Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Vardenafil

Proprietary Product Name: Levitra

Sponsor: Bayer Australia Ltd

February 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Dosage Form and Change in Dosage Instructions
Decision:	Approved
Date of Decision:	12 January 2011
Active ingredient(s):	Vardenafil (as the hydrochloride trihydrate)
Product Name(s):	Levitra
Sponsor's Name and Address:	Bayer Australia Ltd PO Box 903 Pymble NSW 2073
Dose form(s):	Orodispersible tablet
Strength(s):	10 mg
Container(s):	Blister pack
Pack size(s):	1, 4, and 8 tablets
Approved Therapeutic use:	For the treatment of erectile dysfunction in adult males (inability to achieve or maintain penile erection sufficient for satisfactory sexual performance). Levitra is not indicated for use by women.
Route(s) of administration:	Oral
Dosage:	The maximum recommended dose is one Levitra orodispersible tablet daily.
ARTG Number:	165902

Product Background

By inhibiting phosphodiesterase type 5 (PDE5), the enzyme responsible for cGMP degradation in the corpus cavernosum, vardenafil potently enhances the effect of endogenous NO, locally released in the corpus cavernosum upon sexual stimulation. The inhibition of PDE5 by vardenafil leads to increased cGMP levels in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum. Vardenafil thus potentiates the natural response to sexual stimulation.

Levitra was considered by the Australian Drug Evaluation Committee (ADEC) at its 226th meeting on 6-7 February 2003. The clinical trial program which supported the application for initial registration included two Phase III pivotal studies and seven supportive studies. At the time the members of the committee were agreed that, despite the issue of nitrate interaction not having been fully explored[1] and the lack of information on interaction with anti-hypertensive drugs, the data package for vardenafil showed on balance that it was an

[1] It was noted by the members of the committee that the issue of interaction with nitrates was only examined with a small dose of vardenafil (10 mg) and a small dose of nitrates (0.4 mg) and that there was only a small effect.

effective agent which demonstrated safety within the limits demonstrated by other agents in this class.

Levitra (vardenafil) film coated tablets are approved in Australia for the treatment of erectile dysfunction in adult males (inability to achieve or maintain penile erection sufficient for satisfactory sexual performance). It is not indicated for use in females. Levitra is registered as 5 mg, 10 mg, and 20 mg film coated tablets.

Bayer Australia Limited (the sponsor) is seeking approval of a new dosage form for Levitra consisting of an orodispersible tablet (ODT) 10 mg for the treatment of erectile dysfunction in adult males. In addition, the submission included data to support proposed Product Information (PI) amendments relating to the recommended starting dose in elderly males (> 65 years) changing from "a starting dose of 5 mg should be considered" to "dose adjustment is not required". The sponsor also proposed to make a number of amendments to the *Adverse Effects* section of the PI, and to include precautionary statements in the PI relating to a potential pharmacokinetic (PK) drug-drug interaction between Levitra and clarithromycin.

It was proposed that this product will have the same indications as the immediate release film-coated tablets.

Regulatory Status

The medicine has been marketed in Australia as a film coated tablet (FCT) since April 2003.

Similar applications to that provided to the Therapeutic Goods Administration (TGA) have been approved in the European Union (EU) (1 September 2010), and submitted in Switzerland (4 September 2009), New Zealand (30 September 2009) and Canada (2 July 2010). The Australian application is similar to the application submitted to the EU. A submission to the USA was approved on 17 June 2010.

The sponsor states that a variation to remove the recommendation relating to the 5 mg starting dose in the elderly was submitted to the EU in September 2008 and approved in February 2009, and gave an assurance that the data set provided to the EU supporting this variation is identical to that submitted to the TGA.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

The drug substance is controlled as per Levitra film-coated tablets. The drug substance is achiral, but is presented as the micronized form of the hydrochloride trihydrate. Details of the manufacture and control of this material are as registered. The specifications include adequate control of synthetic impurities, residual solvents and particle size distribution. Vardenafil hydrochloride trihydrate is Biopharmaceutical Classification System (BCS) Class 2.[2]

There are no compendial monographs for the drug substance or finished products containing this drug substance.

[2] The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

Drug Product

Formulation and manufacture

The orodispersible tablets are to be manufactured and packaged by Bayer Schering Pharma AG in Leverkusen, Germany. The bulk orodispersible tablets can be stored for 12 months prior to final packaging and data to support this storage was provided.

The specifications have acceptable expiry limits and release limits that allow for the changes that occur over the shelf life. No dissolution limits are required for this dosage form. Instead there is a test for disintegration time with a limit of not more than (NMT) 30 seconds. This ensures rapid dispersion in the mouth prior to absorption and is consistent with the British Pharmacopoeia general monograph stipulations for orodispersible tablets.

The degradant impurity N-oxide is limited at release and at expiry. This impurity is also a metabolite and the expiry limit was therefore acceptable.

The degradant impurities metabolite 1 and sulfotriazinone are limited to NMT 0.2% at release and NMT 0.5% at expiry. The International Council on Harmonisation (ICH) qualification threshold is 0.5%.[3]

Unidentified degradants are NMT 0.2% at release and expiry. The ICH identification threshold is 0.2%.

The open orodispersible tablets were found to undergo humidity, photolytic and temperature dependent degradation to the N-oxide on storage. However, the degradation is almost negated when the product is stored at 30ºC in the proposed blister packs. The stability data was provided supported an unopened shelf life of 3 years when stored below 30ºC in blister packs. The storage conditions 'store in original container' will also apply.

Specifications

Assay limits at expiry comply with the appropriate Therapeutic Goods Order; though at the time of the evaluation it was not clear if the release limit was appropriate. The limits for related substances comply with ICH guidance apart from that for the N-oxide. However this limit has been accepted as the N-oxide is a human metabolite. No dissolution test is required for this dosage form and a disintegration test with appropriate limit is used.

Stability

On storage there was a slight increase in the N-oxide impurity and an increase in water content. The stability data supported a shelf life of 3 years when stored below 30°C. The condition 'store in original container' will also apply.

Bioavailability

The sponsor stated that the Phase III clinical efficacy studies were performed with the formulation orodispersible tablet proposed for registration.

The submission included one bioavailability study to compare the bioavailability of the proposed orodispersible tablets (ODT) to that of the registered immediate release film-coated tablets in healthy volunteers. This study also determined the effect of food and water on the bioavailability of the orodispersible tablets.

[3] Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

The submission also included a pharmacokinetic study comparing the bioavailability of the orodispersible tablets to the registered immediate release formulation in male ED patients of different ages. This study (13396) was evaluated by the clinical evaluator.

Study 12769 was a four-way crossover study in 16 male subjects (13 completed) with the following treatments. The study was of an appropriate design and the test method used to determine the levels of vardenafil and the active metabolite (metabolite 1) in the subject plasma samples was satisfactorily validated for this purpose. There were four treatments as follows:

(a) 10 mg orodispersible tablet dissolved on the tongue with no water fasted

(b) 10 mg orodispersible tablet dissolved on the tongue with no water 30 minutes after start of a high fat meal

(c) 10 mg orodispersible tablet swallowed with water fasted

(d) 10 mg immediate release tablet swallowed with water fasted

The results of the study indicated that:

- The proposed 10 mg ODT (administered without food or water) was not bioequivalent to the registered 10 mg Levitra immediate release tablet (administered with water): The area under the plasma concentration time curve (AUC) was 44% higher, the maximal plasma concentration (C_{max}) was 15% higher and the time to maximal plasma concentration (T_{max}) was 45 minutes longer.
- When administered with water, the bioavailability of the 10 mg ODT was decreased by 29% compared to when administered without water. In addition T_{max} was slightly shorter though C_{max} was unaffected.
- When administered with food (high fat meal), the bioavailability of the 10 mg ODT was not affected compared to when administered without food though C_{max} was decreased by 35% (T_{max} was unaffected).
- Regardless of the mode of administration (without water, with water, with food) the 10 mg ODT returned very similar inter-subject variability in exposure as the registered 10 mg Levitra immediate release tablet.
- The sponsor claims that the higher levels observed with the ODT tablet compared to the registered 10 mg Levitra immediate release tablet can be considered clinically safe as there is also a 20 mg Levitra immediate release tablet registered in Australia.

Quality Summary and Conclusions

Approval of this submission was recommended with respect to the chemistry and quality.

In relation to bioavailability:

- The extent of bioavailability from the ODT is 44% higher than from the registered 10 mg Levitra immediate release tablet.
- Administration with water decreases the extent of bioavailability of the ODT compared to dissolving on the tongue.
- Food decreases the rate of bioavailability of the ODT compared to when taken fasted, but the extent of bioavailability is unaffected.

III. Nonclinical Findings

Nonclinical Summary and Conclusions

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical Findings

Introduction

The sponsor stated that the new ODT formulation offers an alternative and potentially more convenient dosage form to the approved FCT formulations. However, no data have been provided specifically addressing these claims. The sponsor considers the ODT to be "more discrete" (presumably compared with the current FCT) and will benefit patients with erectile dysfunction who have difficulty swallowing. The ODT formulation has been developed to be administered without water by placing it on the tongue where it disperses and is swallowed with saliva. The submission includes data supporting only the 10 mg strength of the ODT formulation. The sponsor justifies this on the grounds that the ODT 10 mg is within the approved dosage range for Levitra FCT and, consequently, a higher or lower dose was considered unnecessary. Furthermore, the sponsor states that the 10 mg dose of Levitra FCT is the recommended starting dose for the majority of patients.

The data submitted in support of approval of the vardenafil 10 mg ODT formulation included:

- one pharmacokinetic (PK) study examining the bioavailability of the proposed formulation in healthy young males following single dose administration and including a fasted and fed comparison and two PK studies in young and elderly males with erectile dysfunction (ED) following single and multiple dose administration [Study12769, Study 13396 and Study 12093];
- one PK study examining absorption of a vardenafil solution across the oral mucosa in healthy young males [Study 10021];
- two pivotal, randomized, multinational, placebo-controlled, efficacy and safety studies [POTENT I (Study 12093) and POTENT II (Study 12094)];
- and an integrated efficacy and safety summary of the two pivotal clinical studies [PH-35849].

The submission also included three post-marketing documents [Dendrite Drug Utilization Study; UHC; and PDE5 Inhibitor Survey (protocol)]. These post-marketing documents have been examined but not evaluated as they are considered to be not relevant to the application to register the vardenafil 10 mg ODT formulation. There are no specific post-marketing data on the ODT formulation as it has not yet been marketed in any country. The ODT 10 mg formulation used in the PK and clinical efficacy and safety studies is stated to be identical to the proposed commercial formulation. The submission also included a *Clinical Overview*, and written summaries of the clinical pharmacology, clinical efficacy and clinical safety studies. The submission also included an *EU Risk Management Plan (RMP)* for Levitra ODT and FCT formulations.

The submission to amend the starting dose recommendations in the PI relating to elderly patients was supported by three integrated analyses and four expert statements. The data were supported by a specific *Clinical Overview* relating to the amendment and nine literature references. It was considered that the *Clinical Overview* and literature references provided background information.

The submission to include a precautionary statement in the PI relating to increased vardenafil exposure when co-administered with clarithromycin was supported by a justification document reviewing relevant published literature, and an *in vitro* interaction study investigating the effect of CYP3A4 inhibitors on vardenafil concentration [PH-34161].

The submission to update the *Adverse Effects* section of the PI was supported by a *Global Pharmacovigilance Document* dated 14 August 2009. The updated information included the placebo-controlled safety data from the current submission seeking registration of the vardenafil 10 mg ODT formulation.

The studies supporting the approval of the vardenafil 10 mg ODT formulation were conducted according to the Good Clinical Practice (GCP) guidelines of the ICH.

Pharmacokinetics

Introduction

The submission included three PK studies to support the clinical development of Levitra 10 mg ODT. One included healthy young males aged 18-50 years [Study 12769], one included males with erectile dysfunction stratified by age [Study 13396] and one included a subgroup of males with erectile dysfunction in the pivotal Phase III study [Study 12093]. The ODT 10 mg formulation used in the PK studies was stated to be identical to the proposed commercial formulation. The FCT 10 mg formulation used in the PK studies was identical to that registered in Australia. The three studies are briefly described below in Table 1.

Table 1: PK studies assessing the pharmacokinetics of the vardenafil 10 mg ODT formulation.

Study	Description
12769	Phase I, single-dose, four-way, crossover study in healthy young males aged 18-50 years (n=13). The study compared the PKs of vardenafil administered as Levitra 10 mg ODT (fasting without water) and Levitra FCT 10 mg (fasting with 180 mL of water), and investigated the effect of a high calorie breakfast on Levitra 10 mg ODT taken without water.
13396	Phase I study investigating single and multiple dose vardenafil PKs in males with erectile dysfunction. It compared the effects of age (≤ 45 years, n=14; ≥ 65 years) on the PKs of vardenafil and its metabolite M-1 following administration of Levitra 10 mg ODT and Levitra 10 mg FCT.
12093	Single-dose study investigating the PKs of vardenafil following administration of Levitra 10 mg ODT to a subset of 25 male patients with erectile dysfunction in the pivotal study POTENT I.

In addition to the three PK studies investigating the proposed ODT 10 mg formulation, the submission also included a PK study in healthy young males investigating absorption of vardenafil from a solution administered sublingually, and comparing sublingual and oral vardenafil bioavailability following administration of a solution [Study 10021].

The submission included new data on the absorption and metabolism of vardenafil following administration of the ODT 10 mg formulation. There were no new data on distribution or elimination of vardenafil following administration of the ODT 10 mg formulation as these mechanisms were considered to be no different from those following administration of the FCT 10 mg formulation.

Absorption

The relative bioavailability (AUC) of vardenafil following single dose ODT 10 mg (fasting, without water) was 44% higher than single dose FCT 10 mg (fasting with water) in healthy young males: ratio AUC = 1.4412 [90% Confidence Intervals (CI): 1.3167, 1.5775]. In the

same study [12769], the vardenafil C_{max} for the corresponding comparison was 15% higher: ratio C_{max} = 1.1466 [90%CI: 0.9404, 1.3980]. The ODT 10 mg and FCT 10 mg formulations are not bioequivalent. The T_{max} was 1.5 hours with the ODT 10 mg formulation and 0.75 hours with the FCT 10 mg formulation and the respective terminal half-lives were 4.15 and 3.85 hours. The approved Levitra PI states that vardenafil undergoes extensive first-pass metabolism and that the absolute bioavailability after FCT 10 mg is 15%.

The increased vardenafil bioavailability following ODT 10 mg dosing is due to a fraction of the administered dose remaining in the mouth (rather than being swallowed) and being absorbed through the oral mucosa. In a mechanistic study in healthy young males it was observed that about 8% (0.8 mg) of a 10 mg vardenafil solution administered sublingually and kept in the mouth for 15 minutes was absorbed through the oral mucosa [Study 10021]. This small, orally absorbed fraction of the total administered dose of vardenafil avoids first-pass metabolism to the N-desmethyl metabolite (M-1). The T_{max} of the vardenafil solution administered sublingually (that is, not swallowed) was 2.75 hours compared with 0.75 hours for the vardenafil solution administered orally (swallowed). The AUC corrected for the amount of vardenafil actually absorbed following administration of the vardenafil solution was three fold higher following sublingual (non swallowed) than oral (swallowed) administration.

The sponsor stated that vardenafil ODT disintegrates on the tongue within a few seconds and a small amount is dissolved at the neutral pH of saliva and is available for absorption in the oral cavity. The remainder is swallowed with saliva and absorbed in the gastrointestinal tract. However, no *in vivo* study could be identified in the submission supporting the sponsor's claim of rapid disintegration of the ODT formulation when placed on the tongue.

Metabolism

The major metabolite (M-1) of vardenafil has been shown to account for about 7% of the drug's overall clinical efficacy (Levitra PI). The AUC ratio of the M-1 metabolite for single dose ODT 10 mg (fasting, without water) compared with FCT 10 mg (fasting, with water) was 1.0909 [90%CI: 0.9106, 1.3070] in young men (≤ 45 years) with ED and 0.8144 [90%CI: 0.7002, 0.9473] in elderly men (≥ 65 years) with ED [Study 13396]. The C_{max} ratio for the corresponding comparison was 0.7280 [95%CI: 0.6156, 0.8610] for young men and 0.7389 [90%CI: 0.6248, 0.8739] for elderly men. In young men with ED, the terminal half-life of the M-1 metabolite following single dose administration of ODT 10 mg (vs single dose administration of FCT 10 mg) was 2.7 hours (vs 2.4 hours) and in elderly men the corresponding comparison was 2.8 hours (vs 3.5 hours). There was no significant accumulation of the M-1 metabolite following repeat once daily dosing of ODT 10 mg in men with ED aged ≤ 45 years or ≥ 65 years as assessed by both the AUC and C_{max}. Overall, the data showed that the difference in the PKs of the M-1 metabolite between ODT 10 mg and FCT 10 mg are unlikely to be clinically significant.

