Single doses of 10 mg ODT administered with and without water in fasting and fed states. A 10 mg Levitra film-coated tablet administered with water in the fasting state.	Pharmacokinetics and Safety
13396	To investigate the effect of repeated once-daily administrations on the pharmacokinetics of 10 mg vardenafil orodispersible tablet (ODT), to compare the bioavailability of ODT to the marketed Levitra formulation, and to assess the effect of age on the pharmacokinetics of 10 mg vardenafil ODT.	36 male patients with erectile dysfunction	Vardenafil 10 mg ODT taken without water followed (after a 2-day washout) by 10 days with once-daily administrations of vardenafil 10 mg ODT	Pharmacokinetics and Safety
12093	To investigate the pharmacokinetics of 10 mg of vardenafil ODT in a subset of subjects participating in the phase 3 trial 12093. Approximately 50% of the subjects were to be ≥ 65 years of age.	24 male patients with erectile dysfunction	A single dose of Vardenafil 10 mg ODT with pK evaluation at baseline, 20, 30 and 45 minutes and 1,2, 3,4,5,6,8,10,12,15, and 24 hours.	Pharmacokinetics and Safety

Table 4. Phase 3 Trials of Vardenafil ODT

Study No.	Study objective/ population	Number Of Subjects	Dosing	Primary Endpoints
12093	To compare the efficacy and safety of vardenafil ODT 10 mg (PRN) with placebo in a general population of men with erectile dysfunction. In this study, approximately 50% of the men on active treatment have to be 65 years-of-age or older.	362 male patients with erectile dysfunction	10 mg ODT or placebo taken as needed for 12 weeks	Three co-primary endpoints: 1. IIEF-EF Domain score at Week 12 or LOCF 2. SEP 2 (success rates of penetration) overall 3. SEP 3 (maintenance of erection) overall
12094	To compare the efficacy and safety of vardenafil ODT 10 mg (PRN) with placebo in a general population of men with erectile dysfunction. In this study, approximately 50% of the men on active treatment have to be 65 years-of-age or older.	339 male patients with erectile dysfunction	10 mg ODT or placebo taken as needed for 12 weeks	Three co-primary endpoints: 1. IIEF-EF Domain score at Week 12 or LOCF 2. SEP 2 (success rates of penetration) overall 3. SEP 3 (maintenance of erection) overall

5.2 Review Strategy

The main focus of clinical review involved studies 12093 and 12094 for purposes of establishing the efficacy of vardenafil ODT 10 mg. Data from these studies, as well as from the phase 1 studies 12769 and 13396, were pooled to evaluate the safety of vardenafil ODT 10 mg. The safety of starting doses of vardenafil greater than 5 mg in patients ≥ 65 years of age was evaluated based on these four studies and also based on an analysis of 58 studies of vardenafil film-coated tablets.

5.3 Discussion of Individual Studies/Clinical Trials

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.

Inclusion 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. It was specified that approximately 50% of the patients on treatment should be 65 years-of-age or older. Subjects must be in a stable, heterosexual relationship for at least 6 months and they should be highly motivated to obtain treatment for ED.

Reviewer's comment: *There are no validated instruments for evaluating erectile function in non-heterosexual men.*

Exclusion Criteria

The following were factors that excluded patients from participating in the trials:

- Any underlying cardiovascular condition, including unstable angina pectoris, which precluded sexual activity.
- History of myocardial infarction, stroke or life-threatening arrhythmia within 6 months prior to Visit 1 (= screening)
- Uncontrolled atrial fibrillation / flutter at screening (defined as ventricular response rate \geq 100 bpm)
- Bleeding disorder
- History of prostatectomy because of prostate cancer, including nerve sparing techniques. Any surgical procedures for the treatment of Benign Prostate Hypertrophy (BPH) were permitted, with the exception of cryosurgery, cryotherapy, or cryoablation
- Hereditary degenerative retinal disorders such as retinitis pigmentosa.
- History of loss of vision because of NAION, history of temporary or permanent loss of vision, including unilateral loss of vision
- History of uni/bilateral hearing loss
- History of congenital QT prolongation
- Presence of penile anatomical abnormalities (e.g. penile fibrosis or Peyronie's disease) which, in the investigator's opinion, could significantly impair sexual performance
- Subjects with confirmed phenylketonuria (PKU)

- Primary hypoactive sexual desire
- Spinal cord injury
- Severe chronic or acute liver disease, history of moderate (Child-Pugh B), or severe (Child-Pugh C) hepatic impairment
- Clinically significant chronic hematological disease which could lead to priapism such as sickle cell anemia, multiple myeloma, and leukemia
- Active peptic ulceration
- Resting hypotension with a resting systolic blood pressure of < 90 mm Hg or hypertension with a resting systolic blood pressure >170 mm Hg or a resting diastolic blood pressure >110 mm Hg
- History of syncope within the last 6 months prior to entry into the study
- History of malignancy within the past 5 years (other than squamous or basal cell skin cancer)
- History of positive test for Hepatitis B surface antigen (HbsAg) or Hepatitis C
- Symptomatic postural hypotension within 6 months of Visit 1
- Any unstable medical, psychiatric, or substance abuse disorder that in the opinion of the investigator was likely to affect the subject's ability to complete the study or precluded the subject's participation in the study

The following medications and treatments were also factors that excluded patients from participating in the trials:

- Subjects taking nitrates or nitric oxide donors
- Subjects exposed to androgens, irrespective of their mode of administration
- Subjects taking anti-androgens. However, 5 alpha-reductase inhibitors, commonly not classified as antiandrogens, were permitted
- Subjects taking alpha-blockers
- Subjects taking the following potent inhibitors of cytochrome P450 3A4: HIV protease inhibitors such as ritonavir or indinavir, the anti-mycotic agents itraconazole or ketoconazole (topical forms were allowed), and the macrolide antibiotics clarithromycin and erythromycin
- Subjects taking medication known to prolong the QT interval, such as Type Ia and Type 3 anti-arrhythmics
- Subjects who had received any investigational drug (including placebo) within 30 days of Visit 1
- Use of any treatment for ED within 7 days of Visit 1 or during the study including oral medications, vacuum devices, constrictive devices, injections, urethral suppositories, gels, any over-the-counter or nonprescription medications, and products purchased via the internet

The following laboratory value abnormalities were also factors that excluded patients from participating in the trials:

- Subjects with a total serum testosterone level of more than 25% below the lower limit of normal according to the range of the testing laboratory

- Subjects with a serum creatinine clearance (calculated) of < 30.0 mL/min
- Subjects with an elevation of AST and/or ALT of >3 times the upper limit of normal

The following were also factors that excluded patients from participating in the trials:

- Subjects unwilling to cease use of any treatment for ED during the study, including oral medications, vacuum devices, constrictive devices, injections, urethral suppositories, gels, any over-the-counter or nonprescription medications, and products purchased via the internet
- Subjects with known hypersensitivity to vardenafil, BAY 38-9456 (also known as SB-782528) or any component of the investigational medication
- Subjects who were illiterate or unable to understand the questionnaires or the Subject Diary
- Subjects who were unwilling or unable to complete the Subject Diary
- Subjects who, in the opinion of the investigator, would have been noncompliant with the visit schedule or study procedures.

Reviewer's comment:

The exclusion criteria are adequate and acceptable.

Baseline Period

Patients who met the inclusion criteria and had no excluding factors then 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.

Treatment

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.

Endpoints

Three co-primary efficacy endpoints were evaluated:

- International Index of Erectile Function – Erectile Domain (IIEF-EF). The IIEF¹ 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)

Safety Evaluation

The following safety variables were assessed during the study:

- Data regarding adverse events were collected at all visits after Visit 1 and, during the 48 hour period after the last dose of study medication.

- Blood and urine samples for laboratory evaluations (routine hematology, serum chemistry, and semi-quantitative urinary dipstick testing) were obtained at Visit 1 (Week -4) and at Visit 4 (Week 12), or at the Premature Discontinuation visit.
- Complete physical examination at Visit 1 (Week -4) and a brief physical examination at Visit 2 (Week 0), Visit 3 (Week 4), and Visit 4 (Week 12), or at the Premature Discontinuation visit.
- 12-lead ECG at Visit 1 (Week -4) and Visit 4 (Week 12), or at the Premature Discontinuation visit.
- Vital signs (supine and standing heart rate and blood pressure) measured at all visits.

6 Review of Efficacy

Efficacy Summary

The Sponsor has conducted two clinical trials 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.

6.1 Indication

Erectile dysfunction in males greater than 18 years of age.

6.1.1 Methods

Phase 3 clinical trials 12093 and 12094 were reviewed in detail. The trial designs were identical and are discussed in detail in [Section 5.3](#).

6.1.2 Demographics

Trial 12093

This trial was conducted at 40 investigational centers in Belgium, France, Germany, Spain, South Africa, and The Netherlands. 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. Demographic characteristics of the safety population are shown in Table 5 and the co-existing diseases occurring in this population are shown in Table 6.

Table 5. 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 N (% rounded)	White	55 (63%)	68 (70%)	53 (65%)	64 (69%)
	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.

Reviewer’s comment: 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 are a fair representation of elderly males >75 years of age from study 12093.

Table 6. 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%)
Bronchospasm 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.

Reviewer’s comment: *A detailed review revealed that co-morbidities were more frequently associated with the older population. That is reasonable in the opinion of this clinical reviewer.*

Trial 12094

This trial was conducted at 35 investigational centers in the US, Canada, Mexico, and Australia. 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. Demographic characteristics of the safety population are shown in Table 7 and the co-existing diseases occurring in this population are shown in Table 8.

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

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

Reviewer’s comment: *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. Additionally, having 34 subjects >75 years of age provides a good representation for that specific population.*

Table 8. 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%)
Bronchospasm 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.

6.1.3 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 358 subjects or 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 reasons for premature discontinuation are listed in Table 9. The subjects that prematurely discontinued medication because of adverse events are individually discussed in section 7.3.3 Dropouts and/or Discontinuations.

Table 9. Reasons for 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%)

Source: NDA 200179, Module 5.3.5.1, Report of Study 12093, Table 10-3.

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 ODT and 166 subjects received placebo treatment.

Two of these patients, 1 in the vardenafil ODT 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 comprises 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 left the study. The reasons for premature discontinuation are listed in Table 10. The subjects that prematurely discontinued medication because of adverse events are individually discussed in section 7.3.3 (Dropouts and/or Discontinuations).

Table 10. Reasons for 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%)

Source: NDA 200179, Module 5.3.5.1, Report of Study 12094, Table 10-2 and Table 10-3.

6.1.4 Analysis of Primary Endpoint(s)

Study 12093

Table 11 and Table 12 show the results for the three co-primary endpoints.

Table 11. 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 12. 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 have each shown 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.