Inter-individual Variability

All the PK studies assessed inter-individual differences by the coefficient of variation (CV%). In all the relevant PK studies, the CV% of vardenafil and the M-1 metabolite for all PK parameters following ODT 10 mg and FCT 10 mg were marked indicating significant inter-individual variability. These findings are consistent with those previously observed with the FCT formulation. The Levitra PI notes that there is considerable "inter-subject and intra-subject variability in the observed pharmacokinetic parameters" due to extensive first-pass metabolism of vardenafil.

Pharmacokinetics in the Elderly

In elderly men with ED (aged≥ 65 years), the vardenafil AUC was 21% higher and the vardenafil C_{max} was 19% lower following single dose ODT 10 mg compared with single dose FCT 10 mg [Study 13369]. In young men with ED (aged≤ 45 years), the vardenafil AUC was 29% higher and C_{max} 8% lower following single dose ODT 10 mg compared with single dose FCT 10 mg [Study 13369].

In the comparison between elderly men (aged≥ 65 years) and younger men (aged < 65 years) with ED following single dose ODT 10 mg administration, the vardenafil AUC was 38% higher and the C_{max} was 21% higher in elderly men compared with younger men [Study 13396]. Similarly, in Study 12093, the corresponding comparisons showed that the vardenafil AUC was 17% higher and C_{max} was 33% higher in elderly men (≥ 65 years) compared with younger men (18-64 years) with ED. In both single dose studies the 90% CI of both ratios (expressed as a percentage) were not contained within the standard bioequivalence interval of 80-125%. Steady state vardenafil AUC and C_{max} following multiple once daily doses of the ODT 10 mg formulation were 31% and 16% higher, respectively, in elderly men (≥ 65 years) compared with young men (≤ 45 years) with ED [Study 13396]. The 90% CI of both the AUC and C_{max} ratios (expressed as a percentage) were not contained within the standard bioequivalence interval of 80-125%.

Pharmacokinetic Studies in Healthy Subjects

Study 10021 – PKs of a Vardenafil Solution

Study 10021 was designed to investigate whether absorption of vardenafil was faster after sublingual (non-swallowed) than oral (swallowed) administration. The primary objective was to investigate the absorption and relative bioavailability of vardenafil solution after a single sublingual dose of 10 mg in healthy young male subjects. The secondary objectives were to investigate PKs, safety and tolerability of a 10 mg vardenafil solution following sublingual (non-swallowed) and oral (swallowed) administration. The study was conducted in Germany between 8 December 1998 and 8 January 1999.

The main results of the study will be only briefly discussed as neither the vardenafil solution nor sublingual administration is being proposed for approval. The study was a randomized, non-blinded, two-way crossover design. It included ten healthy young male subjects (mean age 33.8 years [range 26-43], all Caucasian). The subjects received a single sublingual or oral dose of vardenafil in randomized order. Fasting sublingual administration was carried out in the morning with subjects sitting and being instructed not to swallow. After 15 minutes the contents of the mouth were emptied and collected and vardenafil concentrations analysed in order to estimate the amount of drug absorbed following sublingual administration. The mouth was then rinsed five times by 20 mL of tap water each. Fasting oral (swallowed) was carried out in the morning with 100 mL of tap water. After both administrations subjects remained fasting for 4 hours.

Results

Based on the area under the plasma concentration time curve from zero time to infinity ($AUC_{0\text{-}inf}$) ratio, the vardenafil relative bioavailability of the sublingual (non-swallowed) 10 mg solution was 24.6% [90% CI: 17.0, 35.6%] compared with the oral (swallowed) 10 mg solution. The vardenafil T_{max} following sublingual (non-swallowed) administration was 2.75 hours [range 1.25-4.00] compared with 0.75 hours [range 0.33-1.25] following oral (swallowed) administration. The mean terminal half-lives were similar for the sublingual (3.5 hours) and oral (3.6 hours) doses. The lag time was pronounced after oral (swallowed)

administration with vardenafil being quantifiable at first time points between 0.33 and 2.0 hours for half of the subjects and 8 hours and later for the other half of the subjects.

The amount of vardenafil recovered in the mouth washings following sublingual (non-swallowed) administration was 92% of the administered dose [range 48% to 113%]. If it is assumed that a negligible amount of vardenafil was swallowed when administered sublingually, it can be inferred that only about 8% (0.8 mg) of the administered 10 mg dose was absorbed through the oral mucosa. The geometric mean vardenafil $AUC_{0\text{-}inf}$ following sublingual (non-swallowed) administration was 4.9 µg*h/L (CV=33%) and 19.9 µg*h/L (CV=32%) following oral (swallowed) administration. If it is assumed that 10 mg of vardenafil is absorbed following oral administration and 0.8 mg is absorbed following sublingual (non-swallowed) administration then the relative bioavailability of vardenafil (sublingual/oral) based on the actual dose absorbed is 308%: that is, the ratio of AUC/Dose (absorbed) for sublingual and swallowed administration.

Evaluator's Comments

This was a good quality PK study. The relative bioavailability (ratios of AUC) of vardenafil 10 mg was 24% following sublingual (non-swallowed) administration compared with oral (swallowed) administration. The results showed that only about 8% of a sublingual dose is absorbed through the oral mucosa.

Study 12769 [PH-35349] – PKs of the ODT 10 mg Formulation

Study 12679 was a Phase I, randomised, open-label, single-dose, four-way crossover study in healthy young male volunteers. This study is summarised in Section II. The primary objectives were to compare the PKs (fed vs fasting) of the vardenafil 10 mg ODT formulation taken with a high-fat, high-calorie breakfast (without water) and taken fasting (with water). The secondary objectives were to compare the PKs (ODT vs FCT) of the 10 mg ODT formulation taken fasting (without water) and the 10 mg FCT formulation taken fasting (with water), and to investigate the safety and tolerability of the treatments.

The study was conducted at a single centre in Germany between 18 July 2007 and 5 September 2007.

The inclusion criteria included healthy, white males aged 18-50 years with normal body weight. The exclusion criteria were typical for PK studies involving a PDE5 inhibitor.

Subjects were randomized to one of four treatment groups (see Table 2 below). In Treatments 1 (reference) and 2 (test 1), sitting subjects placed the ODT on the tongue and were instructed not to chew the tablet but to manipulate it with the tongue against the palate once every second and swallow once the tablet had disintegrated. In Treatments 3 (test 2) and 4 (comparator), the respective ODT and FCT tablets were swallowed with approximately 180 mL of water.

Table 2: Study 12769 – Four vardenafil treatment groups.

1 - Reference	Vardenafil ODT 10 mg taken without water in the fasting condition.
2 - Test 1	Vardenafil ODT 10 mg taken without water 30 minutes after start of a high-fat, high-calorie American breakfast eaten within 30 minutes or less.
3 - Test 2	Vardenafil ODT 10 mg swallowed with water in the fasting condition.
4 - Comparator	Vardenafil FCT 10 mg swallowed with water in the fasting condition.

The treatment sequence was determined by a randomization list and randomization was carried out after the pre-study examination. Each subject participated in the four treatment periods with a wash-out period of at least 5 days (that is, more than 5 times the terminal half-life of vardenafil of about 4-5 hours). The total duration of the study for each participant was 6 weeks.

The study included PK parameters of vardenafil and M-1. The primary PK parameters were:

- AUC - area under the plasma concentration vs time curve from zero to infinity after single (first) dose,
- C_{max} - maximum drug concentration in plasma after single dose administration, and
- AUC_{0-tn} - AUC from time 0 to the last data point (this was primary only if mean AUC_{tn-inf} (AUC from the last data point to infinity) was > 20% of AUC.

The secondary PK parameters were:

- AUC_{0-tn} unless primary,
- AUC_{norm} - AUC divided by dose per kg body weight,
- AUC/D - AUC divided by dose (mg),
- $C_{max,norm}$ - maximum drug concentration in plasma after single dose administration divided by dose (mg) per kg body weight,
- C_{max}/D - maximum drug concentration in plasma after single dose administration divided by dose (mg),
- CL/f - total body clearance,
- MRT - mean residence time,
- T_{max}
- $t_{1/2}$ (half-life).

The sample size of at least 12 valid subjects was chosen empirically. Standard statistical methods were used to summarise subject demographic and baseline characteristics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables, and frequency tables). The PK parameters were calculated using the model-independent (compartment-free) method in accordance with sponsor guidelines and the PC-program WinNonlin Version 4.1. The PK variables were calculated and analysed using standard statistical methods. The logarithms of AUC and C_{max} were analysed using an analysis of variance (ANOVA) including sequence, subject (sequence), period and treatment effects. Point estimates (geometric least-square mean) and exploratory 90% CIs for the relevant AUC and C_{max} ratios were calculated by re-transformation of the logarithmic data.

The study enrolled 17 subjects: one withdrew informed consent before dosing and was replaced; and two discontinued before completion of all four periods due to adverse events (1 x elevated creatinine kinase [CK] associated with exercise, 1 x elevated CK due to motor-bike accident). The total number of subjects available for PK analysis was 13. Four of the 17 enrolled subjects had no valid PK data: one subject withdrew consent; two subjects discontinued prematurely because of adverse effects (AEs); and one subject had markedly reduced exposure in study period 1 due to vomiting following vardenafil 10 mg ODT (fasting).

Vardenafil Pharmacokinetic Parameters

The point estimates of the ratio and 90% confidence intervals for the primary vardenafil PK parameters of C_{max} and AUC are summarised in Table 3. The bioavailability of vardenafil (assessed by the AUC) was 44% higher with single dose ODT 10 mg (fasting without water) than with single dose FCT 10 mg (fasting with water), and the 90% CI for the ratio was not

within the standard bioequivalence range of 80-125%. The vardenafil C_{max} was 15% higher with single dose ODT 10 mg compared with single dose FCT 10 mg, and the 90% CI for the ratio was not within the standard bioequivalence range. The median time to reach T_{max} was 1.25 hours longer with single dose ODT 10 mg (fasting without water, 1.5 hours) compared with single dose FCT 10 mg (fasting with water, 0.75 hours), but the terminal half-lives were similar (4.2 and 3.9 hours, respectively). When the formulations were swallowed with water (fasting) the vardenafil AUC with single dose ODT 10 mg was 3% higher than with single dose FCT 10 mg, and the 90% CI of the ratio was within the standard bioequivalence range. The vardenafil C_{max} was 10% higher and the 90% CI of the ratio was outside the standard bioequivalence range for the corresponding comparison. The terminal half-lives were similar for single dose ODT 10 mg swallowed with water and single dose FCT 10 mg swallowed with water (3.8 and 3.9 hours, respectively). The vardenafil AUC was 29% lower when single dose ODT 10 mg was swallowed fasting with water compared with single dose ODT 10 mg administered fasting without water. The vardenafil C_{max} was 4% lower.

Table 3: Study 12769 - Point estimators (LS-means) and two-sided 90% confidence intervals for the ratios of the primary parameters AUC and C_{max} of vardenafil (results of ANOVA), n=13.

Ratio	Parameter	Ratio %	90% CI
ODT fasting with water /ODT fasting without water	AUC	71.39	65.29, 78.05
	Cmax	96.23	79.11, 117.05
ODT fed with breakfast without water/ODT fasting without water	AUC	97.94	89.48, 107.20
	Cmax	64.66	53.03, 78.83
ODT fasting without water/FCT fasting with water	AUC	144.12	131.67, 157.75
	Cmax	114.66	94.04, 139.80
ODT fasting with water/FCT fasting with water	AUC	102.88	93.99, 112.61
	Cmax	110.33	90.49, 134.53
ODT with breakfast/FCT fasting with water	AUC	141.15	129.10, 154.33
	Cmax	74.13	60.95, 90.17

Effect of Food on Vardenafil Pharmacokinetics

When single dose ODT 10 mg was administered with a high fat, high calorie breakfast (without water) the vardenafil AUC was reduced by about 2% compared with single dose ODT 10 mg administered fasting (without water), and the 90% CI of the ratio was within the standard bioequivalence range. The vardenafil C_{max} was about 35% lower and the 90% CI was outside the standard bioequivalence range for the corresponding comparison. Food increased the median T_{max} by 1 hour, from 0.5 hours fasting to 1.5 hours with food. The terminal vardenafil half-lives were similar following single dose ODT 10 mg with food without water (4.7 hours) compared with single dose ODT fasting without water (4.7 and 4.2 hours, respectively).

M-1 Metabolite Pharmacokinetics

The point estimate of the ratio and 90% confidence intervals for the M-1 PK parameters for C_{max} and AUC are summarised below in Table 4.

Table 4: Study 12769 - Point estimators (LS-means) and two-sided 90% confidence intervals for the ratios of the primary parameters AUC and C_{max} of the M1 metabolite (results of ANOVA), n=13.

Ratio	Parameter	Ratio %	90% CI
ODT fasting with water /ODT fasting without water	AUC	87.75	80.74, 95.36
	Cmax	116.75	97.08, 140.40
ODT with breakfast without water/ODT fasting without water	AUC	68.95	63.38, 75.02
	Cmax	48.45	40.20, 58.41
ODT fasting without water/FCT fasting with water	AUC	117.56	107.86, 128.13
	Cmax	100.27	83.19, 120.87
ODT fasting with water/FCT fasting with water	AUC	103.15	94.61, 112.46
	Cmax	117.07	97.12, 141.11
ODT with breakfast/FCT fasting with water	AUC	81.06	74.41, 88.31
	Cmax	48.59	40.40, 58.43

Evaluator's Comments

This was a good quality single dose PK study in healthy young males. Vardenafil was "suprabioavailable" as assessed by the AUC following single dose ODT 10 mg (fasting without water) compared with single dose FCT 10 mg (fasting with water). The AUC was 44% higher and the C_{max} was 15% higher after single dose ODT 10 mg fasting (without water) compared with single dose FCT 10 mg fasting (with water), and the 90% CI of both ratios was outside the standard bioequivalence range. The median T_{max} was 1.25 hours longer with ODT 10 mg fasting (without water) than with FCT 10 mg fasting (with water). The "suprabioavailability" of the ODT formulation appears to be due to that proportion of the administered dose which is absorbed though the oral mucosa and consequently not subject to first-pass metabolism.

When single dose ODT 10 mg was swallowed with water (fasting) it was no longer "suprabioavailable" when compared with single dose FCT 10 mg when swallowed with water (fasting). The vardenafil AUC for the ODT formulation was only 3% higher than for the FCT formulation, and the 90% CI of the ratio was within the standard bioequivalence range. The vardenafil C_{max} was 10% higher for the ODT formulation compared with the FCT formulation, and the 90% CI of the ratio was outside the standard bioequivalence range. The median T_{max} was similar for ODT 10 mg (0.5 hours) and FCT 10 mg (0.75 hours). The ODT and FCT comparison show that no untoward clinical effects would be expected if a patient inadvertently swallowed a 10 mg ODT tablet as systemic exposures are not markedly different for the two formulations.

A high fat, high calorie breakfast had little effect on the bioavailability (AUC) of vardenafil following single dose ODT 10 mg, with the 90% CI for the "fed/fasted" ratio being within the standard bioequivalence range. However, food reduced the vardenafil C_{max} by about 35% and the 90% CI for the "fed/fasted" ratio was not within the standard bioequivalence range. Food had no effect on the T_{max} (median 1.5 hours both fed and fasted), and little effect on the terminal half-life (4.7 hours fed and 4.2 hours fasting). The fed/fasted data suggest that ODT 10 mg can be taken with or without food. In the pivotal clinical efficacy and safety studies,

ODT 10 mg was taken one hour before sexual activity without liquid, but there was no reference in the protocol to whether the drug was to be taken with or without food.

Pharmacokinetics in Males with Erectile Dysfunction

Study 13396 - Multiple Dose Study in Males with ED Stratified by Age

Study 13396 was a Phase 1, non-randomized, non-blinded, non-controlled, age-stratified, single-centre PK study in males with ED. The primary objectives were to investigate the effect of multiple once daily administration of ODT 10 mg on the PKs of vardenafil, to compare the bioavailability of ODT 10 mg to FCT 10 mg, and to assess the effect of age on the PKs of vardenafil following administration of ODT 10 mg. The secondary objectives were to investigate the safety and tolerability of the treatments. The study was conducted at the same centre as Study 12769 and conducted between 7 January 2009 and 19 March 2009. It was undertaken and conducted in accordance with the same procedures and guidelines as those in Study 12769.

The inclusion criteria included males aged 18 years with a history of ED for at least 6 months. ED was defined as "the inability to achieve and maintain an erection of the penis sufficient to complete satisfactory sexual intercourse".[4] The exclusion criteria were extensive but appropriate for a Phase I PK study of a PDE5 inhibitor.

The study enrolled 16 subjects aged 18 - 45 years, 6 subjects aged 46 - 64 years, 7 subjects aged 65 - 69 years, and 9 subjects aged ≥70 years. Vardenafil FCT 10 mg was given as a single dose at the start of the treatment period (Day 1). After a wash-out phase (Day 2 and Day 3), a multiple dose phase of 10 days with once daily administration of vardenafil ODT 10 mg without water followed (Days 4 - 13). For each subject, the study consisted of a 13 day study period with 3 profile days (Day 1, Day 4, and Day 13). On the profile days, the study drug was administered after fasting for at least 10 hours. On all other days of the treatment period, the study drug was administered after a standardised continental breakfast at the study centre.

The PK parameters of vardenafil and M-1 were calculated using standard model independent (compartment free) methods.

On Day 1, the primary PK parameters of FCT 10 mg were AUC and C_{max}, and the secondary PK parameters were AUC_{norm}, AUC/D, $C_{max.norm}$, Cmax/D, T_{max}, $t_{1/2}$, MRT, and CL/f. On Day 4, the primary PK parameters of ODT 10 mg were AUC, AUC_{τ}, C_{max}, f_{rel} [ODT (Day 3) / FCT (Day 1)], and the secondary parameters were the same as those for FCT 10 mg on Day 1. On Day 13, the primary PK parameters of ODT 10 mg were $AUC_{\tau,ss}$ and $C_{max,ss}$, and the secondary parameters were mostly the steady state equivalents of those for ODT 10 mg assessed on Day 4. The definitions of the PK parameters were those used in Study 12769.

The PK parameters were summarised by age group using standard descriptive statistical methods. The logarithms of AUC and C_{max} were analysed using an ANOVA model which included fixed effects for the factors of day, age group, and the day x age group interaction as well as random effects for the subject (age group) factor. Based on these analyses, point estimates (least square means) and exploratory 90 % CIs for age group and/or formulation ratios were calculated by re-transformation of the logarithmic data.

The study enrolled 36 subjects and 34 were included in the PK analysis. The PK analysis compared subjects aged ≥ 65 years vs subjects aged ≤ 45 years ; subjects aged ≥ 65 years vs subjects aged <65 years; and all 4 age strata (18 - 45 years, 46 - 64 years, 65 - 69 years, and

[4] NIH: Consensus Conference 1993:83.

≥70 years). The primary PK comparison was undertaken between subjects aged≥ 65 years (n=14) and subjects aged ≤ 45 years (n=14). This comparison excluded PK data on 6 subjects aged 46-64 years.

Single dose comparison of FCT 10 mg (Day 1) and ODT (Day 4).

Following single dose ODT 10 mg, AUC and C_{max} were 39% and 21% higher, respectively, in the ≥ 65 years age group than in the ≤ 45 year age group. Following single dose FCT 10 mg, AUC and C_{max} were 48% and 38% higher, respectively, in the≥ 65 years age gro up than in the ≤ 45 year age group. These results are likely to be due to decreased systemic clearance of vardenafil in the older compared with the younger age group (mean $t_{1/2}$ = 4.7 hours [FCT] and 4.2 hours [ODT] in patients aged < 45 years, and mean $t_{1/2}$ = 6.2 hours [FCT] and 6.0 hours [ODT] in patients aged ≥ 65 years). The median T_{max} was the same for both age groups for FCT 10 mg (0.75 hours), but the median T_{max} for ODT 10 mg was shorter for the older than the younger age group (0.9 and 1.50 hours, respectively). The inter-subject variability in both the C_{max} and AUC was marked for both formulations in both age groups.

The relevant point estimates and 90% CIs for the AUC and C_{max} ratios in the ≥ 65 years and ≤ 45 year age groups for single dose ODT 10 mg and single dose FCT 10 mg are summarised in Table 5. The bioavailability in both age groups was greater following single dose ODT 10 mg compared with single dose FCT 10 mg as assessed by the AUC ratio: 129.2 % [90%CI: 116.6-143.2] in the younger age group, and 120.9% [90% CI: 109.1-133.9] in the older age group. However, the C_{max} in both age groups was lower with single dose ODT 10 mg compared with single dose FCT 10 mg: 8% [90%CI: 15-25] lower in the younger age group, and 19% [90% CI: 0-35] lower in the older age group. The AUC ratio [ODT/FCT] of M-1 was 109% [90%CI: 91.1-130.1] in the younger age group and 81.4% [90%CI: 70.0-94.7] in the younger age group, and the respective C_{max} ratios were 72.8% [90%CI: 61.6-86.1] and 74.0% [90%CI: 62.5-87.4].

Table 5: Study 13396 – Point estimates (geometric mean LS) and 90% CIs of vardenafil AUC and C_{max} following single doses of FCT 10 mg (Day 1) and ODT 10 mg (Day 4) in the ≤ 45 years (n=14) and ≥ 65 (n=14) years age groups.

Parameter	Subgroup	Ratio	Geo. Mean (LS)	90% CI
AUC	FCT 10 mg	≥ 65: ≤ 45 years	1.4830	1.3385 – 1.6432
	ODT 10 mg	≥ 65: ≤ 45 years	1.3872	1.2520 – 1.5371
	≤ 45 years	ODT:FCT	1.2922	1.1663 – 1.4318
	≥ 65 years	ODT:FCT	1.2088	1.0909 – 1.3393
Cmax	FCT 10 mg	≥ 65: ≤ 45 years	1.3850	1.1207 – 1.7116
	ODT 10 mg	≥ 65: ≤ 45 years	1.2112	0.9801 – 1.4969
	≤ 45 years	ODT:FCT	0.9239	0.7476 – 1.1417
	≥ 65 years	ODT:FCT	0.8080	0.6538 – 0.9985

Comparison of ODT 10 mg multiple dose (Day 13) with single dose (Day 4).

Following multiple dosing with ODT once daily, the vardenafil accumulation index for AUC (R_{Lin} = $AUC_{r,ss}/AUC_{day4}$) at Day 13 was 109% [90%CI: 95-124] in the ≤ 45 year age group, and 103% [90%CI: 91-116] in the ≥ 65 year age group. The 90% CI of the R_{Lin} for the two age groups was within the standard bioequivalence interval of 80-125%. The corresponding

vardenafil accumulation index for C_{max} ($R_AC_{max} = C_{max,ss}/C_{max}$) at Day 13 was 116% [90%CI: 91-148] in the ≤ 45 year age group, and 111% [90%CI: 89-140] in the ≥ 65 year age group. The 90% CI for the R_AC_{max} for both age groups was not within the standard bioequivalence interval of 80-125%. Similar accumulation results were observed for M-1 as seen for vardenafil.

The mean elimination half-life of vardenafil following multiple once daily administration of ODT 10 mg was 4.5 hours in younger patients and 5.7 hours in older patients. The $T_{max.ss}$ was 1.0 hour in the younger patients and 0.75 hours in the older patients. The vardenafil AUCτ,ss and $C_{max,ss}$ at Day 13 following ODT 10 mg multiple daily dosing were 31% and 16% higher, respectively, in older compared with younger patients. The corresponding results for M-1 were 48% for the AUCτ,ss and 41% for the $C_{max,ss}$ in older compared with younger patients. The main repeat dose PK parameters for vardenafil are found in Table 6.

Table 6: Study 13396 – Point estimates (geometric mean LS) and 90% CIs of vardenafil AUC and C_{max} following multiple doses (MD) of ODT 10 mg (Day 4-13) in the ≤ 45 years (n=14) and ≥ 65 (n=14) years age groups.

Parameter	Subgroup	Ratio	Geo. Mean (LS)	90% CI
AUCss at Day 13	ODT 10 mg SD	≥ 65: ≤ 45 years	1.3872	1.2232 – 1.5732
	ODT 10 mg MD	≥ 65: ≤ 45 years	1.3111	1.1445 – 1.5019
	≤ 45 years	ODT MD : ODT SD	1.0864	0.9483 – 1.2445
	≥ 65 years	ODT MD: ODT MD	1.0267	0.9054 – 1.1644
Cmax,ss at Day 13	ODT 10 mg SD	≥ 65: ≤ 45 years	1.2112	0.9659 – 1.5189
	ODT 10 mg MD	≥ 65: ≤ 45 years	1.1639	0.9114 – 1.4862
	≤ 45 years	ODT MD : ODT SD	1.1588	0.9074 – 1.4797
	≥ 65 years	ODT MD : ODT SD	1.1135	0.8879 – 1.3963

Evaluator's Comments

Study 13396 was a good quality PK study. Following single dose ODT 10 mg, the vardenafil AUC and C_{max} were 39% and 21% higher, respectively, in subjects aged ≥ 65 years compared with those aged ≤ 45 years. Following multiple dose ODT 10 mg once daily from Day 4 to Day 13, the vardenafil $AUC_{\tau,ss}$ and $C_{max,ss}$ were 31% and 16% higher, respectively, in the older compared with the younger age group. Following single dose FCT 10 mg, the vardenafil AUC and C_{max} were 48% and 39% higher, respectively, in the older compared with the younger age group. The single dose vardenafil AUC (that is, bioavailability) was 29% higher with ODT 10 mg compared with FCT 10 mg in the younger age group and 21% higher in the older age group. The single dose vardenafil C_{max} was 8% lower with ODT 10 mg compared with FCT 10 mg in the younger age group and 19% lower in the older age group.

Comparison between single and multiple dose ODT 10 mg administration showed that vardenafil, as assessed by the relevant AUC ratio, did not significantly accumulate at Day 13 following once daily administration from Day 4 in subjects aged ≤ 45 years and ≥ 65 years (109% and 103%, respectively). The observed increase in the C_{max} from Day 4 to Day 13 in the younger and older age groups was 16% and 11%, respectively. The vardenafil elimination half-life was similar following single dose ODT 10 mg (Day 4) and multiple dose ODT 10 mg (Day 14) in both the younger (4.2 and 4.5 hours, respectively) and older (6.0 and 5.7

hours, respectively) age groups. The vardenafil elimination half-life was 1.2 hours longer in the younger age group (4.5 hours) than the older age group (5.7 hours) following multiple dose ODT 10 mg.

Study 12093 – Sub-group PK Study Stratified by Age - Pivotal Study 12093

The pivotal efficacy and safety study included a PK sub-group analysis in 25 patients (n=12 aged 18-64 years; n=13 aged ≥ 65 years). The sub-group analysis assessed the PKs of vardenafil and M-1 following open-label single dose ODT 10 mg at Visit 5 (12 weeks + 2 days), irrespective of previous treatment (ODT 10 mg or placebo). Single dose ODT 10 mg was given without water following an overnight fast and dosing was preceded by a wash-out of at least 48 hours.

Standard PK parameters were calculated and standard statistical PK methodology was used to analyse the results (consistent with the methods described in the previously reviewed PK studies). A sample size of 24 patients had 82% power to detect a difference between a null hypothesis regression slope of 0.000 and an alternative regression slope of 0.012 assuming that the standard deviation of age was 24.3 years and the standard deviation of the residuals was 0.453.

The estimated ratio [age ≥ 65/age 18-64] and 90% CI of the C_{max} and $AUC_{0\text{-}inf}$ values for vardenafil and M-1 are summarised in Table 7. Bioavailability of vardenafil in patients aged ≥ 65 years was 17% greater [90% CI: -20, 73 %] than in patients aged 18-64 years as assessed by the $AUC_{0\text{-}inf}$. The respective value for the C_{max} was 33% higher [90%CI: -13, 102 %]. The 90% CIs for the $AUC_{0\text{-}inf}$ and C_{max} ratios were outside the accepted bioequivalence range of 80-125%. The CVs were large for vardenafil $AUC_{0\text{-}inf}$ and C_{max} in both treatment groups indicating marked inter-subject variability. The elimination half-life was similar in the 18-64 year and ≥ 65 year groups (5.4 hours [range 2.2-8.1] and 5.9 hours [range 4.0-10.1], respectively). The T_{max} of vardenafil was 1.50 hours [range 0.50-2.50] in the 18-64 year group and 1.00 hour [range 0.50-3.00] in the ≥ 65 year group. The effects of age on the PKs of M-1 were similar to those observed for vardenafil.

Table 7: Study 12093 - Point estimators (LS-means) and two-sided 90% confidence intervals for the ratios of $AUC_{0\text{-}inf}$ and C_{max} of vardenafil and M-1 (all subjects valid for PK).

Ratio	Analyte	Parameter	n	Estimated Ratio (%)	90% CI
Age ≥ 65/Age 18-64	Vardenafil	$AUC_{0\text{-}inf}$	24	117.42	79.59 – 173.23
Age ≥ 65/Age 18-64	Vardenafil	C_{max}	25	133.07	87.46 – 202.46
Age ≥ 65/Age 18-64	M1	$AUC_{0\text{-}inf}$	22	125.28	73.65 – 213.11
Age ≥ 65/Age 18-64	M1	C_{max}	25	123.84	80.12 – 191.42

Evaluator's Comments

This was a satisfactory PK sub-group study. The AUC and C_{max} were higher in patients aged ≥ 65 years compared with patients aged 18-64 years. The 90% CI of both the mean AUC and C_{max} ratios was not within the accepted bioequivalence interval.

Clinical Evaluator's Overall Comment on the Pharmacokinetic Data

The bioavailability of vardenafil following single dose ODT 10 mg (fasting, without water) as assessed by the AUC was higher than that of single dose FCT 10 mg (fasting, with water) in healthy young men (44%), and young (29%) and elderly (21%) men with ED [Study 12769; Study 13396]. The corresponding values for the vardenafil C_{max} for the three respective groups were +15%, -8%, and -19%. The 90% CIs for the respective AUC and C_{max} ratios were not within the accepted bioequivalence interval of 80-125%. The data showed that

single dose ODT 10 mg (fasting, without water) and single dose FCT 10 mg (fasting, with water) are not bioequivalent in healthy young men and young and elderly men with ED.

In the single dose ODT 10 mg fed vs fasting study, food (high fat, high calorie breakfast) reduced the vardenafil AUC by 2% and the C_{max} by 35% [Study 12769]. The 90% CI for the AUC was within the accepted bioequivalent interval of 80-125%, but the 90% CI for the C_{max} was not within the accepted interval. Overall, the data suggest that the clinical effects of ODT 10 mg are unlikely to be significantly different irrespective of whether or not the formulation is taken with food.

The single dose ODT 10 mg data in men with ED showed that the AUC was 38% higher in men aged ≥ 65 years compared with men age ≤ 45 years [Study 13396]. The corresponding value for the vardenafil C_{max} was 21%. The multiple dose ODT 10 mg data in men with ED showed that vardenafil AUC_{ss} and $C_{max,ss}$ were 31% and 16% higher, respectively, in men aged ≥ 65 years compared with men aged ≤ 45 years [Study 13396]. In Study 12093, vardenafil AUC and C_{max} were also 17% and 33% higher, respectively, in men aged≥ 65 years compared with men aged 18-64 years with ED following single dose ODT 10 mg. Overall, the comparative data showed that vardenafil AUC and C_{max} were higher in elderly men compared with younger men with ED. This might be due to reduced vardenafil clearance in elderly compared with younger men. The multiple once daily ODT 10 mg data showed that accumulation of vardenafil was not marked, and did not significantly differ between age groups. The AUC was 8.6% (≤ 45 years) and 2.7% (≥ 65 years) higher following multiple dose compared with single dose in men with ED, and the corresponding values for the C_{max} were 16% and 11% [Study 13396].

Efficacy

Introduction

The submission included two, pivotal, Phase III, efficacy and safety studies of identical design, *Study 12093* [POTENT 1] and *Study 12094* [POTENT II]. The studies will be reviewed and reported on together. The acronym POTENT stands for "**P**ivotal phase III trial to investigate the efficacy and safety of **O**rodispersible **T**ablet vardenafil versus placebo in the treatment of men with **E**rectile dysfunction (ED) – a fixed-dose, double-blind, ra**N**domized multi-centre **T**rial". The basic features of the two pivotal studies are summarised in Table 8.

Table 8: Summary of the two pivotal studies POTENT I (Study 12093) and POTENT II (Study 12094).