Reviewer's comment: *For both Study 12093 and Study 12094, each of the three co-primary endpoints show a difference between the vardenafil-treated group and the placebo-treated group that is 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.*

6.1.5 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. These results are shown in Table 13.

Table 13. Proportion of subjects with IIEF-EF scores >25 at week 12

Study	Vardenafil	Placebo	Treatment – Placebo Difference Significance
12093	72/181 (40%)	20/172 (12%)	$p < 0.0001$
12094	76/167 (46%)	15/160 (9%)	$P < 0.0001$

Source: NDA 200179, Module 5.3.5.1, Report of Study 12093, Table 11-13 and Report of Study 12094, Table 11-13.

2. SEP Diary Questions other than 2 and 3.

The rate at which questions 1, 4, 5, and 6 of the Sexual Encounter Profile were answered “Yes” during the treatment period was compared to the rate during the baseline period. The results are shown in Table 14.

Table 14. Change in Rate of “Yes” responses to SEP questions 1, 4, 5 and 6 from baseline period to treatment period

SEP Question	Study 12093			Study 12094		
	Vardenafil ODT	Placebo	Significance	Vardenafil ODT	Placebo	Significance
1. Enlargement	15.34	1.01	p<0.0001	14.28	-2.78	p<0.0001
4. Hardness	50.73	11.16	p<0.0001	46.07	11.36	p<0.0001
5. Overall Satisfaction	48.42	10.65	p<0.0001	45.44	8.96	p<0.0001
6. Ejaculation	31.25	8.43	p<0.0001	28.82	4.10	p<0.0001

Source: NDA 200179, Module 5.3.5.1, Report of Study 12093, Table 11-11 and Report of Study 12094, Table 11-11.

3. Number of sexual attempts till first successful (SEP 3) attempt.

The mean number of sexual attempts until the first successful attempt, as indicated by a “yes” response to SEP 3, is shown in Table 15.

Table 15. Number of Sexual attempts till first successful attempt

Study	Vardenafil ODT	Placebo
12093	1.2±2.9	3.6±6.2
12094	1.4±4.1	3.1±3.7

Source: NDA 200179, Module 5.3.5.1, Report of Study 12093, Table 11-15 and Report of Study 12094, Table 11-15.

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. The results are shown in Table 16.

Table 16. Treatment Satisfaction Scale Treatment – Baseline Changes

TSS Question	Study 12093			Study 12094		
	Vardenafil ODT	Placebo	Significance	Vardenafil ODT	Placebo	Significance
Ease of Erection	26.85	3.01	p<0.0001	19.19	3.46	p<0.0001
Erectile Function Satisfaction	33.61	5.44	p<0.0001	34.21	5.46	p<0.0001
Pleasure of Sexual Activity	27.43	0.5	p<0.0001	24.5	1.36	p<0.0001
Satisfaction with Orgasm	28.8	6.78	p<0.0001	24.09	2.29	p<0.0001
Confidence for Completion	27.41	4.7	p<0.0001	31.4	3.59	p<0.0001
Satisfaction with medication	55.15	22.07	p<0.0001	50.89	20.13	p<0.0001

Source: NDA 200179, Module 5.3.5.1, Report of Study 12093, Table 11-12 and Report of Study 12094, Table 11-12.

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?” The results are shown in Table 17.

Table 17. Percentage of Subjects responding Yes to the Global Assessment Question

Study	Vardenafil ODT	Placebo	Treatment – Placebo Difference Significance
12093	130/180 (72%)	43/168 (26%)	p<0.0001
12094	107/160 (67%)	37/157 (24%)	P<0.0001

Source: NDA 200179, Module 5.3.5.1, Report of Study 12093, Table 11-14 and Report of Study 12094, Table 11-14.

Reviewer’s comment: *The key secondary endpoints support the conclusion that vardenafil 10 mg ODT is an effective treatment for erectile dysfunction.*

6.1.6 Other Endpoints

No other efficacy endpoints were evaluated.

6.1.7 Subpopulations

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

IIEF-EF

Table 18. IIEF-EF Scores by Age (Mean ± SD)

	Study 12093		Study 12093		Study 12094		Study 12094	
	Vardenafil 10mg ODT		Placebo		Vardenafil 10 mg ODT		Placebo	
	<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

Source: NDA 200179, Module 5.3.5.1, Report of Study 12093, Table 11-5 and Report of Study 12094, Table 11-5.

An analysis of these data shows the following levels of significance:

Table 19. 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

Source: MO Analysis.

Reviewer's comment: Vardenafil ODT is significantly more effective than placebo in improving the IIEF-EF score in both <65 and ≥65 age groups.

SEP 2

Table 20. SEP 2 Scores by Age (Mean ± SD)

	Study 12093				Study 12094			
	Vardenafil ODT 10mg		Placebo		Vardenafil 10 mg ODT		Placebo	
	<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
Week 12 (LOCF)	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

Source: NDA 200179, Module 5.3.5.1, Report of Study 12093, Table 11-7 and Report of Study 12094, Table 11-7.

An analysis of these data shows the following levels of significance:

Table 21. 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 ODT vs <65 Placebo	<0.0001	<0.0001
≥65 Vardenafil ODT vs ≥65 Placebo	<0.0001	<0.0001

Source: MO Analysis.

Reviewer's comment: Vardenafil ODT is significantly more effective than placebo in improving the SEP 2 score, in both the <65 and ≥65 age groups.

SEP 3

Table 22. SEP 3 Scores by Age (Mean ± SD)

	Study 12093				Study 12094			
	Vardenafil 10mg ODT		Placebo		Vardenafil 10 mg ODT		Placebo	
	<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 ± 21.63	14.5 ± 20.27	16.4 ± 18.71	9.3 ± 18.5	15.5 ± 19.68	15.5 ± 22.29
Week 12 (LOCF)	70.8 ± 33.33	59.6 ± 38.71	29.7 ± 35.05	22.3 ± 28.94	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

Source: NDA 200179, Module 5.3.5.1, Report of Study 12093, Table 11-9 and Report of Study 12094, Table 11-9.

An analysis of these data shows the following levels of significance:

Table 23. 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 ODT vs <65 Placebo	<0.0001	<0.0001
≥65 Vardenafil ODT vs ≥65 Placebo	<0.0001	<0.0001

Source: MO Analysis.

Reviewer's comment: Vardenafil ODT is significantly more effective than placebo in improving the SEP 3 score, in both the <65 and ≥65 age groups.

Overall, these data show that vardenafil ODT is effective in treating erectile dysfunction in subjects <65 years of age and also in subjects that are ≥65 years of age.

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 shows that the medication has significant efficacy in each of these subpopulations.

Table 24. ANCOVA results for baseline adjusted Week 12 (LOCF) IIEF-EF subscore, by co-existing condition

	Subjects with Diabetes		Subjects without Diabetes	
	Placebo (N=248)	Vardenafil ODT (N=246)	Placebo (N=84)	Vardenafil ODT (N=102)
Diabetes*Treatment LS-mean difference	-7.7 (-8.9, -6.4)		-5.4 (-7.5, -3.4)	
p (t-test) Treatment LS-means	<0.0001		<0.0001	
	Subjects with Hypertension		Subjects without Hypertension	
	Placebo (N=184)	Vardenafil ODT (N=210)	Placebo (N=148)	Vardenafil ODT (N=138)
Hypertension*Treatment LS-mean difference	-7.0 (-8.4, -5.6)		-6.9 (-8.6, -5.3)	
p (t-test) Treatment LS-means	<0.0001		<0.0001	
	Subjects with Dyslipidemia		Subjects without Dyslipidemia	
	Placebo (N=223)	Vardenafil ODT (N=212)	Placebo (N=109)	Vardenafil ODT (N=136)
Dyslipidemia*Treatment LS-mean difference	-7.4 (-8.8, -6.1)		-6.6 (-8.4, -4.8)	
p (t-test) Treatment LS-means	<0.0001		<0.0001	

Source: NDA 200179, Module 2.7.3, Tables 3-14, 3-15 and 3-16.

Table 25. ANCOVA results for baseline adjusted Week 12 (LOCF) SEP2 subscore, by co-existing condition

	Subjects with Diabetes		Subjects without Diabetes	
	Placebo (N=246)	Vardenafil ODT (N=246)	Placebo (N=84)	Vardenafil ODT (N=101)
Diabetes*Treatment LS-mean difference	-30.4 (-35, -24.9)		-20.2 (-29.2, -11.1)	
p (t-test) Treatment LS-means	<0.0001		<0.0001	
	Subjects with Hypertension		Subjects without Hypertension	
	Placebo (N=184)	Vardenafil ODT (N=211)	Placebo (N=146)	Vardenafil ODT (N=136)
Hypertension*Treatment LS-mean difference	-25.1 (-31.2, -18.9)		--30.1 (-37.4, -22.8)	
p (t-test) Treatment LS-means	<0.0001		<0.0001	
	Subjects with Dyslipidemia		Subjects without Dyslipidemia	
	Placebo (N=222)	Vardenafil ODT (N=212)	Placebo (N=108)	Vardenafil ODT (N=135)
Dyslipidemia*Treatment LS-mean difference	-28.9 (-34.7, -23.0)		-25.8 (-33.7, -18.0)	
p (t-test) Treatment LS-means	<0.0001		<0.0001	

Source: NDA 200179, Module 2.7.3, Tables 3-18, 3-19 and 3-20.

Table 26. ANCOVA results for baseline adjusted Week 12 (LOCF) SEP3 subscore, by co-existing condition

	Subjects with Diabetes		Subjects without Diabetes	
	Placebo (N=241)	Vardenafil ODT (N=245)	Placebo (N=83)	Vardenafil ODT (N=101)
Diabetes*Treatment LS-mean difference	-38.8 (-44.5, -33.0)		-31.9 (-41.3, -22.6)	
p (t-test) Treatment LS-means	<0.0001		<0.0001	
	Subjects with Hypertension		Subjects without Hypertension	
	Placebo (N=180)	Vardenafil ODT (N=210)	Placebo (N=144)	Vardenafil ODT (N=136)
Hypertension*Treatment LS-mean difference	-36.5 (-42.9, -30.0)		-36.5 (-44.0, -28.9)	
p (t-test) Treatment LS-means	<0.0001		<0.0001	
	Subjects with Dyslipidemia		Subjects without Dyslipidemia	
	Placebo (N=216)	Vardenafil ODT (N=211)	Placebo (N=108)	Vardenafil ODT (N=135)
Dyslipidemia*Treatment LS-mean difference	-37.1 (-43.2, -31.0)		-36.9 (-45.1, -28.7)	
p (t-test) Treatment LS-means	<0.0001		<0.0001	

Source: NDA 200179, Module 2.7.3, Tables 3-22, 3-23 and 3-24.