Study number (Report number)	Study design	Study population	Study treatment	Primary efficacy variable	Statistical test	Safety assessment
12093 (A44851)	Fixed dose, double-blind, randomized, multi-center	Males with erectile dysfunction in stable heterosexual relationship, 50% elderly (≥65 years)	Levitra 10 mg ODT vs placebo 12 week on-demand treatment (PRN)	IIEF-EF Domain score at Week 12 or LOCF SEP2 (success rate of penetration) at Week 12 overall SEP3 (success rate of maintenance of erection) at Week 12 overall	Efficacy of the vardenafil ODT formulation is to be concluded if the baseline adjusted scores of the IIEF-EF domain and the overall success rates of SEP2 and SEP3 simultaneously prove to be statistically significant different ($p<0.05$) in favor of vardenafil compared to placebo	Laboratory parameters (blood, urine) Physical exam, ECG Vital signs AEs PK sampling in 24 subjects after completion of efficacy assessment
12094 (A45684)	Fixed dose, double-blind, randomized, multi-center	Males with erectile dysfunction in stable heterosexual relationship, 50% elderly (≥65 years)	Levitra 10 mg ODT vs placebo 12 week on-demand treatment (PRN)	IIEF-EF Domain score at Week 12 or LOCF SEP2 (success rates of penetration) at Week 12 overall SEP3 (success rate of maintenance of erection) at Week 12 overall	Efficacy of the vardenafil ODT formulation is to be concluded if the baseline adjusted scores of the IIEF-EF domain and the overall success rates of SEP2- and SEP3 simultaneously prove to be statistically significant different ($p<0.05$) in favor of vardenafil compared to placebo	Laboratory parameters (blood, urine) Physical exam ECG Vital signs AEs

Source:

Pivotal Studies POTENT I [12093] and POTENT II [12094].

Methods

The primary objectives of the two, pivotal Phase III studies were to compare the efficacy and safety of vardenafil ODT 10 mg with placebo over a 12 week treatment period in a general population of men with ED. The study medications were taken approximately 1 hour before intended sexual activity on an as required basis, but not more than once daily. Both studies required approximately 50% of the men on active treatment to be aged ≥ 65 years.

Both studies were multicentred, randomized, placebo-controlled, and parallel-group in design. *POTENT I* was carried out in 40 active investigational centres in Belgium, France, Germany, Spain, South Africa and the Netherlands between 25 April 2008 and 19 January 2009. *POTENT II* was carried out in 35 active investigation centres in the US, Canada, Mexico, and Australia between 28 April 2008 and 13 February 2009. Both studies were undertaken by urologists specialising in the diagnosis and treatment of male sexual disorders.

The protocols of both studies were approved by the appropriate ethics committees of all participating centres/countries. The studies were carried out under the supervision of the appropriate ethics committees and according to GCP ICH guidelines, relevant local laws, regulations, and organizational requirements. The studies were also conducted in accordance with the ethical principles of the Declaration of Helsinki.

The inclusion and exclusion criteria were identical for both studies. Inclusion criteria were:

1. Males aged ≥ 18 years.
2. Stable, heterosexual relationship for at least 6 months.
3. A history of ED for at least 6 months, defined by the NIH Consensus Development Panel on Impotence as “the inability to achieve and maintain an erection of the penis sufficient to complete satisfactory sexual intercourse”.
4. Subjects needed to have made at least four attempts at sexual intercourse on four separate days during the 4 week untreated baseline period. This was determined by the response to the following question at Visit 2: “Was sexual activity initiated with the intention of intercourse?”
5. At least 50% of attempts at sexual intercourse during the 4 week untreated baseline period needed to be unsuccessful. This was determined by the response to the following

questions at Visit 2 with at least one of the questions to be answered in the negative: (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?"; and (c) "Did your erection last long enough for you to have successful intercourse?"

6. Subjects were required to be highly motivated to obtain treatment for ED.
7. Written informed consent.

Evaluator's Comments

The exclusion criteria were extensive and consistent with studies of PDE5 inhibitors for the treatment of ED. Homosexual men were not included in the studies as there were no validated questionnaires available to assess efficacy in these men.

Treatment was identical in both studies. There was a 4-week run-in, without study medication followed by a 12-week treatment period with either vardenafil 10 mg orodispersible tablets (ODT) or matching placebo. In the 4-week run-in period, subjects reported attempts at sexual intercourse diary. The diary was reviewed at Visit 2 (Week 0) and subjects who had fail to meet the inclusion criteria relating to the number of attempts at sexual intercourse and the percentage of failed attempts at sexual intercourse were withdrawn from the study. In the 12-week treatment period dosing about 1 hour before sexual intercourse as required, but no more than one dose of study medication per day was to be taken. There was a 48-hour follow-up period after the last intake of study medication in which adverse events were recorded. There was a separate PK subgroup analysis undertaken after the 12-week treatment period. This PK subgroup analysis has been reviewed and described above in the relevant PK section.

Each subject was required to visit the site on four separate occasions over a period of 16 weeks (Visit 1 = Week -4; Visit 2 = Week 0; Visit 3 = Week 4; Visit 4 = Week 12). The end of the study was defined as the Last Patient Last Visit date (that is, date of the last follow-up telephone call after Visit 4 or Visit 5 for PK subjects).

Randomization took place at Visit 2 (Week 0). At this visit, subjects were stratified according to age (18 to 64 years; and ≥ 65 years) and randomized in a 1 to 1 ratio to vardenafil or placebo. In order to achieve balanced allocation of 50% of all subjects aged ≥ 65 years a forced randomization procedure was used based on previously allocated patients. Randomization was carried out using an Interactive Voice Response System (IVRS). Investigators and subjects were blinded to treatment allocation.

Vardenafil was supplied as 10 mg ODT and matching placebo tablets with the same peppermint taste. At Visit 2 (Week 0), all subjects received 30 tablets of study medication, which was sufficient for the first 4 weeks of treatment and at Visit 3 (Week 4), 60 tablets of study medication which was sufficient for the last 8 weeks of treatment. Subjects were instructed to place the tablet on the tongue and not to immediately swallow or chew the tablet, but to manipulate it with the tongue against the palate once every second and swallow once the tablet had disintegrated. Subjects were instructed not to take the tablet with liquid, and were instructed not to chew the particles after the tablet had disintegrated.

The three co-primary efficacy variables in both studies were:

1. IIEF-EF Domain score at Visit 4 (Week 12): This variable assessed the change from baseline to Week 12 (using the last observation carried forward [LOCF] for missing values) in the International Index of Erectile Function–Erectile Function (IIEF-EF) Domain scores. The IIEF is a standard, multi-dimensional, self-report questionnaire for the assessment of

male sexual function. [5] It includes 5 domains covering "erectile function", "orgasmic function," "sexual desire," "intercourse satisfaction", and "overall satisfaction".[5] The IIEF consists of 15 items, and the erectile function (EF) domain consists of Items 1, 2, 3, 4, 5 and 15. The scores on Items 1-5 range from 0-5 and the scores on Item 15 range from 1-5. The maximum score on the EF domain is 30 with lower scores representing more clinically severe ED. The EF total scores can be interpreted as: 6-10 severe dysfunction; 11-16 moderate dysfunction; 17-21 mild to moderate dysfunction; 22-25 mild dysfunction; and 26-30 no dysfunction.[6] Each subject was asked to complete the IIEF-EF questionnaire during Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 12) or at the Premature Discontinuation Visit.

2. SEP 2 (success rates of penetration) at Visit 4 (Week 12) overall: This variable assessed success rate of penetration by the question: "Were you able to insert your penis into your partner's vagina?" This is question 2 from the Sexual Encounter Profile (SEP 2).

3. SEP 3 (maintenance of erection) at Visit 4 (Week 12) overall: This variable assessed maintenance of erection by the question: "Did your erection last long enough for you to have successful intercourse?" This is question 3 from the Sexual Encounter Profile (SEP 3).

Both the SEP 2 and SEP 3 questions were included in the subject's diary and answers were recorded at each visit from randomisation to Week 12 and the overall success rate was used to assess efficacy. Investigators were not allowed to change or modify a subject's self-rating as documented in the diaries. Subjects were instructed to make diary entries within 24 hours after each attempt at sexual intercourse to increase accuracy. The subject brought his diary to each clinic visit so that data could be collected on an ongoing basis. A new subject diary was provided at each visit. The investigator or an appointed delegate instructed the subjects about the completion of the diary.

Evaluator's Comments

The primary efficacy variables are acceptable. These variables were used in the initial application to register Levitra film coated tablets, and are the standard variables used to assess efficacy of PDE5 inhibitor medicines. The IIEF and the EF domain have been psychometrically and linguistically validated in several languages. Only the EF domain of the IIEF is considered relevant to the claim of efficacy of vardenafil for the treatment of ED as it relates directly to the ability to achieve and maintain an erection sufficient for sexual intercourse.

The secondary efficacy variables included the following parameters:

1. Percentage of subjects achieving "back to normal" erectile function (IIEF-EF score ≥ 26) at Visit 4 (Week 12).

2. All diary questions, other than SEP 2 and 3, that concerned erectile function assessed over the entire treatment period (that is, ability to obtain an erection; satisfaction with the hardness of an erection; overall satisfaction with intercourse; ability to ejaculate).

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

4. The Treatment Satisfaction Scale (TSS) comparing baseline versus endpoint. The TSS is a validated self-report measure assessing satisfaction with various aspects of erectile function and treatment. It included two modules: the "unmedicated module" (8 items) was

[5] Rosen RC et al. The International Index of Erectile Function (IIEF): a multidimensional scale of assessment of erectile dysfunction. Urology 1997: 49: 822-830.

[6] Cappelleri JC et al. Diagnostic evaluation of the Erectile Function Domain of the International Index of Erectile Function. Urology 1999:54: 346-351.

administered at Visit 2 and was designed to cover the unmedicated 4-week, run-in period; and the "medicated module" (13 items) was administered at Visit 4 (or at the Premature Discontinuation Visit). Items were rated on a 5-point Likert scale. Both TSS modules contained the domains "Ease with Erection," "Erectile Function Satisfaction," "Pleasure from Sexual Activity," "Satisfaction with Orgasms" and "Confidence to Complete Sexual Activity." The after-treatment medicated module (administered at Visit 4 or the Premature Discontinuation Visit) also contained an additional domain of "Satisfaction with Medication."

5. A Global Assessment Question (GAQ) administered at the final visit only (or at the Premature Discontinuation Visit). The question was: "Has the treatment you have been taking over the past four weeks improved your erections? (Please compare to your erections before your participation in this study)."

The sample size was based on the three co-primary efficacy variables. Based on pooled data analyses from previous studies it was expected that elderly subjects (≤ 65 years) would show less improvement than younger subjects. As it was intended that *POTENT I* and *II* include at least 50% of elderly subjects it was expected that the treatment effect would be < 5 points (IIEF-EF) and 18% (SEP 2 and 3). Therefore, the study was powered on difference in treatment effects of 4 points for IIEF-EF scores, and 15% for SEP 2 and SEP 3 responses. Assuming standard deviations (SDs) of 7.5 points (IIEF-EF) and 30% (SEP 2, SEP 3), a two-sided t-test for independent samples would have 96% power (SEP 2, SEP 3) and 98% power (IIEF-EF) power if 112 subjects per treatment group were available for the ITT analysis. Adjusting this sample size for a 20% loss of subjects with no follow-up measurement after randomization required 140 subjects per treatment group.

All quantitative and categorical clinical variables were tabulated as descriptive statistics using standard statistical methods. Efficacy of drug treatment was claimed if the primary efficacy variables of IIEF-EF, and the overall success rates of the diary questions SEP 2 (penetration) and SEP 3 (maintenance) were simultaneously significant ($p<0.05$). No alpha adjustment for multiple testing of the co-primary endpoints was required under the restriction that the IIEF-EF, the SEP 2, and the SEP 3 had to be simultaneously significant. The analyses of the primary efficacy endpoints were based on the General Linear Model (GLM) using a fixed effects model with "treatment", "age stratum", and "pooled countries" as factors. An analysis of covariance (ANCOVA) model was the main method of analysis of the primary efficacy variables. Sequential separate ANCOVAs were conducted for Visits 3, 4, and LOCF for IIEF-EF scores, and "overall" success rates (that is, over the entire study period from Week 0 to Week 12) for SEP 2 and 3. The statistical models for the diary questions (including SEP 2 and 3) included an interaction factor of "pooled countries x treatment". The pooling of centres was done before unblinding the data. The intention was to have comparable sample sizes and homogenous clusters of centres which were comparable with regard to their health systems and cultural areas. This resulted in 4 country pools: (i) Germany, (ii) France and Spain, (iii) Netherlands and Belgium, and (iv) South Africa. The analyses of the secondary efficacy variables used a variety of standard statistical methods (for example, Fisher's exact test, ANCOVA). However, there was no adjustment of the alpha for multiple secondary analyses. Consequently, the p values > 0.05 for the secondary efficacy variable analyses are considered to be "nominally" significant rather than "confirmatory".

The primary analyses of the primary efficacy variables were in the intent-to-treat (ITT) population with secondary analyses in the per-protocol (PP) population. The secondary efficacy variables were analysed in the ITT population only. The ITT population included all randomized subjects who had taken at least one dose of study medication and who had

baseline and any post-baseline efficacy data using the LOCF method for missing data. The PP population included all ITT subjects with the following additional criteria: 12 weeks of randomized treatment provided they had no additional major protocol violations or if they did not prematurely discontinue due to lack of efficacy or due to drug-related adverse events; and no major protocol violations.

Evaluator's Comments

The statistical methodology was satisfactory and consistent with the TGA-adopted EU guideline.[7]

Results

In *POTENT I*, 409 patients were enrolled and 362 (88.5%) of these were randomized to vardenafil 10 mg ODT (n=186) or placebo (n=176). Of the 362 randomized patients, 170 (47.0%) were aged < 65 years and 192 (53.0%) were aged ≥ 65 years. Of the 362 randomized patients, 355 (98.1%) were included in the ITT analysis with 7 (1.9%) being excluded (4 because they never took the study drug and 3 because no post-baseline efficacy data were available). There were 32 (9%) randomized patients who terminated the study prematurely, 13 (7%) patients in the vardenafil group and 19 (11%) patients in the placebo group. The primary reasons for premature termination discontinuation stratified by age for all randomized patients are summarised in Table 9.

In *POTENT II*, 473 patients were enrolled and 339 (71.6%) of these were randomized to vardenafil 10 mg ODT (n=172) or placebo (n=167). Of the 339 randomized patients, 171 (50.4%) were aged < 65 years and 168 (49.6%) were aged ≥ 65 years. Of the 339 randomized patients, 331 (97.6%) were included in the ITT analysis and 8 (2.4%) were excluded (2 because they never took the study drug and 6 because no baseline efficacy data were available). There were 44 (13.0%) randomized patients who terminated the study prematurely, 21 (12.2%) in the vardenafil group and 23 (13.8%) in the placebo group. The primary reasons for premature termination discontinuation stratified by age for all randomized patients are summarised in Table 9.

[7] EMEA, ICH Topic E9, Statistical Principles for Clinical Trials, 18 March 1998. Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96).

Table 9: POTENT I and II - Primary reason for premature termination in randomized patients.

	POTENT I				POTENT II			
	V ODT < 65 yrs	V ODT ≥ 65 yrs	Placebo < 65 yrs	Placebo ≥ 65 yrs	V ODT < 65 yrs	V ODT ≥ 65 yrs	Placebo < 65 yrs	Placebo ≥ 65 yrs
Randomized	88	98	82	94	86	86	85	82
Premature Termination	8 (9%)	5 (5%)	7 (9%)	12 (13%)	11 (13%)	10 (12%)	13 (15%)	10 (12%)
Adverse Event	1 (1%)	2 (2%)	0 (0%)	1 (1%)	3 (3%)	1 (1%)	0 (0%)	1 (1%)
Consent Withdrawn	4 (5%)	1 (1%)	4 (5%)	3 (3%)	3 (3%)	3 (3%)	3 (4%)	1 (1%)
Insufficient Effect	1 (1%)	1 (1%)	2 (2%)	6 (6%)	2 (2%)	0 (0%)	5 (6%)	7 (9%)
Lost to Follow-up	2 (2%)	0 (0%)	0 (0%)	1 (1%)	2 (2%)	2 (2%)	2 (2%)	1 (1%)
Non-compliant	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Protocol Violation	0 (0%)	1 (1%)	0 (0%)	1 (1%)	1 (1%)	4 (5%)	3 (4%)	0 (0%)

Evaluator's Comments

A total of 882 patients were enrolled in the two studies, and 701 were randomized to vardenafil 10 mg ODT (n=358, 51%) or placebo (n=343, 49%). Of the 701 randomized patients, 341 (48.6%) were aged < 65 years and 360 (51.4%) were aged ≥ 65 years. The combined ITT populations included 686 patients (97.9% of the randomized patients). Patient disposition was similar in both studies. However, the percentage of randomized patients prematurely discontinuing was higher in POTENT II (13.0%, n=44) than in POTENT I (9%, n=32). The difference was due to a greater proportion of placebo-treated patients discontinuing in POTENT II (7.2%, 12/167) compared with POTENT I (4.5%, 8/176), and a greater proportion of patients with protocol violations in POTENT II (2.4%, 8/339) compared with POTENT I (0.6%, 2/362). The percentage of randomized patients aged ≥ 65 years was 53.0% in POTENT I and 49.6% in POTENT II. These figures were consistent with the objective of the studies to include at least 50% of patients aged at least 50 years in the active treatment group.