Reviewer's comment: *The Sponsor has demonstrated efficacy for all three primary endpoints in subjects with diabetes, hypertension and dyslipidemia as well as for subjects without those conditions.*

7 Review of Safety

Safety Summary

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 \geq 65 years of age. The trials do not indicate a different safety profile in the older men as compared to the younger men.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The phase 1 and phase 3 trials that are the basis for the safety evaluation of vardenafil ODT are shown in Table 27. The results of the primary safety review are discussed in section 7.3.

A secondary review of the safety experience of patients <65 years of age as compared to those \geq 65 years of age is discussed in section 7.5.3. Also discussed in this section is the safety experience of patients in 58 trials of vardenafil film-coated tablets. This analysis is also targeted at evaluating the safety experience of subjects \geq 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.

Table 27. Trials of Vardenafil ODT included in the safety analysis

Study Number	Design	Number Of Subjects	Subjects	Study Duration
Phase 1 Studies				
13396	An open-label, nonrandomized, Age-stratified, group comparison, Single center, safety and Pharmacokinetic study	36	Males having Erectile Dysfunction	Single dose of vardenafil 10 mg ODT, single dose of Levitra film-coated tablet 10 mg.
12769	A randomized, open-label, four-fold crossover study to investigate the effect of a high fat, high calorie breakfast and of water, respectively, on vardenafil 10 mg ODT in comparison to one Levitra film-coated 10 mg tablet	16	Healthy males	Treatment 1 to 3: A single dose of 1 vardenafil 10 mg ODT Treatment 4: A single dose of 10 mg Levitra film-coated tablet
Phase 3 Studies				
12093	A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of vardenafil 10 mg ODT vs. placebo	358	Males having erectile dysfunction	Treatment medication taken as needed for 12 weeks.
12094	A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of vardenafil 10 mg ODT vs. placebo	337	Males having erectile dysfunction	Treatment medication taken as needed for 12 weeks.

Source: NDA 200179, Module 5.2.

This reviewer approached the safety review in the following manner:

- a. Assess and compare the type and frequency of adverse findings.
- b. Assess for any major differences in the safety profile between the two studies.

Reviewer's Comment: *The safety information submitted in this NDA (cumulative and updated safety information from previously conducted 58 trials) included line listings, summary tables, case narratives, and Case Report Forms. The information submitted is adequate.*

7.1.2 Categorization of Adverse Events

In the primary analysis of the vardenafil ODT trials, Version 11.1 of the MedDRA coding dictionary was used to code all adverse events by Preferred Terms and System Organ Class. In the secondary analysis of 58 vardenafil film-coated tablets, Version 10.0 of the

MedDRA coding dictionary was used. The mapping of verbatim terms to MedDRA terms was reviewed and found to be acceptable.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.

The two phase 1 trials were pooled and the two phase 3 trials were pooled. Safety data from two phase 3 trials, in addition to all other integrated safety data, remained the focus of this safety review.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

7.2.1.1 Overall Exposure to Medication

In the two phase 1 studies a total of 36 men were exposed to a single dose of vardenafil 10 mg ODT and 16 men were exposed to 3 doses of vardenafil 10 mg ODT.

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 28. 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 28. Treatment Duration (Days)

	Placebo			Vardenafil ODT			Overall Total
	<65 years	≥65 years	Total	<65 years	≥65 years	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 average number of doses per subject-week was slightly higher in subjects treated with vardenafil ODT (2.7 tablets/week) compared to subjects treated with placebo (2.0

tablets/week).

7.2.1.2 Demographics of Target Populations

The characteristics of the safety population for the two phase 1 studies is shown in Table 29. The characteristics of the safety population for the two phase 3 studies is shown in Table 30.

Table 29. Demographic Characteristics 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

Source: NDA 200179, Module 5.3.5.3.1, ISS, Table 2-1.

Table 30. 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%)

	Placebo (N=340)	Vardenafil ODT (N=355)
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.

Reviewer's Comment:

In the opinion of this clinical reviewer Table 29 and Table 30 are a fair demographic representation of phase I and Phase III study population and reasonably represent the population for which the medication is intended.

7.2.2 Explorations for Dose Response

The Sponsor has only developed a 10 mg formulation of the vardenafil ODT. No dose ranging studies were done.

7.3 Major Safety Results

7.3.1 Deaths

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

7.3.2 Nonfatal 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 judged to be not related to the study drug exposure by the investigator.

Reviewer's Comment: *This clinical reviewer agrees with the determination.*

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. These events are summarized in Table 31.

Table 31. 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.

Subject 12093-10010-0006: The subject is a 65 year-old man who had a myocardial infarction in 1987 with resulting ischemic cardiomyopathy, and a coronary artery stent that was placed in 1997. Hypertension and hypercholesterolemia were diagnosed in 2005. A coronary angiogram in 2006 showed an occlusion of the RIVA and a ventricular aneurysm with an ejection fraction <40%. His only medication on study entry was ASA.

He was randomized to treatment with vardenafil ODT on July 25, 2008. His last dose of vardenafil, prior to the adverse event, was taken on September 18, 2008. On

(b) (6), while on vacation in Italy, he apparently had an episode of ventricular fibrillation with loss of consciousness. A myocardial infarction was diagnosed and an attempt was made to do revascularization (presumably via percutaneous angioplasty). This was unsuccessful (reason unknown) and he was transferred to a hospital near his home in Germany on (b) (6). In Germany, the diagnosis was changed to acute coronary syndrome secondary to ischemic cardiomyopathy. He underwent embolization of the ventricular aneurysm and implantation of a defibrillator. An iatrogenic pneumothorax occurred in association with this procedure, but is not included as a separate SAE because it occurred >7days following his last dose of study medication. The subject was withdrawn from the study because of this event. His final status is listed as “improved.”

Reviewer’s comment: *The details of the interval between the last dosage of vardenafil ODT and the onset of the ventricular fibrillation is not precise enough to allow a meaningful assessment of the potential association between the drug and the event. However, in light of his known pre-existing cardiac disease, this event is most likely unrelated to the study medication.*

Subject 12093-16006-0007: The subject is a 71 year-old man who has had type-2 diabetes since 1985 and hypertension since 1986. A left carotid “calcification” was diagnosed in 2004. He has had “veinolympathic incapacity” since 1998. His medications at study entry were metformin, glipazide, losartan, ASA, saw palmetto and a flavinoid for treatment of his venous insufficiency.

He was randomized to treatment with vardenafil ODT on September 1, 2008. The last dose of vardenafil, prior to the event, was taken on November 18, 2008. On (b) (6) he was diagnosed as having a left femoral artery stenosis (presenting signs and symptoms are not recorded). He was hospitalized for this condition, details regarding treatment are not given. He was not withdrawn from the study. His final status is listed as “recovered.”

Reviewer’s comment: *Femoral artery stenosis is likely to be related to the patient’s underlying disease. It is not likely to be related to study medication.*

Subject 12093-37005-0005: The subject is a 65 year-old man who has had hypertension since 1996, diabetes mellitus type-2 since 2003 and ischemic heart disease since 2004. His medications at study entry were ASA, metformin, diclofenac, atenolol, temisartan/HCTZ, sustained release potassium and magnesium.

He was randomized to vardenafil ODT on October 2, 2008. His last dose of study medication prior to the event was November 9, 2008. On (b) (6) he experienced melena and was hospitalized and a gastric ulcer was treated endoscopically. He required three units of blood transfusion. He was not withdrawn from the study. His final status is listed as “cured.”

Reviewer's comment: *The gastric ulcer is likely to be secondary to ASA and diclofenac. It is not likely to be related to study medication.*

Subject 12093-37007-0003: The subject is a 73 year-old male who has had hypertension since 1987. He has had "inner ear disease" – not further defined. His medication on study entry was losartan/HCTZ. He was randomized to vardenafil ODT on September 23, 2008. His last dose of vardenafil, prior to the event, was December 9, 2008 at 23:10. On [REDACTED] (b) (6), he was hospitalized following a syncopal episode. He was treated with ASA and cinnarizin and was listed as "cured" on [REDACTED] (b) (6). No further details are available regarding his hospital course. He was not withdrawn from the study, however he took no study medication following hospitalization since his scheduled final visit occurred on December 14, 2008.

Reviewer's comment: *The time interval between administration of vardenafil and the syncopal episode is not known. No definitive explanation for the syncope was established. This event should be considered as not related to vardenafil, because his inner ear disease must be considered as a primary possible cause of this brief syncopal episode. It should be noted that the subject had taken vardenafil ODT from September 23, 2008 until December 8, 2008 without an adverse event.*

Subject 12094-14013-0009: The subject is a 55 year-old man with known congenital absence of the left kidney, mild chronic renal insufficiency, depression and anxiety, hypertension and elevated cholesterol. Hypokalemia was diagnosed June 30, 2008. His medications on study entry were lisinopril/HCTZ, pravastatin, paroxetine, metoprolol, and ibuprofen.

He was randomized to vardenafil ODT on July 28, 2008. Lisinopril was added to his medications on September 30, 2008 and his metoprolol dose was increased from 50 to 75 mg/day on that date because of exacerbation of hypertension. His last dose of vardenafil, prior to the event, was October 5, 2008. On [REDACTED] (b) (6) he was hospitalized for exacerbation of hypertension and chest pain. Evaluation included EKG, stress test, and cranial CT scan which were unremarkable. Serial troponin levels were negative. Antihypertensive medication dosages were changed and the patient was discharged [REDACTED] (b) (6) with both hypertension and chest pain listed as "improved." He was not withdrawn from the study and continued study medication until his final visit on October 24, 2008.

Reviewer's comment: *The clinical course of this episode suggests that it is unrelated to vardenafil ODT.*

Subject 12094-14017-0008: The subject is a 51 year-old man who has a history of chronic back pain, hypertension, hyperlipidemia, depression, COPD, congestive heart failure and non-ischemic cardiomyopathy. His medications on study entry were metoprolol, oxycodone and acetaminophen.

He was randomized to vardenafil ODT on August 4, 2008. His last dose of vardenafil, prior to the event, was October 18, 2008. He was hospitalized on (b) (6) because of chest pain. A diagnosis of arrhythmia was made. EKG showed sinus rhythm with occasional, consecutive premature ventricular complexes and possible premature atrial complexes with aberrant conduction, possible left atrial enlargement, left ventricular hypertrophy and non-specific T-wave abnormalities. A repeat EKG on (b) (6), showed sinus rhythm with fragmented consecutive ventricular complexes, "bilateral enlargement", left ventricular hypertrophy and non-specific T-wave abnormalities.

On (b) (6), a transthoracic echocardiogram showed moderate left ventricular dilation, an ejection fraction of 30-35%, moderate to severe decrease in left ventricular systolic function and elevated mean atrial pressure with a dilated left atrium. On (b) (6), a defibrillator was placed. He was discharged from the hospital on (b) (6). The event was listed as "resolved." He was not withdrawn from the study, but took no further vardenafil prior to his previously scheduled final visit on October 28, 2008.

Reviewer's comment: *The subject appears to have significant underlying cardiac disease. The event is not likely to be related to vardenafil ODT.*

Reviewer's comment: *Individual case narratives (as described above) were reviewed to determine whether 1) the cases were coded properly, 2) any convincing evidence exists to exclude drug causality or, 3) there is reasonably a compelling alternative explanation for the event other than the study drug.*

7.3.3 Dropouts and/or Discontinuations

Three subjects withdrew from the phase 1 studies prematurely. They are listed in Table 32.

Table 32. Patients Withdrawing Prematurely from the Phase 1 Studies due to Adverse Events

Subject Number	Age	Event
12769-011	49	Multiple contusions due to motorcycle accident
12769-007	27	Elevated serum CK and AST
13396-01	44	Atrial fibrillation

Source: NDA 200179, Module 5.3.5.3, ISS, page 48.

Subject 12769-011: The subject is a 49 year-old man who was involved in a motorcycle accident two days after his last dose of vardenafil ODT (period 2 of 4). He was hospitalized for observation. His CK value on day -1, prior to the planned administration

in period 3, was 966 U/L (normal 38 – 174). This was approximately four days following the accident. He was withdrawn from the study. It is reported that his CK was normal 2 weeks later.

Reviewer's comment: *The CK elevation is plausibly related to his accident.*

Subject 12769-007 The subject is a 27 year-old man who was found to have an elevated CK and AST on day -1 of period 4. CK 3125 U/L (normal 38 – 174); AST 72.9 U/L (ULN 35). On questioning he was found to have done 30 minutes of exercise 3 days prior to day -1 and suffered a muscle strain. He was withdrawn from the study because of the elevated values. They had returned to normal at his final examination.

Reviewer's comment: *The markedly elevated CK with a mild AST elevation, in association with a history of muscle injury, suggests that the abnormality is unrelated to vardenafil.*

Subject 13396-01 The subject is a 44 year-old man who developed palpitations one day after his last dose of vardenafil ODT. An ECG showed atrial fibrillation with a rate of 130 bpm and isolated ventricular extrasystoles. The event lasted approximately 12 hours and resolved without treatment. A cardiac evaluation 2 days later was unremarkable. The subject reported that he had a similar episode one year prior to this event.

Reviewer's comment: *The information provided is not sufficient to establish an association to vardenafil ODT as contributing to the arrhythmia.*

The reasons for patients withdrawing prematurely from study 12093 are shown in Table 9 and from study 12094 in Table 10. These tables show that 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 33 shows the seven subjects who truly withdrew from the studies because of adverse events.

Table 33. Patients Withdrawing Prematurely from the Phase 3 Studies due to Adverse Events

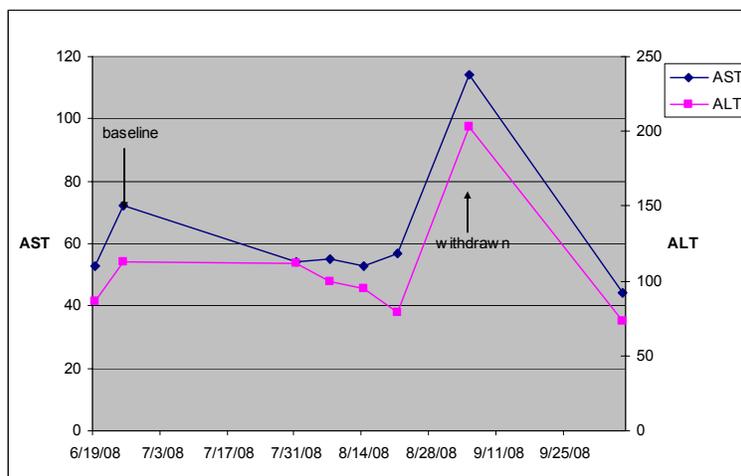
Subject Number	Primary SOC(PT)	Placebo		Vardenafil ODT	
		<65 years	≥65 years	<65 years	≥65 years
12093 10010-0006	Acute Coronary Syndrome	0	0	0	1
12093 30001-0003	ALT Increased	0	0	1	0
12093 37007-0009	Sensorineural hearing loss	0	1	0	0
12094 14013-0009	Chest Pain , Blurry vision	0	0	1	0
12094 14022-0011	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.

Subject 12093-10010-0006 This subject had a serious adverse event which has been discussed above.

Subject 12093-30001-0003 The subject is a 54 year-old man with history of depression and rheumatoid arthritis. On study entry he was taking paroxetine. His baseline AST was slightly elevated, 53 U/L (ULN 41) on June 19, 2008 and 72 U/L on June 26, 2008. His baseline ALT was also elevated, 86 U/L on June 19, 2008 (ULN 45) and 113 U/L on June 26, 2008. Figure 1 shows his AST and ALT values.

Figure 1. Subject 30001-0003 AST and ALT Values



Source: MO Analysis

He was withdrawn from the study on September 5, 2008. He was asymptomatic. He did admit to a greater than usual alcohol intake during the study. His AST and ALT values returned to his baseline after medication was withdrawn.

Reviewer's comment: *Alcohol may have played a role in this AST/ALT elevation. The elevated levels at baseline and the stability of the values for several months on medication suggest that the elevation is likely to be unrelated to study medication.*

Subject 1209414013-0009: The subject is a 39 year-old man who has no significant medical history and who was receiving no medications on study entry. He began vardenafil ODT on September 11, 2008, and continued it on September 12, 13, 14, 17 and 18. On September 14, 2008, he used the medication twice – at 15:30 and 23:00. He experienced a sharp, mild chest pain beginning on September 12 and continuing until September 19, 2008. On September 14, 2008, he experienced blurry vision. The chest pain and blurry vision are not otherwise characterized. He discontinued medication following the September 18, 2008 dose. The chest pain and blurry vision were resolved at the time of his final clinic visit on September 22, 2008.

Reviewer's comment: *It is difficult to assess the relationship of the chest pain to the medication given the information available. The blurry vision occurred on a day on*

which he received two doses of medication, although the timing of the event in relation to the doses is not given. The vision changes are possibly related to medication.

Subject 12094-14022-0011: The subject is a 67 year-old man with a history of migraines, tinnitus, myocardial infarction and coronary artery disease, BPH, dyslipidemia and insomnia. His medications on study entry were folic acid, garlic, selenium, dutasteride, lorazepam, and simvastatin. He received prednisone from June 2, 2008, thru June 9, 2008 for treatment of a bee-sting. He began vardenafil ODT on July 10, 2008. He developed mild lightheadedness and a mild headache on that date. The following day he developed a mild difficulty swallowing. These symptoms persisted thru July 13, 2008. On July 16, 2008, he took another dose of vardenafil ODT and the symptoms recurred and persisted thru July 19, 2008. He discontinued the medication and symptoms were resolved at his final clinic visit on August 6, 2008.

Reviewer's comment: *Although, the time course of the symptoms might suggest a relationship to medication, the patient was also on prednisone. Therefore, it is not clear whether the lightheadedness was due to prednisone or the study medication.*

Subject 12094-40004-0008: The subject is a 62 year-old man with a history of glaucoma, type-2 diabetes, CVA (2001 and 2003), and sleep apnea. His medications on study entry were Avandia, metformin, clopidogrel, candesartan and timolol eye drops. He began vardenafil ODT on October 23, 2008. Beginning October 24 and continuing intermittently until November 11, 2008, he experienced leg cramps, flushing and dizziness. The medication was discontinued on November 8, 2008. His symptoms were reported to be resolved at his final clinic visit on November 27, 2008.

Reviewer's comment: *A possible relationship to medication cannot be ruled out.*

Reviewer's comment: *Clinical review of NDA 200179 further reinforces that the adverse events with a plausible relationship to vardenafil ODT 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.*

7.3.5 Submission Specific Primary Safety Concerns

The following adverse events are of special interest for phosphodiesterase type 5 inhibitor medications: myalgia, cardiac arrhythmia, hypersensitivity reactions, vasodilation 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. These events are summarized in Table 34.

Table 34. Incidence of Treatment Emergent 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%)

Source: MO Analysis.

Reviewer’s comment: *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 and is discussed in the current LEVITRA label.*

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

Immediate hypersensitivity reactions occurred more frequently with vardenafil ODT as opposed to placebo. Episodes of flushing and nasal congestion account for the major portion of this difference. These events occurred more frequently in previous studies of vardenafil and are discussed in the current LEVITRA label.

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

*Dizziness is seen in eight patients receiving vardenafil and in one receiving placebo. These findings confirm prior vardenafil study’s findings and are discussed in the current LEVITRA label. 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 action in 6 of 8 cases. **There were no patients >75 years, who experienced an episode of dizziness.***

One subject (12094-40004-0008 aged 62 years reported dizziness of moderate severity. This subject discontinued due to adverse events and is discussed in Section

7.3.3. Flushing and muscle spasms were given as additional adverse reactions contributing to the subsequent withdrawal from treatment. All AEs, including dizziness, resolved after vardenafil ODT was discontinued.

One subject (12094-14022-0011) aged 67 years reported dizziness of mild severity. This subject discontinued treatment due to adverse events and is discussed in Section 7.3.3. Dizziness, dysphagia and headache, all of mild severity were noted as reasons for discontinuation. All AEs resolved after discontinuation of vardenafil ODT.

The individual cases reporting dizziness in the vardenafil ODT Phase 3 studies indicate that dizziness is basically a tolerability issue that did not require medical intervention and could be managed by stopping treatment.

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

One case of induration of the tongue in a vardenafil ODT treated subject was seen. Review of the CRF and the narrative description of the event indicates 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 ODT 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.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 35 shows the adverse events that occurred in >1% of subjects in either treatment group.

Table 35. 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.

Reviewer's comment: *These adverse event incidences are very similar to those seen in previously conducted trials of vardenafil film-coated tablets. As discussed in section 7.3.5, dysgeusia was not a true adverse event, but rather was an artifact secondary to improper coding at a single clinical site. These clinical trials have identified no safety issues that were not previously identified in the studies of the vardenafil film-coated tablets.*

7.4.2 Laboratory Findings

Table 36 shows the number of subjects having elevated values for laboratory tests and Table 37 shows the number having low values for those tests.