Basic Demographics

In *POTENT I*, the average age of all patients in the ITT population treated with vardenafil 10 mg ODT and placebo was about 62 years in each group. The majority of patients in each group were White (about 67%), and information on race was missing in about 20% of patients in both treatment groups. All other basic demographic characteristics were similar in the two treatment groups. In *POTENT II*, the average age of all patients in the ITT population treated with vardenafil 10 mg ODT was about 62 years of age compared with about 61 years of age in the placebo group. The majority of patients in both treatment groups were White (about 69%), and the rest of the population in both groups was predominantly Hispanic (about 20-23%). All other basic demographic characteristics were similar in the two treatment groups. The relatively high average age in both *POTENT I and II* was due to the increased number of elderly patients (≥ 50%) required in the active treatment group in each study.

In *POTENT I*, the average age of patients in both treatment groups was about 53 years in the ITT population aged < 65 years and the other basic demographic characteristics in both treatment groups were similar. The average age of patients in both treatment groups was about 70 years in the ITT population aged ≥ 65 years and all other basic demographic characteristics in both treatment groups were similar. In *POTENT II*, the average age of patients in the vardenafil 10 mg treatment group was 53.5 years and 52.5 years in the placebo group in the ITT population aged < 65 years and the other basic demographic characteristics in both treatment groups were similar. The average age of patients in both treatment groups

was about 70.5 years in the ITT population aged ≥ 65 years of age and all other basic demographic characteristics in both treatment groups were similar.

Symptoms of ED in the Previous 6 Months

In *POTENT I and II*, the most common symptoms associated with ED during the 6 months before enrolment in the safety population were inability to maintain an erection during intercourse (97.2%, 348/358 and 93.8%, 316/337; respectively), followed by inability to penetrate the vagina (90.8%, 325/ 358, and 87.8%, 296/337; respectively), and inability to obtain an erection (75.4%, 270/358 and 80.4%, 271/337; respectively). The ED symptom pattern reported for the total safety population in both studies was comparable in both age strata in both treatment groups.

Medical History

In *POTENT I* vascular hypertensive disorders were the most frequently reported medical condition in the total safety population (41.3%, 148/358), followed by diabetes mellitus (30.2%, 108/358), and elevated cholesterol (21.2%, 76/358). For each of these conditions the incidence was higher in patients aged≥ 65 years than in patients aged < 65 years. In *POTENT II*, vascular hypertensive disorders were the most frequently reported medical condition in the safety population (42.1%, 142/337), followed by diabetes mellitus (20.8%, 70/337), and gastrointestinal atonic and hypomotility disorders (18.1%, 61/337). For each of these conditions the incidence was higher in patients aged≥ 65 years than in patients aged < 65 years.

Post Enrolment Concomitant Medications

In *POTENT I*, 78.5% (n=281) of all subjects in the safety population used concomitant medication post-enrolment (77.7%, n=143 vardenafil vs 79.3%, n=138 placebo). In *POTENT II*, 82.2% (277/337) of all subjects in the safety population used concomitant medication post-enrollment (81.9%, n=140 vardenafil vs 82.5%, n=137 placebo). Concomitant medication used in at least 10% of the safety population in both studies included agents for the renin-angiotensin system (~36%), serum lipid reducing agents (~33-37%), analgesics (~33%), antithrombotic agents (~27-29%), drugs for diabetes (~20-29%), topical products for joint and muscular pain (~22-31%), stomatological preparations (~17-28%), and drugs for "acid related disorders" (~13-16%).

In both *POTENT I and II*, additional treatment emergent medication after randomization were given to 12% (14.7% vardenafil vs 9.2% placebo) and 16% (17.0% vardenafil vs 15.1% placebo), respectively, of the safety population. The most frequently used additional treatment emergent medications given in *POTENT I and II* were analgesics which were reported in 4.4% (6.2% vardenafil vs 2.4% placebo group) and 5.5% (5.3% vardenafil vs 5.6% placebo), respectively, of the safety population.

Post Enrolment Use of Sexually Enhancing Treatments

In *POTENT I*, 11 subjects (3.1% of the safety population) received a sexually enhancing drug after initiation of the study drug (5 in the vardenafil group and 6 in the placebo group). In *POTENT II*, there were no reports of patients receiving a sexually enhancing drug after initiation of the study drug. In both *POTENT I and II,* one patient (aged ≥ 65 years) in the placebo group used a vacuum pump after randomization.

Previous Use of Sexually Enhancing Treatments

In *POTENT I*, 52.2% (187/358) of all subjects in the safety population had previously used "sexually enhancing medications" for ED before initiating the study drug: 51.2% of subjects

aged < 65 years (48.1% placebo vs 54.0% vardenafil), and 53.2% of subjects aged≥ 65 years (55.9% placebo vs 50.5% vardenafil). In addition, 7 subjects (2.0%) had previously used sexually enhancing devices. In *POTENT II*, 56.4% (190/337) of all subjects in the safety population had previously used "sexually enhancing medications" for ED before initiating the study drug: 55.3% of subjects aged < 65 (53.6% placebo vs 57.0% vardenafil), and 57.5% of subjects aged ≥ 65 years (61.0% placebo vs 54.1% vardenafil). In addition, 6 subjects (1.8%) had previously used sexually enhancing devices.

Compliance

In *POTENT I*, the average number of doses for the ITT population in the vardenafil group was 2.8 tablets per week (range 0-16) compared with 2.2 tablets per week (range 0-7) in the placebo group. Patients aged < 65 years in the vardenafil group took an average 3.2 tablets per week (range 1-16) compared with 2.1 tablets per week (range 0-7) in the placebo group. Patients aged ≥ 65 years in both the vardenafil and placebo groups took an average of 2.4 tablets per week (range 0-7). In *POTENT II*, the average number of doses for the ITT population in the vardenafil group was 2.7 tablets per week (range 0-8) compared with 1.8 tablets per week (range 0-7) in the placebo group. Patients aged 65 < years in the vardenafil group took an average of 3.0 tablets (range 0-8) per week compared with 1.9 per week (range 0-7) in the placebo group. Patients aged ≥ 65 years in the vardenafil group took an average of 2.3 tablets per week (range 0-6) compared with 1.7 tablets (range 0-7) in the placebo group. In general, in both *POTENT I and II* patients in the vardenafil groups took more vardenafil tablets per week than patients in the placebo groups.

Evaluator's Comments

Overall, baseline characteristics in the vardenafil and placebo groups in both pivotal studies were similar. The results suggest that significant bias in either pivotal study due to significant baseline differences between the two treatment groups is unlikely. The use of post enrollment medication did not differ significantly between treatment groups.

Results – Primary Efficacy Variables

<u>IIEF-EF Domain</u>

The summary statistics for the IIEF-EF change from baseline to Visit 4/Week 12 (LOCF) mean (SD) scores in the ITT population are summarised below in Table 10 [POTENT 1] and Table 11 [POTENT II]. The IIEF-EF scores can range from 1 (worst outcome) to 30 (best outcome).

Table 10: POTENT I - Mean (SD) scores and change from baseline to Visit 4/Week 12 (LOCF) for IIEF-EF in the ITT population.

	V 10 mg ODT < 65 years	V 10 mg ODT ≥ 65 years	Placebo < 65 years	Placebo ≥ 65 years	V 10 mg ODT Total	Placebo Total
Number	85	96	80	92	181	172
Baseline (Visit 2)	13.4 (4.78)	12.2 (4.87)	13.4 (4.74)	12.3 (5.44)	12.8 (4.85)	12.8 (5.14)
Week 12 (LOCF)	23.0 (6.95)	19.0 (8.81)	15.4 (7.64)	13.2 (7.42)	21.4 (8.12)	14.2 (7.59)
Change from B/Line	9.6 (6.28)	7.7 (8.19)	2.1 (7.33)	0.96 (6.42)	8.6 (7.40)	1.4 (6.86)

Table 11: POTENT II - Mean (SD) scores and change from baseline to Visit 4/ Week 12 (LOCF) for IIEF-EF in the ITT population.

	V 10 mg ODT < 65 years	V 10 mg ODT ≥ 65 years	Placebo < 65 years	Placebo ≥ 65 years	V 10 mg ODT Total	Placebo Total

Number	83	84	80	80	167	160
Baseline (Visit 2)	12.6 (5.57)	11.1 (5.79)	13.5 (5.08)	12.5 (6.35)	11.8 (5.72)	12.9 (5.75)
Week 12 (LOCF)	22.9 (8.43)	17.8 (9.08)	15.0 (7.58)	13.6 (7.82)	20.49 (9.11)	14.3 (7.71)
Change from B/Line	10.3 (7.78)	6.7 (8.06)	1.7 (2.68)	1.1 (6.01)	8.5 (8.11)	1.4 (1.6)

The results from the ANCOVA model for the least square (LS) mean treatment difference (vardenafil 10 mg ODT minus placebo) are summarised in Table 12 [POTENT I] and Table 13 [POTENT II]. In *POTENT I*, the result (ANCOVA) for age (< 65 minus ≥ 65 years) showed that the LS mean difference significantly favoured the younger over the older group (2.0 points [95%CI: 0.54, 3.47]; p=0.0076), while the result (ANCOVA) for "country" was not statistically significant (p=0.1297). In *POTENT II*, the result (ANCOVA) for age (< 65 minus ≥ 65 years) showed that the LS mean difference also significantly favoured the younger over the older group (2.35 points [95%CI: 0.81, 3.89]; p=0.0029), while the result (ANCOVA) for "country" was not statistically significant (p=0.2456). There was no analysis of the comparison of IIEF-EF scores between vardenafil and placebo in the separate age strata (< 65 years and ≥ 65 years).

Table 12: POTENT I – ANCOVA change from baseline to Visit 4/ Week 12 (LOCF) for IIEF-EF (ITT).

	Vardenafil 10 mg ODT (n=181)	Placebo (n=172)
Baseline (Visit 2): LS mean	12.86	12.85
Week 12 (LOCF): LS mean	21.48	14.38
Treatment Difference: LS mean	-7.11 [95%CI: -8.56, -5.66]	
P value	p < 0.001	

Table 13: POTENT II - ANCOVA change from baseline to Visit 4/ Week 12 (LOCF) for IIEF-EF (ITT).

	Vardenafil 10 mg ODT (n=167)	Placebo (n=160)
Baseline (Visit 2): LS mean	11.70	12.76
Week 12 (LOCF): LS mean	20.80	13.88
Treatment Difference: LS mean	-6.92 [95%CI: -8.45, -5.38]	
P value	< 0.0001	

SEP 2 (success rates of penetration)

The summary statistics for the change from baseline to Week 12 (overall interval) in the SEP 2 success rate for vaginal penetration in the ITT population are provided in Table 14 [POTENT I] and Table 15 [POTENT II]. The summary statistics report the arithmetic mean (SD) percentage success rates and the absolute changes in the mean (SD) rates from baseline to Week 12 (that is, overall treatment interval). Per-subject success rates were calculated as the total number of successes divided by the total number of sexual attempts in the overall interval from Week 0 to Week 12.

Table 14: POTENT I – Arithmetic mean success rates % (SD%) and change from baseline (Visit 2) to Visit 4/ Week 0-12 (Overall) for SEP 2 success rate in the ITT population.

	V 10 mg ODT < 65 years	V 10 mg ODT ≥ 65 years	Placebo < 65 years	Placebo ≥ 65 years	V 10 mg ODT All Patients	Placebo All Patients
Number	85	94	79	90	179	169
Baseline (Visit 2)	44.7 % (36.68)	34.6% (33.85)	43.1 % (36.86)	32.5% (34.77)	39.4 % (35.48)	37.5% (36.04)
Overall (Week 0-12)	80.5% (26.84)	69.8% (35.87)	48.6% (39.55)	41.2% (37.22)	74.9% (32.26)	44.7% (38.38)
Change from B/Line	35.8 % (33.63)	35.2% (38.06)	5.5% (42.82)	8.7% (28.41)	35.5% (35.93)	7.2% (35.79)

Table 15: POTENT II – Arithmetic mean success rates % (SD%) and change from baseline (Visit 2) to Visit 4/ Week 0-12 (Overall) for SEP 2 success rate in the ITT population.

	V 10 mg ODT < 65 years	V 10 mg ODT ≥ 65 years	Placebo < 65 years	Placebo ≥ 65 years	V 10 mg ODT All Patients	Placebo All Patients
Number	84	84	81	80	168	161
Baseline (Visit 2)	42.9% (35.61)	31.6% (36.11)	44.2% (33.53)	34.1% (36.11)	37.2% (36.20)	39.2% (35.10)
Overall (Week 0-12)	76.1% (33.85)	58.9% (39.33)	48.8% (38.83)	37.1% (37.18)	67.5% (37.59)	43.0% (38.35)
Change from B/Line	33.2% (33.27)	27.3% (37.39)	4.6% (34.12)	3.0 % (33.33)	30.2% (35.40)	3.8% (33.63)

The results from the ANCOVA model for the LS mean treatment difference (vardenafil 10 mg ODT minus placebo) are summarised below in Table 16 [POTENT I] and Table 17 [POTENT II]. In *POTENT I*, the results (ANCOVA) for "age" (p=0.2591) and "country" (p=0.3516) were not statistically significant, but there was a statistically significant interaction between "treatment" and "country" (p=0.0436). The statistically significant interaction between "treatment" and "country" reflected greater reported average differences between vardenafil and placebo in European countries (29.7% to 37.4%) compared with South Africa (9.5%). In *POTENT II*, the result (ANCOVA) for age (< 65 minus ≥ 65 years) showed that the LS mean difference significantly favoured the younger over the older group (7.7% [95%CI: 0.9, 14.5]; p=0.027]), and the result (ANCOVA) for "country" was also significant (p=0.0187). The nominally statistically significant difference for "country" appears to be due to lower SEP 2 success rates in Australian subjects compared with other countries. The LS mean of the SEP 2 endpoint was 51.0% in Australian subjects compared with 53.2% in the pooled Western US centres, 53.3 % in pooled Eastern US and Canada centres, and 66.5% in Mexico. There was no analysis of the comparison of SEP 2 success rates between vardenafil and placebo in the separate age strata (< 65 years and ≥ 65 years).

Table 16: POTENT I - ANCOVA change from baseline to Visit 4/Week 0-12 (Overall) for SEP 2.

	Vardenafil 10 mg ODT (n=179)	Placebo (n=169)
Baseline (Visit 2): LS Mean	40.38 %	38.76%

Overall (Week 0-12): LS Mean	73.73%	46.68%
Treatment Difference: LS mean	-27.04% [95%CI: -33.66, -20.43]	
P value	p < 0.0001	

Table 17: POTENT II - ANCOVA change from baseline to Visit 4/Week 0-12 (Overall) for SEP 2

	Vardenafil 10 mg ODT (n=168)	Placebo (n=161)
Baseline (Visit 2): LS Mean	36.37%	38.33%
Overall (Week 0-12): LS Mean	68.99%	43.02%
Treatment Difference: LS mean	-25.97 [95%CI: -32.69, -19.26]	
P value	p < 0.0001	

SEP 3 (success rates for maintenance)

The summary statistics for the change from baseline to Week 12 (overall interval) in the SEP 3 success rate for maintenance of erection in the ITT population are provided in Table 18 [POTENT I] and Table 19 [POTENT II]. The summary statistics report the arithmetic mean (SD) percentage success rates and the absolute changes in the mean (SD) rates from baseline to Week 12 (overall interval). Per-subject success rates were calculated as the total number of successes divided by the total number of sexual attempts in the overall interval from Week 0 to Week 12.

Table 18: POTENT I – Arithmetic mean success rates % (SD%) and change from baseline (Visit 2) to Visit 4/ Week 0-12 (Overall) for SEP 3 (ITT).

	V 10 mg ODT < 65 years	V 10 mg ODT ≥ 65 years	Placebo < 65 years	Placebo ≥ 65 years	V 10 mg ODT All Patients	Placebo All Patients
Number	85	93	78	86	178	164
Baseline (Visit 2)	16.3% (21.95)	10.4% (18.89)	14.5% (21.63)	14.5% (20.27)	13.2% (20.56)	14.5% (20.86)
Overall (Week 0-12)	70.8% (33.33)	59.6% (38.71)	29.7% (35.05)	22.3% (28.94)	65.0% (36.57)	25.8% (32.11)
Change from B/Line	54.5% (32.72)	49.2% (37.28)	15.2% (31.30)	7.7% (25.72)	51.7% (35.18)	11.3 % (28.67)

Table 19: POTENT II – Arithmetic mean success rates % (SD%) and change from baseline (Visit 2) to Visit 4/ Week 0-12 (Overall) for SEP 3 (ITT).

	V 10 mg ODT < 65 years	V 10 mg ODT ≥ 65 years	Placebo < 65 years	Placebo ≥ 65 years	V 10 mg ODT All Patients	Placebo All Patients
Number	84	84	81	79	168	160
Baseline (Visit 2)	16.4% (18.71)	9.3% (18.50)	15.5% (19.68)	15.5% (22.29)	12.9% (18.89)	15.5% (20.94)
Overall (Week 0-12)	69.6% (35.27)	48.1% (39.81)	30.7% (33.33)	24.3% (31.47)	58.8% (39.01)	27.5% (32.48)
Change from B/Line	53.2% (33.22)	38.8% (38.32)	15.2% (29.55)	8.7% (29.15)	46.0% (36.47)	12.0% (29.44)

The results from the ANCOVA model for the LS mean treatment difference (vardenafil 10 mg ODT minus placebo) are summarised in Table 20 [POTENT I] and Table 21 [POTENT II]. In *POTENT I*, the result (ANCOVA) for age (< 65 minus ≥ 65 years) showed that the LS mean difference significantly favoured the younger over the older group (7.10% [95%CI: 0.37, 13.83]; p=0.0386), but the results (ANCOVAs) for country" (p=0.9488) and the interaction between "country" and "treatment" (p=0.0796) were not statistically significant. In *POTENT II*, the results (ANCOVA) for age (< 65 minus ≥ 65 years) showed that the LS mean difference significantly favoured the younger group over the older group (10.9% [95%CI: 3.8, 17.9];p=0.0026), and the result (ANCOVA) for "country" was also significant (p=0.0369). The nominally statistically significant difference for "country" appears to be due to lower SEP 3 success rates in Australian subjects compared with other countries. The LS mean of the SEP 3 endpoint was 34.9% in Australian subjects compared with 44.9% in the pooled Western US centres, 42.5 % in pooled Eastern US and Canada centres, and 50.9% in Mexico. There was no analysis of the comparison of SEP 3 success rates between vardenafil and placebo in the separate age strata (< 65 years and ≥ 65 years).

Table 20: POTENT I - ANCOVA results for change from baseline to Visit 4/Week 0-12 (Overall) for SEP 3 (ITT).

	Vardenafil 10 mg ODT (n=178)	Placebo (n=164)
Baseline (Visit 2): LS Mean	13.60%	15.16%
Overall (Week 0-12): LS Mean	64.89%	26.70%
Treatment Difference: LS mean	-38.19% [95%CI: -45.02, -31.37]	
P value	p < 0.0001	

Table 21: POTENT II - ANCOVA results for change from baseline to Visit 4/Week 0-12 (Overall) for SEP 3 (ITT).

	Vardenafil 10 mg ODT (n=168)	Placebo (n=160)
Baseline (Visit 2): LS Mean	12.52%	15.18%
Overall (Week 0-12): LS Mean	60.02%	26.59%
Treatment Difference: LS mean	-33.45% [95%CI: -40.44, -26.33]	
P value	p < 0.0001	

Evaluator's Comments

Treatment with vardenafil 10 mg ODT was statistically significantly superior to placebo in both pivotal studies for the three primary endpoints. The results are clinically meaningful and satisfactorily establish the efficacy of vardenafil 10 mg ODT for the treatment of men with ED. There were no analyses of the primary efficacy endpoints comparing treatments in men stratified by age (that is, < 65 year and≥ 65 years). The reason for the lower SEP 2 and SEP 3 success rates in Australian subjects compared with subjects from other centres is unknown.

Secondary Efficacy Variables

In *POTENT I* and *II*, analyses of all secondary efficacy variables were nominally statistically significant in favour of vardenafil 10 mg ODT compared with placebo. The results are summarised below:

In *POTENT I* and *II*, vardenafil 10 mg ODT produced greater changes from baseline to Week 0 to 12 (overall) for SEP 1 "ability to obtain an erection", SEP 4 "satisfaction with hardness of erection", SEP 5 "overall satisfaction", and SEP 6 "ability to ejaculate"; $p < 0.001$ vs placebo for all comparisons.

In *POTENT I* and *II*, vardenafil ODT produced greater changes from baseline to Week 12 (LOCF) for all Treatment Satisfaction Scale (TSS) domains; $p < 0.0001$ vs placebo for all comparisons.

In *POTENT I*, vardenafil 10 mg ODT resulted in a higher percentage of patients reporting "back to normal" erectile function (40%, 72/181 vs 12%, 72/181 placebo); $p<0.0001$). Similarly in *POTENT II*, vardenafil 10 mg ODT resulted in a higher percentage of patients reporting "back to normal" erectile function (46%, 76/167 vardenafil vs 9%, 15/160 placebo; $p< 0.0001$).

In both *POTENT I* and *II*, treatment with vardenafil 10 mg ODT resulted in a statistically higher percentage of patients responding positively to the Global Assessment Question - "Has the treatment you have been taking for the past four weeks improved your erection?" In *POTENT I*, the vardenafil 10 mg ODT response was 72% (130/180) compared with the placebo response of 26% (43/168); $p<0.0001$. In *POTENT II*, the vardenafil 10 mg ODT response was 67% (107/160) compared with the placebo response of 24% (37/157); $p<0.0001$.

In both *POTENT I* and *II*, treatment with vardenafil 10 mg ODT resulted in fewer sexual attempts needed until first successful maintenance of erection (1.2 vs 3.6) and (1.4 vs 3.1), respectively. No statistical analyses of the results were provided.

Analysis Performed Across Trials – Study [PH-35849]

The submission included an integrated analysis [PH-35849] of the two pivotal Phase III studies [POTENT I and II]. The main objective of the integrated analysis was the assessment of overall safety, as well as safety in pre-defined subgroups, comparing vardenafil 10 mg

ODT with placebo. The secondary objective was the confirmation of the efficacy of vardenafil 10 mg ODT as assessed by the three main efficacy variables of IIEF-EF, SEP 2 and SEP 3, overall and in pre-defined subgroups.

The efficacy analysis was conducted in the ITT population. This population consisted of all randomized subjects who had taken at least one dose of the study drug and had baseline and any post baseline efficacy data. Missing post baseline data were handled by the last observation carried forward (LOCF) method.

The following patients subgroups were analysed: age dichotomised < 65 and≥ 65 year; age grouped <45 years, 45-<65 years, 65-<75 years, ≥ 75 years; history of cardiac disorders; history of arteriosclerosis, excluding cardiac and cerebral localisation; history of central nervous system (CNS) haemorrhages and cerebrovascular accidents; history of diabetes/diabetic complications; history of dyslipidaemia; history of hypertension; current antihypertensive treatments (0, 1, 2 or more different types); presence of renal impairment, creatinine clearance (CL_{CR}) > 80 mL/min (normal), CL_{CR} > 50-80 mL/min (mild), CL_{CR} > 30-50 mL/min (moderate), patients with severe renal impairment ($CL_{CR} \leq 30$ mL/min) were excluded from the pivotal studies; presence of hepatic impairment, excluding pregnancy related hepatic disorders, subjects with moderate and severe hepatic impairment as defined by Child-Pugh classes B and C were excluded from the pivotal studies.[8]

The primary efficacy variables were the baseline-adjusted IIEF-EF score at the last available observation (LOCF), and the success rates over the treatment period to (a) penetrate the partners' vagina (SEP 2), and to (b) maintain the erection to successful intercourse (SEP 3). The efficacy primary variables were identical to the primary efficacy variables in the two pivotal studies. There were no secondary efficacy variables in the integrated analysis. The statistical analysis of the IIEF-EF, SEP 2, and SEP 3 was conducted via an ANCOVA with baseline as covariate, and with treatment, age stratum and study as factors. The analyses were exploratory and, consequently, no alpha adjustments were made for multiplicity. The p-values of < 0.05 were considered to be "nominally" significant rather than "confirmatory". This approach differed from that in *POTENT 1* and *II* where no alpha adjustment for multiple testing of the three primary efficacy variables was required because successful efficacy needed all three primary variables to be significant ($p < 0.05$).

A subgroup was considered sufficiently sized if it contained at least 75 subjects per treatment subgroup (150 subjects in total equaling around 20% of study population). Underlying assumptions were an effect size (delta) of 4 with SD of 7.5 for IIEF-EF, and an effect size (delta) of 15% with SD of 30% for SEP 2 and SEP 3. Three subgroups were chosen for efficacy analysis: subjects with a history of diabetes / diabetic complications; subjects with a history of dyslipidaemia; and subjects with a history of hypertension.

In total, 701 subjects were randomized, 695 were valid for safety and 686 were valid for ITT analysis. Of 701 randomized subjects, 358 (51%) were randomized to vardenafil and 343 (49%) to placebo.

IIEF-EF Score

The summary statistics for the IIEF-EF scores are provided in Table 22. The ANCOVA result for the effect of treatment on the baseline adjusted Visit 4/Week 12 (LOCF) for IIEF-EF

[8] The **Child-Pugh score** is used to assess the prognosis of chronic liver disease. The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

score in the ITT population is summarised in Table 23. The ANCOVA showed nominally statistically significant superiority (p<0.0001) for vardenafil treatment when compared with placebo. There was no nominally statistical significant difference between the two pivotal studies (p=0.648).

Table 22: Integrated Analysis - Mean (SD) scores and change from baseline to Visit 4/ Week 12 (LOCF) for IIEF-EF (ITT).

	V 10 mg ODT < 65 years	V 10 mg ODT ≥ 65 years	Placebo < 65 years	Placebo ≥ 65 years	V 10 mg ODT Total	Placebo Total
Number	168	180	160	172	348	332
Baseline (Visit 2)	13. 0 (5.2)	11.7 (5.3)	13.3 (4.9)	12.4 (5.9)	12.3 (5.3)	12.8 (5.4)
Week 12 (LOCF)	23.0 (7.7)	18.9 (9.0)	15.2 (7.6)	13.3 (7.6)	20.9 (8.6)	14.2 (7.6)
Change from B/Line	10.0 (7.1)	7.2 (8.1)	1.9 (6.8)	1.0 (6.2)	8.6 (7.7)	1.4 (6.5)

Table 23: Integrated Analysis - ANCOVA results for change from baseline to Visit 4/ Week 12 (LOCF) for IIEF-EF (ITT).

	Vardenafil 10 mg ODT (n=348)	Placebo (n=332)
Baseline (Visit 2): LS mean	12.3 [95%CI: 11.8, 12.9]	12.8 [95%CI: 12.3, 13.4]
Week 12 (LOCF): LS mean	21.1 [95%CI: 20.4, 21.8]	14.1 [95%CI: 13.3, 14.8]
Treatment Difference: LS mean	-7.0 [95%CI: -8.1, -6.0]	
P value	p < 0.0001	

In the subgroup analysis of subjects < 65 years of age and ≥ 65 years of age the LS mean difference in IIEF-EF scores significantly favoured vardenafil compared with placebo in both age groups (ANCOVA; nominal p < 0.0001 for both groups). In subjects < 65 years of age the LS mean difference was 8.0 points [95%CI: 6.5, 9.6] in favour of vardenafil, and in subjects ≥ 65 years of age the LS mean difference was 6.1 points [95%CI: 4.6, 7.5] in favour of vardenafil. The overall LS mean difference between the two age groups was 2.1 points ([95%CI: 1.1, 3.2]; p=0.0001) in favour of the younger age group.

In the subgroup analyses of subjects with/without a history of diabetes mellitus, dyslipidaemia, or hypertension, the LS mean difference in IIEE-EF scores significantly favoured vardenafil compared with placebo in all subjects irrespective of history.

SEP 2 – 'Penetration'

The summary statistics for the SEP 2 ("penetration") results are summarised in Table 24. The ANCOVA result for the effect of treatment on the baseline adjusted Visit 4/Week 12 (LOCF) for IIEF-EF score in the ITT population is summarised in Table 25. The ANCOVA showed nominally statistically significant superiority (p<0.0001) for vardenafil compared with placebo. There was no nominally statistical significant difference between the two pivotal studies (p=0.051).

Table 24: Integrated Analysis - Arithmetic mean success rates % (SD%) and change from baseline (Visit 2) to Visit 4/ Week 0-12 (Overall) for SEP 2 (ITT).

	V 10 mg ODT < 65 years	V 10 mg ODT ≥ 65 years	Placebo < 65 years	Placebo ≥ 65 years	V 10 mg ODT All Patients	Placebo All Patients
Number	169	178	160	170	347	330
Baseline (Visit 2)	43.8% (36.1)	33.2% (34.9)	43.6% (35.1)	33.3% (35.3)	38.4% (35.8)	38.3% (35.5)
Overall (Week 0-12)	78.3% (30.5)	64.7% (37.8)	48.7% (39.1)	39.3% (37.2)	71.3% (35.1)	43.8% (38.3)
Change from B/Line	34.5% (33.4)	31.5% (37.9)	5.0% (38.5)	6.0% (30.9)	32.9% (35.7)	5.6% (34.8)

Table 25: Integrated Analysis - ANCOVA results for change from baseline to Visit 4/Week 0-12 (Overall) for SEP 2 (ITT).

	Vardenafil 10 mg ODT (n=347)	Placebo (n=330)
Baseline (Visit 2): LS Mean	38.5% [95%CI: 34.8, 42.2]	38.5% [95%CI: 34.6, 42.3]
Overall (Week 0-12): LS Mean	71.3% [95%CI: 68.0, 74.6]	43.9% [95%CI: 40.5%, 47.3]
Treatment Difference: LS mean	-27.4% [95%CI: -32.1, 22.7]	
P value	p < 0.0001	

In the subgroup analysis of subjects < 65 years of age and ≥ 65 years of age the LS mean difference in SEP 2 success rate at endpoint significantly favoured vardenafil compared with placebo in both age groups (ANCOVA; nominal p < 0.0001 for both groups). In subjects < 65 years of age the LS mean difference was 30.2% [95%CI: 23.5, 37.0] in favour of vardenafil, and in subjects≥ 65 years of age the LS mean difference was 24.7% [95%CI: 18.1, 31.3] in favour of vardenafil. The overall LS mean difference between the two age groups was 6.1% ([95%CI: 1.3, 10.8]; p=0.012) in favour of the younger age group.

In the subgroup analyses of subjects with/without a history of diabetes mellitus, dyslipidaemia, or hypertension, the LS mean difference in SEP 2 success rates significantly favoured vardenafil compared with placebo in all subjects irrespective of history.

SEP 3 – 'Maintenance'

The summary statistics for the SEP 3 ("maintenance") results are summarised in Table 26. The ANCOVA result for the effect of treatment on the baseline adjusted Visit 4/Week 12 (LOCF) for IIEF-EF score in the ITT population is summarised in Table 27. The ANCOVA showed a nominally statistically significant superiority (p<0.0001) for vardenafil treatment when compared with placebo. There was no nominally statistical significant difference between the two pivotal studies (p=0.261).

Table 26: Integrated Analysis - Arithmetic mean success rates % (SD%) and change from baseline (Visit 2) to Visit 4/ Week 0-12 (Overall) for SEP 3 (ITT).

	V 10 mg ODT < 65 years	V 10 mg ODT ≥ 65 years	Placebo < 65 years	Placebo ≥ 65 years	V 10 mg ODT All Patients	Placebo All Patients
Number	169	177	159	165	346	324
Baseline (Visit 2)	16.4% (20.4)	9.9% (18.7)	15.0% (20.6)	15.0% (21.2)	13.1% (19.7)	15.0% (20.9)
Overall (Week 0-12)	70.2% (34.2)	54.1% (39.6)	30.2% (34.1)	23.2% (30.1)	62.0% (37.8)	26.7% (32.3)
Change from B/Line	53.8% (32.9)	44.2% (38.0)	15.2% (30.3)	8.2% (27.3)	48.9% (35.9)	11.6% (29.0)

Table 27: Integrated Analysis - ANCOVA results for change from baseline to Visit 4/Week 0-12 (Overall) for SEP 3 (ITT).

	Vardenafil 10 mg ODT (n=346)	Placebo (n=324)
Baseline (Visit 2): LS Mean	13.1% [95%CI: 11.0, 15.2]	15.0% [95%: 12.8, 17.3]
Overall (Week 0-12): LS Mean	62.7% [95%CI: 59.3, 66.0]	26.0% [95%: 22.5, 29.5]
Treatment Difference: LS mean	-36.7% [95%CI: -41.5, -31.8]	
P value	p < 0.0001	

In the subgroup analysis of subjects < 65 years of age and ≥ 65 years of age the LS mean difference in SEP 3 success rates at endpoint nominally significantly favoured vardenafil compared with placebo in both age groups (ANCOVA; p < 0.0001 for both groups). In subjects < 65 years of age the LS mean difference was 39.0% [95%CI: 32.1, 45.0] in favour of vardenafil, and in subjects≥ 65 years of age the LS mean difference was 34.4% [95%CI: 27.6, 41.2] in favour of vardenafil. The overall LS mean difference between the two age groups was 9.4% [95%CI: 4.5, 14.2]; p=0.0002) in favour of the younger age group.