Table 36. Incidence Rates of High Laboratory Abnormalities

Test	Placebo (Num/Num at Risk)	Vardenafil ODT (Num/Num at Risk)
Hematology		
Hematocrit	6/276 (2.2%)	7/276 (2.5%)
RBC	1/289 (0.3%)	4/289 (1.4%)
WBC	3/291 (1.0%)	3/289 (1.0%)
Platelets	7/275 (2.5%)	8/279 (2.9%)
Chemistry		
Glucose,unspecified	23/251 (9.2%)	31/252 (12.3%)
Hemoglobin a1C	0/0	0/0
Potassium	8/312 (2.6%)	4/326 (1.2%)
Creatinine	15/280 (5.4%)	12/294 (4.1%)
SGOT/AST	5/305 (1.6%)	8/320 (2.5%)
SGPT/ALT	11/293 (3.8%)	17/313 (5.4%)
Creatine kinase	19/282 (6.7%)	8/277 (2.9%)
CK- isoenzyme MB	0/1 (0.0%)	0/0 (0.0%)
Testosterone	0/0 (0%)	0/1 (0.0%)

Source: NDA 200179, Module 5.3.5.3, ISS, Table 5-55 and Table 5-57.

Table 37. Incidence Rates of Low Laboratory Abnormalities

Test	Placebo (Num/Num at Risk)	Vardenafil ODT (Num/Num at Risk)
Hematology		
Hematocrit	23/278 (8.3%)	22/280 (7.9%)
RBC	39/227 (17.2%)	39/235 (16.6%)
WBC	4/283 (1.4%)	5/285 (1.8%)
Platelets	3/274 (1.1%)	7/285 (2.5%)
Chemistry		
Glucose,unspecified	2/308 (0.6%)	4/329 (1.2%)
Hemoglobin a1C	0/0	0/0
Potassium	2/317 (0.6%)	1/328 (0.3%)
Creatinine	5/312 (1.6%)	2/321 (0.6%)
SGOT/AST	0/0	0/0
SGPT/ALT	0/0	0/0
Creatine kinase	0/311	0/329
CK- isoenzyme MB	0/0	0/0
Testosterone	0/0	0/1

Source: NDA 200179, Module 5.3.5.3, ISS, Table 5-55 and Table 5-57.

Effect of vardenafil ODT on Hematology tests

There was a slight increase in the number of subjects with an elevation of RBCs in the vardenafil ODT group (1.4%) as compared to the placebo group (0.3%). There was also a slight increase in the number of patients with a low platelet count in the vardenafil ODT group (2.5%) as compared to the placebo group (1.1%). However, none of these hematological changes raise a safety concern at this time. Additionally, there appears to be no other effects of the drug on the hematology parameters evaluated.

The mean baseline RBC count in the placebo group was 4.86 (Normal 4.6 – 5.8). At the last visit the mean in this group was 4.77. The baseline RBC count in the vardenafil ODT group was 4.90 and at the last visit it was 4.80. There does not appear to be a drug effect on RBC count.

The mean baseline platelet count in the placebo group was 246 (Normal 150 – 350). At the last visit the mean in this group was 249. The minimum count in this group was 68 at the last visit. The baseline platelet count in the vardenafil ODT group was 247 and at the last visit it was 249. The minimum count in this group at the last visit was 111. There does not appear to be a significant drug effect on the platelet count.

Effect of vardenafil ODT on Hepatic enzymes

There was no significant effect of vardenafil ODT on the hepatic enzymes.

The mean baseline SGOT/AST was 24.3 and 24.1 in the placebo and vardenafil ODT groups respectively. At the conclusion of treatment the mean values were 24.2 and 24.9. The maximal value seen in the placebo group was 159 and in the vardenafil group 127.

The mean baseline SGPT/ALT was 26.1 and 26.3 in the placebo and vardenafil ODT groups respectively. At the conclusion of treatment the mean values were 27.0 and 27.8. The maximal value seen in the placebo group was 115 and in the vardenafil ODT group 120.

Effect of vardenafil ODT on other chemistry tests

The effect of vardenafil ODT on blood glucose, hemoglobin A1C, potassium, creatinine, and creatine phosphokinase were evaluated. However, there appeared to be no drug effect on these tests.

7.4.3 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 ODT 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 ODT group.

Four subjects were noted to have orthostatic hypotension. Two of these subjects were in the placebo treated group and two in the vardenafil ODT treated group. One of the vardenafil treated subjects was <65 years of age, the second was >65 years of age. All episodes were mild and did not require discontinuation of medication or any further medical intervention.

7.4.4 Electrocardiograms (ECGs)

Table 38 shows a listing of abnormalities present on a post-treatment ECG, that were not present on the pre-treatment study, occurring in >1% of subjects.

Table 38. Incidence of Abnormal Findings on a Post-Treatment ECG that were not present on the Pre-Treatment Study

Finding	Placebo (Num/Num at Risk)	Vardenafil ODT (Num/Num at Risk)
Any Finding	68/166 (41.0%)	86/174 (49.4%)
Rhythm and Rate	30/316 (9.5%)	31/338 (9.2%)
P Wave Abnormalities	3/316 (0.9%)	6/338 (1.8%)
Atrial Conduction Abnormalities	4/316 (1.3%)	7/338 (2.1%)
QRS Complex and Axis Abnormalities	36/316 (11.4%)	44/338 (10.1%)
Ventricular Conduction Abnormalities	31/316 (9.8%)	34/338 (10.1%)
ST Segment, T and U Wave Abnormalities	44/316 (13.9%)	52/338 (15.4%)
Miscellaneous	16/316 (5.1%)	24/338 (7.1%)

Source: NDA 200179, ISS, Table 5-63.

The ECGs in this study were not administered in a uniform timely association with the administration of the study drug.

There were no relevant differences between placebo and vardenafil ODT with respect to the mean change in the heart rate, PR interval, and QRS interval over the time points investigated. Regarding the change from baseline in the QT interval, a slight decrease was observed in both the treatment groups (-5.7 msec on vardenafil ODT vs. -4.1 msec on placebo). The decrease remained smaller when calculating the QT interval according to Bazett or Fridericia.

Table shows a summary of ECG parameters and changes from baseline to last visit.

Table 39. Summary of ECG Parameters with Changes from Baseline to Last Visit – Mean and Standard Deviation

Variable	Time Point	N	Placebo	N	Vardenafil ODT
Heart Rate (bpm)	Baseline	316	65.5 ±10.9	336	66.2 ±11.3
	Last Visit		66.9 ±10.9		67.7 ±11.6
	Change from baseline		1.3 ±8.8		1.5 ±8.7
PR interval (msec)	Baseline	309	172.5 ±26.7	328	170.7 ±25.7
	Last Visit		171.9 ±26.0		169.5 ±26.0
	Change from baseline		-0.5 ±12.9		-0.5 ±7.9
QRS interval (msec)	Baseline	316	96.9 ±14.3	336	97.8 ±14.0
	Last Visit		97.1 ±13.6		97.3 ±14.7
	Change from baseline		0.1 ±7.5		-0.5 ±7.9
QT interval (msec)	Baseline	314	405.7 ±32.0	334	405.6 ±31.8
	Last Visit		401.6 ±32.2		399.9 ±32.7
	Change from baseline		-4.1 ±23.8		-5.7 ±23.4
QTc (Bazett) (msec)	Baseline	314	420.3 ±24.0	334	422.0 ±23.6
	Last Visit		420.0 ±24.1		420.7 ±23.5
	Change from baseline		-0.4 ±19.9		-1.4 ±21.0
QTc (Fredericia)(msec)	Baseline	314	415.1 ±22.0	334	416.2 ±21.1
	Last Visit		413.4 ±21.6		413.3 ±21.3
	Change from baseline		-1.7 ±17.3		-2.9 ±17.9

Source: NDA 200179, Module 5.3.5.3, ISS, Table 5-61.

Reviewer’s comment: Overall, subjects on vardenafil ODT had a higher incidence of ECG findings during study treatment than subjects on placebo (43.8% for vardenafil vs. 39.2% for placebo). The difference in ECG findings was concentrated in the ≥65 years of age group. In this elderly group the incidence of ECG abnormalities was 49.4% for the vardenafil treated patients vs. 41.0% for the placebo group. Younger subjects, <65

yrs of age, had similar incidence rates of ECG findings in both treatment groups (37.8% for vardenafil vs. 37.3% for placebo).

7.4.5 Special Safety Studies/Clinical Trials

Calcium-channel blocker interaction study

The Sponsor has performed a study of the interaction of vardenafil (film-coated tablets) and calcium channel blockers. This study, # 10289, was submitted with NDA 21400 for vardenafil film-coated tablets.

This study was a randomized, double-blind, placebo-controlled, 2-way crossover study in 22 hypertensive male patients (age 27-65) to determine if there is an additive effect on the blood pressure reduction and heart rate elevation produced by a calcium-channel blocker. They studied men who had blood pressure controlled on either 30 mg or 60 mg of nifedipine. They were treated with either placebo or vardenafil 20 mg and blood pressure and pulse, supine and standing, were monitored for four hours after vardenafil administration.

This study was reviewed in the Clinical Pharmacology Review of NDA 21400. The conclusions of the reviewer were that, when given on the background of nifedipine control of blood pressure, there did not appear to be a significant difference between placebo and vardenafil 20mg in their effects on blood pressure and heart rate.

Other Drug-Drug Interaction Studies

As part of the submission for NDA 21400, the Sponsor also submitted studies evaluating the interaction of vardenafil with nitrates, alpha-blockers, ritonavir, and aspirin.

As a result of these studies nitrate use has been considered a contraindication to the use of vardenafil because of significant blood pressure reduction with concomitant use.

Reviewer's comment: *This contraindication should be continued with vardenafil ODT.*

Alpha-blockers were found to have additive effects on blood pressure and vardenafil labeling has advised caution with concomitant use.

Reviewer's comment: *The label for vardenafil ODT should contain the same cautions.*

There was a significant pharmacokinetic interaction between ritonavir and other potent CYP3A4 inhibitors and it was recommended that vardenafil dosage in the face of these medications be limited to 2.5 mg in a 72 hour period.

Reviewer's comment: *Vardenafil ODT will only be available in a 10 mg tablet. Its label should state that vardenafil ODT should not be used with potent CYP3A4 inhibitors.*

Effect of vardenafil on QT interval

The Sponsor has performed a study evaluating the effect of vardenafil on the QT interval as part of their NDA 21400 submission. Study 10929 was designed to rule out a greater than 10 msec effect of a single 80 mg dose of vardenafil (film-coated tablets) on QTc interval compared to placebo. QTc Fridericia was the primary endpoint and an individual correction method (QTci) was also used.

The primary endpoint of this study, (QTcF), showed a 10 msec (90% CI:8, 11) increase for vardenafil 80 mg compared to placebo. The magnitude of QTci was less [(mean 8 msec) 90% CI: 4,7]. The Cardiovascular and Renal Advisory committee evaluated this prior to the approval of NDA 21400 and voted that this was not a clinically meaningful change.