In the subgroup analyses of subjects with/without a history of diabetes mellitus, dyslipidaemia, or hypertension the LS mean difference in SEP 2 success rates between vardenafil and placebo was significant in all subjects.

Clinical Evaluator's Overall Conclusions on Clinical Efficacy

The clinical efficacy of vardenafil 10 mg ODT has been satisfactorily established in two pivotal placebo-controlled studies (POTENT I; POTENT II). In both pivotal studies, vardenafil 10 mg ODT was statistically significantly superior to placebo (p < 0.0001) for each of the three primary efficacy variables. In the two pivotal studies, the nominal p value was < 0.0001 in favour of vardenafil 10 mg ODT compared with placebo for all analysed secondary efficacy variables. However, no adjustment of the nominal significance level of p < 0.05 was made to account for the multiple analyses of the secondary efficacy variables. Consequently, the analyses of the secondary efficacy variables are considered to be exploratory rather than confirmative.

The integrated efficacy analysis of the data from the two pivotal studies showed that treatment with vardenafil 10 mg ODT was nominally statistically significantly superior to placebo for each of the three efficacy variables (p< 0.0001). In addition, subgroup analyses showed that vardenafil 10 mg ODT was nominally statistically significantly superior to placebo for each of the three efficacy variables in patients aged < 65 and≥ 65 years, and patients with or without a history of diabetes mellitus, dyslipidaemias or hypertension (p< 0.05). The subgroup analyses showed that the effect of vardenafil 10 mg ODT was greater in younger patients compared with older patients, and in patients without a history of the investigated conditions compared with patients with a history of the investigated conditions.

Safety

Introduction

The review of safety will focus on the Integrated Analysis [PH-35849] of the data from the two pivotal, randomized, placebo-controlled studies [POTENT I and II]. The safety data included:

- Adverse effects (AEs) and serious adverse effects (SAEs) collected at all four visits and during the 48 hours after the last dose;
- Laboratory data collected in the 4-week non-medicated run-in period and at Week 12;
- Vital signs measured at all four visits;
- Physical examination carried out in the 4-week non-medicated run-in period and at Weeks 0, 4, and 12; and
- 12-lead electrocardiogram (ECG) in the 4-week non-medicated run-in period and at Week 12.

The safety data also included information from the Phase I PK studies. The safety information from the individual PK studies was also reviewed. They showed no unexpected or new safety signals.

Patient Exposure

The safety population included all randomized subjects who had taken the study medication and had one post-baseline safety assessment. The study medications (vardenafil 10 mg ODT or placebo) were taken 1 hour before sexual intercourse (as needed) with no more than 1 tablet per day for 12 weeks. The *Integrated Safety Analysis* of the two pivotal studies included information on a total of 695 patients (safety population), of whom 355 (51.1%) had been exposed to vardenafil 10 mg ODT and 340 (48.9%) to placebo. In the safety population, 173 patients aged < 65 years had been exposed to vardenafil 10 mg ODT compared with 165 exposed to placebo, and 182 patients aged ≥ 65 years had been exposed to vardenafil compared with 175 exposed to placebo. The safety population included 297 patients (42.7%) aged ≥ 65 to 74 years (153 exposed to vardenafil 10 mg ODT, and 144 exposed to placebo), and 60 (8.5%) patients aged > 75 years (29 exposed to vardenafil 10 mg ODT, and 31 exposed to placebo).

The overall mean exposure time to vardenafil 10 mg ODT was 75.7 (range 1 – 117) days and 71.7 (range 1 – 111) days for placebo. In total, 78.0% of patients exposed to vardenafil 10 mg ODT were treated for up to 12 weeks (> 77 days to 84 days) and the remaining 22.0% of patients were treated for more than 12 weeks (> 84 days to > 98 days).

Overall, premature discontinuations occurred in 9% of all patients randomized to vardenafil 10 mg ODT and 12% of patients randomized to placebo. The most common reason for discontinuation in the vardenafil group was withdrawn consent (3% vs placebo 3%). The most common reason for discontinuation in the placebo group was insufficient therapeutic effect (6% vs 1% vardenafil).

Adverse Events

Only treatment emergent adverse events (TEAEs) were included in the *Integrated Safety Summary*. TEAES were defined as AEs occurring within the time window of first application and up to 1 day after the last drug intake. In addition, all AEs present before first drug intake but after informed consent were considered as TEAEs if they deteriorated after the first drug intake.

The overall incidence of TEAEs was 38.0% in the vardenafil 10 mg ODT group and 21.8% in the placebo group. TEAEs occurred more frequently with vardenafil in the younger than in the older age group (41.0% vs 35.2%), and the incidence of TEAEs with placebo in the younger and older age groups was similar (20.6% vs 22.9%, respectively). The incidences of TEAEs, drug related TEAEs, TEAEs leading to discontinuation, TESAEs, and death are summarised below in Table 28.

Table 28: Integrated Analysis – incidence rates in the safety population.

	Placebo Total	Vard. Total	Placebo < 65 yrs	Vard. < 65 yrs	Placebo ≥ 65 yrs	Vard. ≥ 65 yrs
Number	340	355	165	173	175	182
TEAEs	74 (21.8%)	135 (38.0%)	34 (20.6%)	71 (41.0%)	40 (22.9%)	64 (35.2%)
Drug related TEAEs	25 (7.4%)	86 (24.2%)	13 (7.3%)	47 (27.2%)	13 (7.4%)	39 (21.4%)
TEAEs leading to disc.	2 (0.6%)	4 (1.4%)	0 (0%)	3 (1.7%)	2 (1.1%)	2 (1.1%)
TESAEs	2 (0.6%)	4 (1.4%)	1 (0.6%)	1 (0.6%)	1 (0.6%)	3 (1.6%)
Death (TESAEs)	0 (0%)	0 (0%)	0 (0.0%)	0 (0%)	0 (0%)	0 (0%)

The most frequently reported TEAEs (Preferred Term) in all patients with vardenafil ODT 10 mg (vs placebo) were: headache 14.4%, n=51 (vs 1.8%, n=6); flushing 7.6%, n=27 (vs 0.6%, n=2); nasal congestion 3.1%, n=11 (vs 0.3%, n=1); dyspepsia 2.8%, n=10 (vs 0%); dizziness 2.3%, n=8 (vs 0%); and back pain 2.0%, n=7 (vs 1.2%, n=4). In the vardenafil ODT 10 mg group, most of the reported TEAEs were rated as mild in intensity and nearly all resolved by study end with most requiring no action (that is, remedial medications and/or discontinuation).

The most frequently reported TEAEs in vardenafil 10 mg ODT treated patients aged < 65 years (vs ≥ 65 years) were: headache 16%, n=28 (vs 13%, n=23); flushing 9%, n=16 (vs 6%, n=11); nasal congestion 5%, n=9 (vs 1%, n=2); dyspepsia 3%, n=5 (vs 3%, n=5); dizziness 3%, n=5 (vs 2%, n=3); diarrhoea 2%, n=4 (vs 1%, n=2); back pain 2%, n=3 (vs 2%, n=2); and feeling hot 2%, n=3 (vs 0%).

The *Integrated Safety Analysis* included a treatment comparison of TEAEs of special interest. The incidence of TEAEs ≥ 1% in vardenafil 10 mg ODT total treated patients (vs placebo) were: immediate type hypersensitivity reactions 10.7%, n=38 (vs 1.8%, n=6); vasodilatation 8.2%, n=29 (vs 0.6%, n=2); cardiac arrhythmias 2.5%, n=93 (vs 3.5%, n=12); dizziness 2.3%, n=8 (vs 0%); and oral irritation 1.4%, n=5 (0.9%, n=3). Overall, a higher proportion of patients in the vardenafil 10 mg ODT group had TEAEs of special interest compared with placebo (15.5%, n=55 vs 5.9%, n=20). In the age group < 65 years (vs the age group ≥ 65 years) the incidence of immediate type hypersensitivity reactions was 13%, n=23 (vs 8%, n=15) and for vasodilatation was 10% (n=18) (vs 6%, n=11).

Serious Adverse Events and Death

There were no treatment emergent deaths. Serious TEAEs were reported in 6 (0.9%) patients in the total safety population of 695 patients. In the placebo group, 2 (0.6%) patients reported a serious TEAE (neurosensory deafness in a 68 year old; prostate cancer in a 49 year old). In the vardenafil 10 mg ODT group, 4 (1.1%) patients reported a serious TEAE (acute coronary syndrome / post-interventional pneumothorax in a 68 year old; gastrointestinal haemorrhage in a 65 year old; syncope in a 72 year old; hypertension / chest pain in a 55 year old).

Laboratory Findings

The most commonly occurring (≥ 2%) "high" laboratory abnormalities reported during the study for patients treated with vardenafil 10 mg ODT (vs placebo) with normal baseline

values were: glucose 12.3%, 31/252 (vs 9.2%, 23/251); alanine transaminase (ALT) 5.4%, 17/313 (vs 3.8%, 11/293); creatinine 4.1%, 12/294 (vs 5.4%, 15/280); platelets 2.9%, 8/279 (vs 2.5%, 7/275); CK 2.9% 8/277 (vs 6.7%, 19/282); aspartate transaminase (AST) 2.5%, 8/320 (vs 1.6%, 5/305); and haematocrit 2.5%, 7/276 (vs 2.2%, 6/276).

The most commonly occurring "low" (≥ 2%) laboratory abnormalities reported during the study for patients treated with vardenafil 10 mg ODT (vs placebo) with normal baseline values were: red blood cells (RBC) 16.6%, 39/235 (vs 17.2%, 39/227); haematocrit 7.9%, 22/280 (vs 8.3%, 23/278); and platelets 2.5%, 7/285 (vs 1.1%, 3/274).

Overall, there were no notable differences in "high" and "low" laboratory abnormalities between vardenafil 10 mg ODT treated patients and placebo-treated patients. Inspection of the laboratory results for vardenafil 10 mg ODT compared with placebo in the < 65 years and ≥ 65 years of groups showed them to be similar. The most noticeable difference between vardenafil (vs placebo) stratified by age was high glucose 13.1% in the < 65 years group (vs 6.6%).

Vital Signs

The baseline values for blood pressure (standing and supine) and heart rate were measured at the randomization visit (Week 0) and then following initiation of treatment at Weeks 4 and 12.

There were no measurements taken immediately before and immediately after dosing. This limits the interpretation of the observed vital sign changes. Examination of the mean changes from baseline to Week 12 in supine and sitting blood pressure and heart rate in the safety population (total and stratified by age) showed no significant changes for either vardenafil 10 mg ODT or placebo. Mean reductions from baseline to Week 12 for supine systolic BP and sitting systolic and diastolic BP were marginally greater in the older group of vardenafil 10 mg ODT treated patients compared with the younger group.

ECG

A 12-lead ECG was recorded at baseline and Week 12. The lack of a temporal relationship between intake of study medication and ECG recording makes interpretation of the ECG data difficult. Examination of the ECG date for heart rate, PR, QRS and QT intervals in total patients and patients stratified by age showed no significant changes between baseline and last visit for these parameters in either the vardenafil 10 mg ODT or the placebo groups.

Overall, ECG changes were observed in 44% (148/338) of vardenafil-treated patients compared with 39% (124/316) of placebo-treated patients. In the ≥ 65 years age group, treatment with vardenafil 10 mg ODT was associated with a higher incidence of ECG findings during the study than placebo (49.4% vs 41.0%, respectively). The most common abnormalities in patients aged≥ 65 years in both treatment groups were ST segment, T and U wave abnormalities (14.9%, vardenafil vs 15.7%, placebo), followed by QRS complex and axis abnormalities (14.4%, vardenafil vs 14.5%, placebo). The most marked difference between treatments in patients aged ≥ 65 years was "miscellaneous" (9.2%, vardenafil vs 4.8%, placebo). In the < 65 years age group, treatment with vardenafil was associated with a similar incidence of ECG findings during the study as placebo (37.8% vs 37.3%, respectively). The most common abnormality in patients aged < 65 years in both treatment groups was ST-segment, T and U wave abnormalities (15.9%, vardenafil vs 12.0%, placebo). Increases in the QTc interval from baseline of > 30 to≤ 60 milliseconds (ms) were observed in 33 vardenafil-treated patients and 38 placebo-treated patients, increases > 60 ms were observed in 3 vardenafil-treated patients and 2 placebo-treated patients, and increases ≥ 500 ms in 2 vardenafil-treated patients and 1 placebo-treated patient.

Safety in Special Populations

Patients aged < 65 years and ≥ 65 years had similar safety profiles and no special precautions appear to be required for elderly patients treated with vardenafil 10 mg ODT. In general, TEAE incidence rates in vardenafil-treated patients with a history of a pre-specified disease were similar or lower than those in vardenafil-treated patients without a history of the pre-specified disease.

Discontinuations Due to Adverse Events

The data from the integrated analysis showed that a total of 7 (1.0%) patients discontinued prematurely due to TEAEs in the safety population (n=695). In the placebo group, 2 (0.6%) patients discontinued prematurely due to TEAEs (neurosensory deafness in a 68 year old; anxiety in a 71 year old). In the vardenafil 10 mg ODT group, 5 (1.4%) patients discontinued prematurely due to TEAEs (acute coronary syndrome in a 68 year old; ALT increased in a 54 year old; chest pain / vision blurred in a 39 year old; dizziness / headache / dysphagia in a 67 year old; muscle spasms / dizziness / flushing in a 62 year old).

Safety Data from PK Studies

In Study 12769 there were valid safety data on 16 subjects as 1 of the 17 enrolled subjects withdrew consent before treatment. TEAEs were reported by 69% (11/16) subjects treated with ODT 10 mg fasting (without water), 44% (7/16) subjects treated with ODT 10 mg with breakfast (without water), 93% (13/14) subjects treated with ODT 10 mg fasting (with water), and 53% (8/15) subjects treated with FCT 10 mg fasting (with water). The most common TEAEs occurring with ODT 10 mg fasting (without water), ODT 10 mg with breakfast (without water), ODT 10 mg fasting (with water), and FCT 10 mg fasting (with water), were, respectively: headache (25%, 19%, 14%, 13%); flushing (19%, 6%, 36%, 7%); nasal congestion (13%, 13%, 14%, 13%); and abnormal sensation in eye (19%, 6%, 29%, and 13%). TEAEs occurred most commonly in the ODT 10 mg fasting (with water) group. The most commonly occurring TEAEs in this group were flushing (36%, 5/14), abnormal sensation in eye (29%, 4/14), headache (14%, 2/14), and nasal congestion (14%, 2/14). Out of the total 82 reported TEAEs in the study, 54 (65.9%) were considered to be drug-related.

Of the 82 TEAEs reported in the study, 77 were rated as mild and 5 as moderate in intensity Only one subject was reported as experiencing a serious TEAE (motor cycle accident). Two subjects discontinued prematurely: one with multiple contusions and elevated CK following a motor bike accident; and one with elevated CK following exercise. There were no cases of death.

Concerning laboratory abnormalities: in the ODT 10 mg fasting (without water) group there were 2 subjects with an elevated CRP (< 3x ULN), and 1 subject with a CK < 1.5x ULN at final visit; in the ODT with breakfast group (without water) there was 1 subject with an amylase < 2x ULN, 1 subject with a CRP <2.5x ULN, 1 subject with a CK < 1.5x ULN, 1 subject with a GLDH < 1.5x ULN, and 3 subjects with a lipase < 3.5x ULN; in the ODT fasting (with water) group there was 1 subject with a CK < 1.5x ULN; and in the FCT group fasting (with water) there was 1 subject with a CK < 18x ULN, 1 subject with a lipase < 1.5x ULN, and 1 subject with an AST < 2.5x ULN.

No subjects showed clinically significant changes in heart rate or blood pressure during the study. Systematic assessment of the ECG showed no subjects with a QTc (Bazett) increase > 60 ms during the study.

In Study 13396 safety data were available on 36 subjects with ED of mean age 54.5 (range 26-80) years. Of the 36 subjects, 33 (92%) experienced at least 1 TEAE. The majority of

TEAEs were mild with 7 (19%) subjects experiencing a moderate or severe TEAE (6 of these 7 subjects were ≤ 45 years). All TEAEs had resolved by 30 days after the last study dose apart from moderate cough in 1 subject. No TEAEs were considered to be significant or serious and there were no deaths.

The incidence of TEAEs was 87% (13/15) in patients aged≤ 45 years and 100% (15/15) in patients aged ≥ 65 years. The three most common TEAEs in the respective age groups ≤ 45 years, ≥ 65 years, and 46-64 years were, respectively: flushing (40%, 67%, 50%), nasal congestion (40%, 20%, 33%), and headache (40%, 7%, 50%). The only laboratory abnormalities of note in the study were 5 patients≥ 65 years with CRP values > 5x ULN.