7.5 Other Safety Explorations

7.5.1 Dose or Formulation Dependency for Adverse Events

Vardenafil ODT was only studied as a 10 mg formulation. The Sponsor has provided an analysis comparing the adverse events occurring in the two phase three trials of vardenafil ODT with those occurring in eight similar trials of vardenafil film-coated tablets.

The eight trials of vardenafil film-coated tablets were phase 2, 3 or 4 trials using a fixed dose of vardenafil of 10 mg or 20 mg and having a 12 week or greater treatment period. For trials lasting longer than 12 weeks, only the initial 12 weeks were included in the comparison. The eight studies included 3801 subjects.

Table 40 compares the demographics of the vardenafil arms of the ODT trials as compared to the film-coated tablet trials.

Table 40. Demographics of Vardenafil Cohorts in Vardenafil ODT Trials and Vardenafil film-coated Tablet Trials

		Vardenafil ODT 10 mg	Vardenafil Film-coated 10mg	Vardenafil Film-coated 20mg
N		355	1353	1346
Race n(%)	White	241 (67.9)	656 (48.5)	634 (47.1)
	Black	16 (4.5)	45 (3.3)	59 (4.4)
	Asian	24 (6.8)	581 (42.9)	568 (42.2)
	Hispanic	35 (9.9)	20 (1.5)	30 (2.2)
Age	Mean	61.5	54.6	54.3
	<45 y	27 (7.6)	213 (15.7)	204 (15.2)
	≥45 to <65y	146 (41.1)	936 (69.2)	941 (69.9)
	≥65 to <75y	153 (43.1)	189 (14.0)	185 (13.7)
	≥75y	29 (8.2)	15 (1.1)	16 (1.2)
Smoking Hx	Non-smoker	168 (47.3)	481 (35.6)	494 (36.7)
	Current/Past smoker	184 (51.8)	863 (63.8)	840 (62.4)
Pack-Year Hx	Mean	22.6	35.8	33.3

Source: NDA 200179, Module 5.3.5.3, ISS, Tables 5-8 and 14.1/4

Reviewer's comment: Majority of vardenafil ODT subjects were older than the vardenafil film-coated tablet subjects. The Whites/Hispanic population was greater in the ODT trials while Asians were a larger proportion of the film-coated tablet trials. The film-coated tablet trials also had a greater number of smokers with a longer smoking history.

Table 41 shows the treatment emergent adverse events occurring in >1% of any vardenafil group.

Table 41. Treatment Emergent Adverse Events – Comparison of Vardenafil ODT and Vardenafil Film-coated Tablets (n (%))

SOC/Preferred Term	Placebo tablet N=1102	Placebo ODT N=340	Vardenafil ODT 10mg N=355	Vardenafil tablet 10 mg N=1353	Vardenafil tablet 20 mg N=1346
Any Event	326(29.6)	74(21.8)	135 (38.0)	648 (47.9)	706 (52.5)
Cardiac Disorders	16 (1.5)	14 (4.1)	9 (2.5)	34 (2.5)	30 (2.2)
Palpitations	7 (0.6)	1 (0.3)	1 (0.3)	25 (1.8)	17 (1.3)
Supraventricular extrasystoles	0	3 (0.9)	4 (1.1)	0	1 (<0.1)

Clinical Review
Donald McNellis
NDA 200,179
Vardenafil Orally Dispersible Tablet

SOC/Preferred Term	Placebo tablet	Placebo ODT	Vardenafil ODT 10mg	Vardenafil tablet 10 mg	Vardenafil tablet 20 mg
Eye Disorders	4 (0.4)	2 (0.6)	8 (2.3)	32 (2.4)	61 (4.5)
GI Disorders	42 (3.8)	5 (1.5)	23 (6.5)	123 (9.1)	148 (11.0)
Abd Pain upper	2 (0.2)	0	1 (0.3)	13 (1.0)	13 (1.0)
Diarrhea	8 (0.7)	3 (0.9)	6 (1.7)	16 (1.2)	21 (1.6)
Dyspepsia	3 (0.3)	0	10 (2.8)	28 (2.1)	48 (3.6)
Nausea	7 (0.6)	0	1 (0.3)	18 (1.3)	25 (1.9)
General Disorders	21 (1.9)	2 (0.6)	12 (3.4)	50 (3.7)	43 (3.2)
Infections	70 (6.4)	15 (4.4)	19 (5.4)	133 (9.8)	121 (9.0)
Influenza	6 (0.5)	1 (0.3)	2 (0.6)	15 (1.1)	14 (1.0)
Nasopharyngitis	24 (2.2)	4 (1.2)	2 (0.6)	57 (4.2)	47 (3.5)
Injury, Poisoning and Procedural Complications	24 (2.2)	3 (0.9)	7 (2.0)	30 (2.2)	20 (1.5)
Investigations	35 (3.2)	2 (0.6)	7 (2.0)	72 (5.3)	59 (4.4)
CPK Increased	13 (1.2)	Nr	Nr	23 (1.7)	14 (1.0)
Musculoskeletal Disorders	38 (3.4)	6 (1.8)	20 (5.6)	65 (4.8)	54 (4.0)
Back pain	16 (1.5)	1 (0.3)	7 (2.0)	18 (1.3)	12 (0.9)
Muscle spasms	1 (<0.1)	2 (0.6)	4 (1.1)	4 (0.3)	5 (0.4)
Nervous System Disorders	59 (5.4)	11 (3.2)	65 (18.3)	182 (13.5)	233 (17.3)
Dizziness	11 (1.0)	0	8 (2.3)	24 (1.8)	28 (2.1)
Dysgeusia	0	4 (1.2)	4 (1.1)	0	1 (<0.1)
Headache	45 (4.1)	6 (1.8)	51 (14.4)	141 (10.4)	187 (13.9)
Psychiatric Disorder	11 (1.0)	2 (0.6)	0	19 (1.4)	19 (1.4)
Reproductive and Breast Disorders	7 (0.6)	2 (0.6)	1 (0.3)	18 (1.3)	10 (0.7)
Respiratory Disorders	36 (3.3)	7 (2.1)	18 (5.1)	99 (7.3)	125 (9.3)
Nasal congestion	8 (0.7)	1 (0.3)	11 (3.1)	56 (4.1)	73 (5.4)
Skin and Subcutaneous Disorders	11 (1.0)	4 (1.2)	7 (2.0)	32 (2.4)	31 (2.3)
Vascular Disorders	24 (2.2)	7 (2.1)	30 (8.5)	174 (12.9)	205 (15.2)
Flushing	7 (0.6)	2 (0.6)	27 (7.6)	112 (8.3)	134 (10.0)
Hot Flush	8 (0.7)	Nr	Nr	52 (3.8)	65 (4.8)

Source: NDA 200179, Module 5.3.5.3, ISS, Tables 5-23 and 14.3.1/1.1

Reviewer’s comment:

Subjects receiving vardenafil ODT had slightly increased frequency of headaches and dizziness. In the vardenafil ODT subjects, these events were generally mild. These cases are discussed in detail in section 7.3.3.

The validity of comparing these groups of studies is questionable given the demographic differences (shown in Table 40), the timing of the studies (the film-coated studies were done considerably earlier), and the different protocols used. This can be seen in comparing the placebo arms only, where there is a trend seen toward lower incidence of events in the vardenafil ODT trials as compared to the film-coated trials. Within these limitations, however, there does not seem to be a meaningful difference in the adverse events seen with vardenafil ODT and those seen with vardenafil tablets.

7.5.2 Time Dependency for Adverse Events

The Sponsor did not evaluate the time dependency of adverse events.

7.5.3 Drug-Demographic Interactions

The Sponsor has extensively evaluated the relationship between patient age and adverse events. Although there were no elderly subjects in the phase one studies, the two phase three studies were designed to explore this relationship by specifying that 50% of subjects be greater than 65 years of age. Also, to support the findings in the phase 3 studies, the Sponsor has done an evaluation of previous studies of vardenafil film-coated tablets, specifically focusing on the relationship of age and adverse events.

Phase 3 Studies – Age /Adverse Event Evaluation

Table 42 shows the incidence rates of treatment emergent adverse events by age group.

Table 42. Incidence Rates of Adverse Events by Age Group

AE Type	Placebo (N=340)		Vardenafil ODT (N=355)	
	<65 years (N=165)	≥65 years (N=175)	<65 years (N=173)	≥65 years (N=182)
Treatment emergent AEs (TESS)	34 (20.6%)	40 (22.9%)	71 (41.0%)	64 (35.2%)
Drug-related TESS	12 (7.3%)	13 (7.4%)	47 (27.2%)	39 (21.4%)
TESS leading to discontinuation	0	2 (1.1%)	3 (1.7%)	2 (1.1%)
Serious TESS	1 (0.6%)	1 (0.6%)	2 (1.2%)	4 (2.2%)
Deaths	0	0	0	0

Source: NDA 200179, Module 2.7.4, Table 2-2.

The Serious Adverse Events are shown in Table 31 and are individually discussed in section 7.3.2 Nonfatal Serious Adverse Events. Of the six serious events occurring in patients receiving vardenafil ODT, only one, an episode of syncope in a 73 year-old man, may have a possible relation to the drug. In this case, however, the episode occurred after 11 weeks of therapy and there were no prior adverse events. It is believed that the association between the drug and the event is a weak one.

The discontinuations are shown in Table 33 and are individually discussed in section 7.3.3 Dropouts and/or Discontinuations. Of the three discontinuations in patients <65 years old, two were believed to possibly be drug related. These were flushing and dizziness in one subject and blurry vision in the second. Of the two patients who discontinued medication that were >65 years old, one was believed to be possibly drug related. This was a 67 year old man who had recurring headaches, lightheadedness and difficulty swallowing that led to discontinuation of the medication.

The following adverse events are of special interest for phosphodiesterase type 5 inhibitor medications: myalgia, cardiac arrhythmia, hypersensitivity reactions, vasodilation 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 43 shows these events categorized by age group.

Table 43. Incidence of Adverse Events of Special Interest by Age Group

Event of Special Interest	Preferred Term	Placebo (N=340)		Vardenafil ODT (N=355)	
		<65 years N=165	≥65 years N=175	<65 years N=173	≥65 years N=182
Muscular Adverse Events					
	Back pain	0	1 (0.6%)	3 (1.7%)	4 (2.2%)
	Myalgia	0	0	1 (0.6%)	2 (1.1%)
	Muscle Spasms	1 (0.6%)	1 (0.6%)	1 (0.6%)	3 (1.6%)
Cardiac Arrhythmia or Conduction Abnormality					
	Heart rate increased	0	0	1 (0.6%)	0
	Supraventricular extrasystoles	2 (1.2%)	1 (0.6%)	1 (0.6%)	3 (1.6%)

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Event of Special Interest	Preferred Term	Placebo (N=340)		Vardenafil ODT (N=355)	
		<65 years N=165	≥65 years N=175	<65 years N=173	≥65 years N=182
	Bundle branch block	0	0	0	1 (0.5%)
	Palpitations	0	1(0.6%)	1 (0.6%)	0
	Tachycardia	1 (0.6%)	0	0	0
	Bundle branch block left	1 (0.6%)	0	0	1 (0.5%)
	Ventricular extrasystoles	0	2 (1.1%)	2 (1.2%)	1 (0.5%)
	Bundle branch block right	1 (0.6%)	3 (1.7%)	0	0
Hypersensitivity					
	Dyspnea	1 (0.6%)	0	1 (0.6%)	1 (0.5%)
	Erythema	0	0	0	1 (0.5%)
	Flushing	1 (0.6%)	1(0.6%)	16 (9.2%)	11(6.0%)
	Nasal Congestion	1 (0.6%)	0	9 (5.2%)	2 (1.1%)
	Pruritis	0	0	0	1 (0.5%)
	Rash	1 (0.6%)	1(0.6%)	1 (0.6%)	2 (1.1%)
	Syncope	0	0	0	1 (0.5%)
	Wheezing	0	0	0	1 (0.5%)
Vasodilation Events					
	Flushing	1 (0.6%)	1(0.6%)	16 (9.2%)	11(6.0%)
	Feeling Hot	0	0	3 (1.7%)	0
	Dizziness	0	0	5 (2.9%)	3 (1.6%)
	Vertigo	0	0	1 (0.6%)	1 (0.5%)
	Syncope	0	0	0	1 (0.5%)
	Orthostatic hypotension	0	2(1.1%)	1 (0.6%)	1 (0.5%)
Hearing Loss					

Event of Special Interest	Preferred Term	Placebo (N=340)		Vardenafil ODT (N=355)	
		<65 years N=165	≥65 years N=175	<65 years N=173	≥65 years N=182
	Deafness neurosensory	0	1(0.6%)	0	0
Visual Loss					
	Vision blurred	1 (0.6%)	1(0.6%)	1 (0.6%)	0
Oral irritation					
	Dry Mouth	1 (0.6%)	0	0	2 (1.1%)
	Tongue Induration	0	0	0	1 (0.5%)
	Dysgeusia	2 (1.2%)	2(1.1%)	1 (0.6%)	3 (1.6%)

Source: NDA 200179, Module 2.7.4, Table 2-12 and MO Analysis.

Reviewer’s comment: *There does not appear to be an age-related trend in these adverse events. One elderly subject experienced a syncopal episode. This is discussed in Section 7.3.2. This subject had underlying inner ear disease which may be a significant factor in this event.*

Table 44 shows the treatment emergent adverse events occurring in >1% of subjects by age group.

Table 44. Treatment Emergent Adverse Events Occurring in >1% by Age Group

Preferred Term	Placebo N = 340		Vardenafil ODT N=355	
	<65 years N=165	≥65 years N=175	<65 years N=173	≥65 years N=182
Headache	3(1.8%)	3(1.7%)	28(16.2%)	23 (12.6%)
Flushing	1 (0.6%)	1 (0.6%)	16 (9.2%)	11 (6.0%)
Nasal congestion	1 (0.6%)	0	9 (5.2%)	2 (1.1%)
Dyspepsia	0	0	5 (2.9%)	5 (2.7%)
Dizziness	0	0	5 (2.9%)	3 (1.6%)
Back pain	0	1 (0.6%)	3 (1.7%)	4 (2.2%)
Diarrhea	2 (1.2%)	1 (0.6%)	4 (2.3%)	2 (1.1%)
Supraventricular extrasystoles	2 (1.2%)	1 (0.6%)	1 (0.6%)	3 (1.6%)
Dysgeusia	2 (1.2%)	2 (1.1%)	1 (0.6%)	3 (1.6%)
Muscle spasms	1 (0.6%)	1 (0.6%)	1 (0.6%)	3 (1.6%)

Source: NDA 200179, Module 2.7.4, Table 14.3.1/1.1.1

Reviewer’s comment: *During these phase 3 studies, the common adverse events, the serious adverse events, the adverse events leading to discontinuation, and the adverse events of special interest did not appear to trend higher in older subjects.*

Vardenafil film-coated tablet studies – Age /Adverse Event Evaluation

The Sponsor has evaluated 58 studies of vardenafil film-coated tablets (vardenafil tablets). They have been considered in four groups.

- Group 1 - 5 placebo controlled fix dose studies comparing 5mg, 10mg and 20mg vardenafil to placebo
- Group 2 - 11 placebo controlled flexible dose studies without age restriction, starting with 10mg and allowing first titration at week 4, comparing vardenafil and placebo
- Group 3 - Protocol violators from 12 ED studies with age restriction to age less than 65y
- Group 4 - 26 other studies in ED without age restriction and with at least some elderly included

They considered Groups 1 and 2 to be the main analysis populations and Groups 3 and 4 as supportive. This analysis will focus on the main analysis population which consists of studies most similar to those carried out for vardenafil ODT.

Table 45 shows the age distribution of the subjects in Groups 1 and 2.

Table 45. Age and Dose Distribution of Subjects in the Vardenafil Tablet Studies

Age Group	Placebo	5mg vardenafil	10mg vardenafil	20mg vardenafil
Group 1				
<45y	146	142	149	141
45 - <65y	427	440	455	443
65 - <75y	132	120	113	124
≥75y	8	14	7	12
Group 2				
			10mg vardenafil starting dose	
<45y	367		423	
45 - <65y	1008		1339	
65 - <75y	277		314	
≥75y	46		58	

Source: NDA 200179, Module 5.3.5.3.1, Integrated Analysis of Safety Stratified by Age, Table 1, page 1-12.

All of the studies evaluated in these groups lasted at least 4 weeks, most 3 months, and the maximal duration was 2 years. In 3 studies vardenafil was administered daily, in all others it was administered as needed prior to intercourse. Since the purpose of this

analysis was to assess the safety of higher starting doses of vardenafil in elderly subjects, adverse events were only considered if they occurred in the initial four weeks of treatment.

In addition to evaluating overall adverse events, the Sponsor evaluated events in five Standard MEDDRA Queries (SMQ) – MI, CSR (Central Serous Retinopathy), Myalgia, Vasodilation and Dizziness.

Table 46 shows the incidence of treatment emergent adverse events in the Group 1 (fixed dose) studies and Table 47 shows those in the flexible dose studies.

Table 46. Treatment Emergent Adverse Events in Vardenafil Tablet Fixed Dose Studies

	Age Group	Placebo	5mg Vardenafil	10mg Vardenafil	20mg Vardenafil
Group 1					
Number Of Subjects	45 – 65y	427	440	455	443
	65 - <75y	132	120	113	124
	≥75y	8	14	7	12
All AE	45 – 65y	16.4%	25.2%	34.7%	36.8%
	65 - <75y	6.1%	27.5%	23.9%	39.5%
	≥75y	25.0%	21.4%	42.9%	50.0%
Drug Related AEs	45 – 65y	4.9%	17.5%	25.5%	29.3%
	65 - <75y	3.0%	13.3%	14.2%	31.5%
	≥75y	25.0%	7.1%	28.6%	41.7%
AEs leading To discontinuation	45 – 65y	0.2%	0.9%	1.5%	1.8%
	65 - <75y	0	2.5%	1.8%	2.4%
	≥75y	0	7.1%	0	0
Serious AEs	45 – 65y	0.9%	0.5%	0.7%	0.7%
	65 - <75y	0	1.7%	0.9%	1.6%
	≥75y	0	0	0	0
SMQ: MI	45 – 65y	1.2%	0.7%	0.9%	0.7%
	65 - <75y	0.8%	0	0	0.8%
	≥75y	0	0	0	0
SMQ: CSR	45 – 65y	0.2%	0.2%	0.4%	0.9%
	65 - <75y	0	0.8%	0	0.8%
	≥75y	0	0	0	0
SMQ: Myalgia	45 – 65y	0.5%	0.2%	0.7%	0.2%
	65 - <75y	0	0	0	0
	≥75y	0	0	0	0
SMQ: Vasodilation	45 – 65y	1.2%	7.7%	11.6%	12.9%
	65 - <75y	0	5.8%	5.3%	12.1%
	≥75y	0	0	14.3%	16.7%
SMQ: Dizziness	45 – 65y	0.5%	1.1%	1.1%	0.5%
	65 - <75y	0	0.8%	3.5%	2.4%
	≥75y	0	0	14.3%	16.7%

Source: NDA 200179, Module 5.3.5.3.1, Integrated Analysis of Safety Stratified by Age, Table 3.1, page 1-16.

Table 47. Treatment Emergent Adverse Events in Vardenafil Tablet Flexible Dose Studies

	Age Group	Placebo	10mg Vardenafil Starting Dose
Group 2			
Number Of Subjects	45 – 65y 65 - <75y ≥75y	1008 277 46	1339 282 52
All AE	45 – 65y 65 - <75y ≥75y	10.2% 10.5% 8.7%	23.5% 22.3% 15.4%
Drug Related AEs	45 – 65y 65 - <75y ≥75y	2.3% 2.2% 0	16.7% 16.3% 13.5%
AEs leading To discontinuation	45 – 65y 65 - <75y ≥75y	0.5% 2.2% 0	1.1% 16.3% 0
Serious AEs	45 – 65y 65 - <75y ≥75y	0.2% 0 0	0.6% 0.4% 0
SMQ: MI	45 – 65y 65 - <75y ≥75y	<0.1% 0 0	0.5% 0 0
SMQ: CSR	45 – 65y 65 - <75y ≥75y	0 0 0	0.5% 0.4% 0
SMQ: Vasodilation	45 – 65y 65 - <75y ≥75y	0.5% 0.4% 0	6.4% 6.7% 1.9%
SMQ: Dizziness	45 – 65y 65 - <75y ≥75y	<0.1% 0.7% 0	0.4% 0.4% 3.8%

Source: NDA 200179, Module 5.3.5.3.1, Integrated Analysis of Safety Stratified by Age, Table 3.2, page 1-17.

Reviewer’s comment: *There appears to be an age-related increase in dizziness that is seen both in the fixed dose studies, at the 10mg and 20 mg dose levels, and in the flexible dose studies with a 10 mg starting dose. This increase is particularly notable in the subjects ≥75 years of age. In the fixed dose studies, those subjects receiving the 5mg dose did not demonstrate this age-related increase in dizziness. The number of subjects in the elderly age groups is quite small in the fixed dose studies compared to, the flexible dose studies.*

The supportive vardenafil tablet studies (Groups 3 and 4) show this age-related increase at a 20 mg dose, but not at a 10mg dose. At 10 mg, the incidence of dizziness was 0.8%, 0.8% and 0% respectively in the <65, 65-75 and >75 age groups. At 20 mg the respective incidences of dizziness in those age groups was 1.4%, 2.4% and 3.1%.

The increase in dizziness with age was not seen in the vardenafil ODT studies. In those studies, dizziness occurred in 2.9% of those <65 years, 1.6% of those 65 – 75 years, and in 0% of those >75 years.

Although the vardenafil tablet data show evidence of a dose-related increase in adverse events, an age-related increase is not seen in any category other than dizziness. The dizziness relationship is not confirmed in the vardenafil ODT studies which were enriched with elderly patients.

7.5.4 Drug-Disease Interactions

The incidence of treatment emergent adverse events was evaluated in subgroups of subjects with a medical history of cardiac disorders, arteriosclerosis, myocardial infarction, CVA, diabetes mellitus, dyslipidemia, hypertension and renal impairment. A subgroup evaluation of subjects with hepatic impairment was not done because of lack of subjects in this group.

Table 48 shows those adverse events that occurred in at least two subjects and at a rate at least twice that of subjects without the condition being evaluated and also at a rate at least twice that of subjects receiving placebo.

Table 48. Incidence of Treatment Emergent Adverse Events in Subgroups of Subjects with Co-existing Diseases

Co-existing Condition	Adverse Event	Placebo Subgroup with condition	Vardenafil ODT Subgroup without condition (n(%))	Vardenafil ODT Subgroup with condition (n(%))
Cardiac Disease		N=62	N=297	N=58
	Dyspepsia	0	7 (2.4%)	3 (5.2%)
	Dry mouth	0	0	2 (3.4%)
	Any GI Event	1 (1.6%)	15 (5.1%)	8 (13.8%)
	Cough	0	0	2 (1.4%)
Arteriosclerosis		N=21	N=336	N=19
	Back pain	1 (4.8%)	5 (1.5%)	2 (10.5%)

Co-existing Condition	Adverse Event	Placebo Subgroup with condition	Vardenafil ODT Subgroup without condition (n(%))	Vardenafil ODT Subgroup with condition (n(%))
History of MI		N=18	N=340	N=15
	Any GI Event	0	21 (6.2%)	2 (13.3%)
Diabetes mellitus		N=86	N=253	N=102
	Any Eye event	0	4 (1.6%)	4 (3.9%)
Dyslipidemia		N=109	N=216	N=139
	Feeling hot	0	1 (0.5%)	2 (1.4%)
	Back pain	1 (0.9%)	3 (1.4%)	4 (2.9%)
	Dizziness	0	3 (1.4%)	5 (3.6%)
	COPD	0	0	2 (1.4%)
	Dyspnea	0	0	2 (1.4%)
Hypertension		N=150	N=214	N=141
	Diarrhea	1 (0.7%)	1 (0.5%)	5 (3.5%)
	Feeling hot	0	1 (0.5%)	2 (1.4%)
	Pyrexia	0	0	2 (1.4%)
	Any musculoskeletal event	6 (4.0%)	8 (3.7%)	12 (8.5%)
	Back pain	1 (0.7%)	2 (0.9%)	5 (3.5%)
	Myalgia	0	1 (0.5%)	2 (1.4%)
	Pain in extremity	0	0	2 (1.4%)
	Dizziness	0	3 (1.4%)	5 (3.5%)
	Cough	0	0	2 (1.4%)
Dyspnea	0	0	2 (1.4%)	
Mild Renal Impairment		N=86	N=248	N=95
	Myalgia	0	1 (0.5%)	2 (1.4%)

Source: NDA 200179, Module 5.3.5.3, Integrated Summary of Safety, Tables 14.3.1/1.1.2 – 14.3.1/1.1.10, page 611-663.

Reviewer's comment: *These data do not suggest a meaningfully different response to vardenafil ODT in subgroups of subjects with these co-existing pre-morbid medical conditions.*

7.5.5 Drug-Drug Interactions

There was no evaluation of drug-drug interactions in the clinical trials of vardenafil ODT. Subjects who were receiving concomitant treatment with medications known to have a potential interaction with vardenafil, i.e. nitrates, alpha-blockers, or strong inhibitors of cytochrome P450, were excluded from the studies.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There are no data on carcinogenicity of vardenafil in humans.

Vardenafil was not carcinogenic in rats and mice when administered daily for 24 months. In these studies systemic drug exposures (AUCs) for unbound (free) vardenafil and its major metabolite were approximately 400- and 170-fold for male and female rats, respectively, and 21- and 37-fold for male and female mice, respectively, the exposures observed in human males given the Maximum Recommended Human Dose (MRHD) of 20 mg. Vardenafil was not mutagenic as assessed in either the *in vitro* bacterial Ames assay or the forward mutation assay in Chinese hamster V79 cells. Vardenafil was not clastogenic as assessed in either the *in vitro* chromosomal aberration test or the *in vivo* mouse micronucleus test.

7.6.2 Human Reproduction and Pregnancy Data

A study has shown that daily vardenafil treatment for six months in men with normal baseline semen characteristics had no detrimental effects on semen characteristics².

Vardenafil is not indicated in women and there are no data on its effects on human female reproduction.

Vardenafil did not impair fertility in male and female rats administered doses up to 100 mg/kg/day for 28 days prior to mating in male, and for 14 days prior to mating and through day 7 of gestation in females. In a corresponding 1-month rat toxicity study, this dose produced an AUC value for unbound vardenafil 200 fold greater than AUC in humans at the MRHD of 20 mg.

7.6.3 Pediatrics and Assessment of Effects on Growth

Vardenafil is not indicated for use in the pediatric population and neither vardenafil film coated tablets nor vardenafil ODT have been investigated in this population.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The maximum dose of vardenafil for which human data are available is a single 120 mg dose of film-coated tablets administered to eight healthy male volunteers. The majority of these subjects experienced reversible back pain/myalgia and/or “abnormal vision.”

In cases of overdose, renal dialysis is not expected to accelerate clearance because vardenafil is highly bound to plasma proteins and is not significantly eliminated in the urine.

There have been no studies of the abuse potential of vardenafil.

7.7 Additional Submissions / Safety Issues

The sponsor has submitted information to support the market name - STAXYN. The previously submitted tradenames, (b) (4), (b) (4), and (b) (4) have been found to be unacceptable by the Division of Medication Error Prevention (DMEPA). STAXYN was found to be an acceptable tradename by DMEPA on June 15, 2010.

8 Postmarketing Experience

There are no safety data related to vardenafil ODT in the post marketing setting. However, post-marketing safety experience is available for vardenafil film-coated tablets. Vardenafil is currently authorized to be marketed in 117 countries. Vardenafil film-coated tablets have been marketed in the US since 2003.

Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely post-marketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including vardenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including but not necessarily limited to: low cup to disc ratio (“crowded disc”), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking.

Reviewer’s comment: *It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient’s underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors. Bayer Healthcare is currently conducting a study “Prospective Case Crossover Study to Assess Whether PDE5 Inhibitor Exposure in Men with Erectile Dysfunction Increases the Risk for the Development of Non-arteritic Anterior Ischemic Optic Neuropathy (NAION).”*

Visual disturbances including vision loss (temporary or permanent), such as visual field defect, retinal vein occlusion, and reduced visual acuity, have also been reported rarely in post-marketing experience.

Cases of sudden decrease or loss of hearing have been reported post-marketing in temporal association with the use of PDE5 inhibitors, including vardenafil. In some cases, medical conditions and other factors were reported that may have also played a role in the otologic adverse events.

Seizure and seizure recurrence have been reported post-marketing in temporal association with vardenafil.

Reviewer's comment: *It is not possible to determine from the information available whether these events are related directly to the use of vardenafil or to the patient's underlying risk factors for visual, auditory or seizure events.*

9 Appendices

9.1 Literature Review/References

¹ Rosen RC, Riley A, Wagner G et al. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997;49(6): 822- 830.

² Jarvi K, Dula E, Drehobl M et al. Daily vardenafil for 6 months has no detrimental effects on semen characteristics or reproductive hormones in men with normal baseline levels. *J Urology* 2008;179: 1060-1065.

9.2 Labeling Recommendations

It is appropriate for the vardenafil ODT label to incorporate much of the content of the vardenafil film-coated tablet (LEVITRA) label. The following changes to that content are recommended due to the differing pharmacokinetics of vardenafil ODT as compared to vardenafil film-coated tablets, and also due to the more limited dosing options for vardenafil ODT.

Highlights of prescribing information

Dosing and Administration section should contain statements that vardenafil ODT is not bioequivalent to vardenafil 10 mg film-coated tablets. Also, that vardenafil ODT is not interchangeable with vardenafil 10 mg film-coated tablets.

Section 2 – Dosage and Administration

This section should also contain statements that vardenafil ODT is not bioequivalent to vardenafil 10 mg film-coated tablets and that vardenafil ODT is not interchangeable with vardenafil 10 mg film-coated tablets .

This submission has not demonstrated a safety profile in elderly subjects (>65 years) that differs from the safety profile in younger patients. Therefore, this section should indicate that there is no need for dose modification in elderly patients.

Section 2.3 – Dosage and Administration, Special Populations

This section should contain information stating that this medication should not be used in patients with moderate or severe hepatic impairment or in patients on renal dialysis.

Section 2.4 – Dosage and Administration, Concomitant Medications

Because of the pharmacokinetics of this formulation of vardenafil, this section should contain information stating that this medication should not be used with moderate or strong CYP3A4 inhibitors and that it should not be used as the initial formulation of vardenafil to be given to patients receiving alpha-blockers.

Section 5 – Warnings and Precautions

This section should also contain information stating that this medication should not be used with moderate or strong CYP3A4 inhibitors and that it should not be used as the initial formulation of vardenafil to be given to patients receiving alpha-blockers.

Section 6.2 – Postmarketing Experience

This section should state that the information presented refers to experience with the film-coated tablets, not the ODT formulation.

Section 7.2 – Effect of Other Drugs on Vardenafil

Because vardenafil ODT will only be available in a 10 mg form, this section should contain statements that vardenafil ODT should not be used with medications which are inhibitors of CYP3A4.

Section 8.6 – Hepatic Insufficiency

Because vardenafil ODT will only be available in a 10 mg form, this section should contain a statement that vardenafil ODT should not be used in patients with moderate or severe hepatic insufficiency.

Section 8.7 – Renal Insufficiency

Because vardenafil ODT will only be available in a 10 mg form, this section should contain a statement that vardenafil ODT should not be used in patients on renal dialysis.

9.3 Advisory Committee Meeting

Vardenafil ODT is a new formulation of a previously approved medication. The current submission demonstrates efficacy and contains no new safety signals. Therefore, no Advisory Committee meeting was held.

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

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/s/

DONALD R MCNELLIS
06/17/2010

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06/17/2010