The ECGs were examined systematically. At the final examination, 93% (14/15) subjects aged ≤ 45 years had a QTc (Bazett) ≤ 450 ms and 7% (1/15) had a QTc (Bazett) > 450-500 ms. The corresponding results for subjects aged≥ 65 years were 80% (12/15) and 20% (3/15), and for subjects 46-64 years were 100% (6/6) and 0% (0/6). There were no reports of QTc (Bazett) > 500 ms. The majority of subjects in the three age groups had increases in QTc (Bazett) from baseline of≤ 30 ms. No subjects had increases of ≥ 60 ms from baseline. Overall, no clinically significant changes in the QTc were detected in the subjects included in this study.

Clinical Evaluator's Overall Conclusion on Safety

The safety profile of vardenafil 10 mg ODT formulation appears to be similar to that for the FCT formulations and raises no new safety concerns. There were no safety data on patients exposed to vardenafil 10 mg ODT for more than 6 months. There were no data on how long patients with ED are likely to continue to take vardenafil 10 mg ODT. The pooled safety population from the two pivotal studies included 695 patients of whom 355 (51.1%) had been exposed to vardenafil 10 mg ODT and 340 (48.9%) to placebo for less than six months. The ICH guidelines on the extent of population exposure to assess safety for medicines intended for long-term treatment of non life threatening conditions suggests 300-600 patients to be treated for 6 months. These numbers are higher than those observed in the safety population. However, the relatively small exposure numbers should be interpreted in the context of the known safety data for the FCT formulation and the likely intermittent use of vardenafil. Furthermore, one of the strengths of the pivotal studies was the significant inclusion of patients aged ≥ 65 years. Consequently, there are good comparative safety data on patients aged ≤ 65 years compared with patients aged < 65 years. Of the 695 patients in the safety population, 357 (51.4%) were aged ≥ 65 years and 338 were aged < 65 years. Of the 357 patients aged ≥ 65 years, 182 (51.0%) had been exposed to vardenafil and 175 (49.0%) exposed to placebo. Of the 338 patients aged < 65 years, 173 (51.2%) had been exposed to vardenafil and 165 (48.8%) to placebo. The safety population also included 297 patients (42.7%) aged ≥ 65 to 74 years (153 exposed to vardenafil 10 mg ODT, and 144 exposed to placebo), and 60 (8.5%) patients aged > 75 years (29 exposed to vardenafil 10 mg ODT, and 31 exposed to placebo).

The most commonly reported TEAEs in patients treated with vardenafil ODT 10 mg (vs placebo) were: headache 14.4%, n=51 (vs 1.8%, n=6); flushing 7.6%, n=27 (vs 0.6%, n=2); nasal congestion 3.1%, n=11 (vs 0.3%, n=1); dyspepsia 2.8%, n=10 (vs 0%); dizziness 2.3%, n=8 (vs 0%); back pain 2.0%, n=7 (vs 1.2%, n=4). In the vardenafil ODT 10 mg group, most of the reported TEAEs were rated as mild in intensity and nearly all resolved by study end with most requiring no action (i.e. remedial medications and/or discontinuation). Serious TEAEs were reported in 1.1% (n=4) of vardenafil 10 mg ODT treated patients and 0.6% (n=2) of placebo-treated patients. The differences do not give rise to concern. There were no treatment emergent deaths reported in the two pivotal studies. Discontinuations due to AEs

occurred in 1.4% (n=5) of vardenafil-treated patients and 0.6% (n=2) of placebo-treated patients. The differences do not give rise to concern. The interpretation of laboratory and ECG findings were limited due to the lack of a meaningful temporal relationship between study medications taken on an as needed basis one hour before sexual intercourse and an no more than 1 a day and laboratory and ECG assessments. Overall, there was no significant difference in the safety profile for patients aged < 65 years and ≥ 65 years.

Clinical Summary and Conclusions

Clinical Aspects

Pharmacokinetics

The PKs of vardenafil 10 mg ODT have been adequately characterized following single dosing in healthy young men, and single and multiple once daily dosing in men with ED aged < 65 years and ≥ 65 years. The bioavailability of vardenafil following single dose ODT 10 mg (fasting, without water) as assessed by the AUC was higher than that of single dose FCT 10 mg (fasting, with water) in healthy young males (44%), and young (29%) and elderly (21%) males with ED [Study 12769; Study 13396]. The corresponding values for the vardenafil C_{max} for the three respective groups were +15%, -8%, and -19%. The 90% CIs for the respective AUC and C_{max} ratios were not within the accepted bioequivalence interval of 80-125%. The data showed that ODT 10 mg (fasting, without water) and FCT 10 mg (fasting, with water) are not bioequivalent in healthy young men and young and elderly men with ED.

Food (high fat, high calorie breakfast) reduced the vardenafil AUC by 2% and the C_{max} by 35% following single dose vardenafil ODT 10 mg fed vs fasting [Study 12769]. The 90% CI for the AUC ratio was within the accepted bioequivalence interval of 80-125%, but the 90% CI for the C_{max} ratio was not within the accepted interval. Overall, the data suggest that the clinical effects of ODT 10 mg are unlikely to be significantly different irrespective of whether or not the formulation is taken with food. In the two pivotal clinical efficacy and safety studies, vardenafil 10 mg ODT was taken without regard to food.

The AUC of vardenafil following single dose ODT 10 mg was 38% higher in elderly men (≥ 65 years) compared with young men (≤ 45 years) with ED, and the vardenafil C_{max} was 21% higher [Study 13396]. Following multiple once daily doses of ODT 10 mg, the vardenafil AUC_{ss} and $C_{max,ss}$ values were higher in elderly men (≥ 65 years) than in young men (≤ 45 years) with ED with the respective values being 31% and 16% [Study 13396]. Increased vardenafil AUC of 17% and C_{max} of 33% were also seen in elderly men (≥ 65 years) compared with younger men (18-64 years) with ED following single dose ODT 10 mg [Study 12093]. Overall, the comparative data showed that vardenafil AUC and C_{max} values were higher in elderly men compared with younger men with ED. This might be due to reduced vardenafil clearance in elderly compared with younger men. However, the multiple once daily ODT 10 mg data showed that accumulation of vardenafil was not marked. The AUC was 8.6% (≤ 45 years) and 2.7% (≥ 65 years) higher following multiple dose compared with single dose in men with ED and the corresponding values for the C_{max} were 16% and 11% [Study 13396].

There were no PK studies with vardenafil 10 mg ODT in patients with hepatic impairment. The PI states that patients with moderate hepatic impairment should be started on one 5 mg FCT which may be subsequently increased to 10 mg based on tolerability and efficacy. It should be clearly stated that patients with moderate hepatic impairment should be advised not to use the 10 mg ODT tablet to up-titrate from 5 mg FCT. If patients with moderate hepatic impairment up-titrate from 5 mg FCT then the 10 mg FCT should be used. The proposed PI includes a precautionary statement recommending against the use of the 10 mg ODT

formulation in patients with hepatic impairment. This precautionary statement should be upgraded to a contraindication for the 10 mg ODT formulation. The sponsor noted that it had made both moderate and severe hepatic impairment a contraindication but there was no contraindication for use in mild hepatic impairment.

There were no PK studies with vardenafil 10 mg ODT in patients with renal impairment. The PI indicates that no adjustment is required in patients with renal impairment. Consequently, it is considered that the proposed dose of 10 mg ODT can be used in patients with renal impairment with the same precautions as currently in the PI relating to vardenafil not being used in patients requiring dialysis.

Clinical Efficacy

The clinical efficacy of vardenafil 10 mg ODT has been satisfactorily established in two, pivotal, placebo-controlled studies (POTENT I; POTENT II), supported by an integrated analysis of the primary efficacy data from these two studies. The majority of patients in the pivotal studies were White. There were no efficacy (or safety) data comparing vardenafil 10 mg ODT with a FCT formulation. However, it would have been difficult to choose an appropriate FCT comparator as the PK data suggest that systemic exposure to vardenafil following 10 mg ODT is somewhere between that of the 10 mg and 20 mg FTC formulations. There would also have been difficulties achieving successful patient "blinding" as a double-dummy approach would have been required due to the different administration routes for the ODT and FCT formulations. Overall, it is considered that the use of a placebo control was the most appropriate way of assessing the efficacy (and safety) of the vardenafil 10 mg ODT formulation, given the problems associated with using an FCT formulation comparator.

In *POTENT I* and *II*, treatment with vardenafil 10 mg ODT administered when required about one hour before sexual activity, but no more than once a day, was statistically significantly superior to placebo ($p< 0.0001$) as assessed by the three primary efficacy variables. The three primary efficacy variables were change from baseline to Week 12 (LOCF) in the IIEF-EF domain scores, and SEP 2 and SEP 3 overall success rates from Week 0 to Week 12. Neither *POTENT I* nor *POTENT II* included analyses comparing the effects of vardenafil 10 mg ODT and placebo in the two age strata (that is, < 65 and ≥ 65 years). The efficacy of vardenafil 10 mg ODT was supported by an integrated analysis of the primary efficacy variables from *POTENT I* and *II*. Integrated subgroup efficacy analyses showed that vardenafil 10 mg ODT was nominally statistically superior to placebo ($p< 0.05$) in patients aged < 65 years and ≥ 65 years, and in patients with and without a history of diabetes, dyslipidaemias, or hypertension.

In *POTENT I* vardenafil 10 mg ODT was shown to be statistically significantly superior to placebo with respect to change from baseline to Week 12/LOCF in the IIEF-EF domain scores (LS mean difference of 7.1 points [95% CI: 5.66, 8.56]; $p< 0.0001$). Vardenafil 10 mg ODT also showed statistically significant superiority ($p< 0.0001$) compared with placebo in the change from baseline to Week 12 overall in SEP 2 ("penetration") success rate (LS mean difference of 27.0% [95% CI: 20.43, 33.66]; $p< 0.0001$), and in SEP 3 ("maintenance") success rate (LS mean difference of 38.2 % ([95% CI: 31.37, 45.02]; $p< 0.0001$). In *POTENT II* vardenafil 10 mg ODT was shown to be statistically significantly superior to placebo with respect to change from baseline to Week 12/LOCF in the IIEF-EF domain scores (LS mean difference of 6.9 points [95% CI: 5.38, 8.45]; $p< 0.0001$). Vardenafil 10 mg ODT also showed statistically significant superiority ($p<0.0001$) compared with placebo in the change from baseline to Week 12 overall in SEP 2 ("penetration") success rate (LS mean difference of 26.0% [95% CI: 19.26, 32.69]; $p< 0.0001$), and in SEP 3 ("maintenance") success rate (LS mean difference of 33.5 % [95% CI: 26.33, 40.44]; $p< 0.0001$).

In *POTENT I* and *II*, treatment with vardenafil 10 mg ODT resulted in nominally statistically significant superior ($p< 0.0001$) results for all analysed secondary efficacy variables. These included: changes from baseline to Week 0 to 12 (overall) for SEP 1 "ability to obtain an erection", SEP 4 "satisfaction with hardness of erection", SEP 5 "overall satisfaction", and SEP 6 "ability to ejaculate"; changes from baseline to Week 12 (LOCF) for all Treatment Satisfaction Scale (TSS) domains; higher percentages of patients reporting "back to normal" erectile function; and higher percentage of patients responding positively to the Global Assessment Question. However, no adjustment of the nominally significance level of $p < 0.05$ was made to account for the multiple analyses of the secondary efficacy variables. Consequently, these analyses are considered to be exploratory rather than confirmative.

In an integrated efficacy analysis of the data from the two pivotal studies, treatment with vardenafil 10 mg ODT was nominally statistically significantly superior ($p< 0.0001$) to placebo as assessed by IIEF-EF scores and SEP 2 and 3 success rates. The LS mean difference in the IIEF-EF score at Week 12 (LOCF) was 7.0 points [95%CI: 6.0, 8.1] higher in the vardenafil group compared with the placebo group. The LS mean difference in the SEP 2 success rate at Week 12 (overall) was 27.4% [95%CI: 22.7, 32.1] higher in the vardenafil group compared with the placebo group. The LS mean difference in the SEP 3 success rate at Week 12 (overall) was 36.7% [95%CI: 31.8, 41.4] higher in the vardenafil group compared with the placebo group. The LS mean differences between vardenafil and placebo for each of the three efficacy variables are considered to be clinically meaningful. In addition, in the integrated efficacy analysis subgroup assessment showed that vardenafil 10 mg ODT was nominally statistically significantly superior ($p< 0.05$) to placebo in patients aged < 65 and $\geq$ 65 years, and in patients with or without a history of diabetes mellitus, dyslipidaemias or hypertension. However, the effect of vardenafil 10 mg ODT was smaller in older patients compared with younger patients, and in patients with a history of the three assessed conditions compared with patients without a history.

Clinical Safety

The safety profile of the vardenafil 10 mg ODT formulation appears to be similar that of the vardenafil FCT formulations and raises no new safety concerns or signals. There were no significant differences between the vardenafil 10 mg ODT safety profiles for patients aged $<$ 65 years and $\geq$ 65 years. Consequently, no specific precautions for vardenafil 10 mg ODT due to age alone appear to be warranted. There were no safety data on patients exposed to vardenafil 10 mg ODT for more than 6 months, and there were no data on how long patients are likely to continue to take vardenafil 10 mg ODT. The mean exposure time was 76 days for vardenafil 10 mg ODT and 72 for placebo, and the mean number of tablets taken per week was 2.7 for vardenafil 10 mg ODT and 2.0 for placebo.

The pooled safety population from the two pivotal studies included 695 patients of whom 355 (51.1%) had been exposed to vardenafil 10 mg ODT and 340 (48.9%) to placebo for less than six months. The ICH guidelines on the extent of population exposure to assess the safety of medicines intended for long-term treatment of non life threatening conditions suggests 300-600 patients treated for 6 months. The numbers in the guideline are higher than those observed in the safety population for vardenafil 10 mg ODT. However, the relatively small exposure numbers should be interpreted in the context of the known safety data for the FCT formulation and the likely intermittent use of vardenafil. Furthermore, one of the strengths of the pivotal studies was the significant number of included patients aged $\geq$ 65 years. Consequently, there are good comparative safety data on patients aged $\leq$ 65 years compared with patients aged $<$ 65 years. Of the 695 patients in the safety population, 357 (51.4%) were aged $\geq$ 65 years and 338 were aged $<$ 65 years. Of the 357 patients aged $\geq$ 65 years, 182

(51.0%) had been exposed to vardenafil and 175 (49.0%) exposed to placebo. Of the 338 patients aged < 65 years, 173 (51.2%) had been exposed to vardenafil and 165 (48.8%) to placebo. The safety population also included 297 patients (42.7%) aged ≥ 65 to 74 years (153 exposed to vardenafil 10 mg ODT, and 144 exposed to placebo), and 60 (8.5%) patients aged > 75 years (29 exposed to vardenafil 10 mg ODT, and 31 exposed to placebo).

The most commonly occurring TEAEs reported with vardenafil were headache (14.4%), flushing (7.6%), nasal congestion (3.1%), dyspepsia (2.8%), dizziness (2.3%) and back pain (2.0%). These TEAEs all occurred more frequently with vardenafil 10 mg ODT than with placebo, and have been previously reported as occurring with vardenafil. Serious TEAEs were reported in 1.1% (n=4) of vardenafil 10 mg ODT treated patients and 0.6% (n=2) of placebo-treated patients. The difference between treatments in serious TEAES does not give rise to concern. There were no treatment emergent deaths reported in the two pivotal studies.

Discontinuations due to AEs occurred in 1.4% (n=5) of vardenafil-treated patients and 0.6% (n=2) of placebo-treated patients. The difference between treatments in discontinuation does not give rise to concern. The interpretation of laboratory and ECG findings were limited due to the lack of a meaningful temporal relationship between study medication and measurements.

Benefit-Risk Assessment

Benefits

The submission has satisfactorily established the benefits of vardenafil 10 mg ODT taken 1 hour before sexual intercourse on an as needed basis for the treatment in ED in men aged < 65 years and ≥ 65 year. Based on the IIEF-EF LS mean scores in the integrated efficacy analysis it can be inferred that ED clinically improved from moderate intensity at baseline to mild intensity after 12 weeks treatment with vardenafil 10 mg ODT. However, in the placebo-treated patients there was no meaningful improvement in ED with intensity being moderate both before and after treatment. Furthermore, erectile function success rates as measured by vaginal penetration (SEP 2) and maintenance of erection (SEP 3) were both higher in vardenafil 10 mg ODT treated patients compared with placebo and the differences are considered to be clinically meaningful.

Risks

In general, the safety data for vardenafil 10 mg ODT were consistent with the known data for the registered FCT formulations. However, the 10 mg ODT formulation should not be used in patients with hepatic impairment due to the risks associated with suprabioavailability of the 10 mg ODT formulation compared with the 10 mg FCT formulation. This risk can be managed by contraindicating the use of 10 mg ODT in patients with hepatic impairment. There are also risks associated with patients assuming that the 10 mg ODT and 10 mg FCT formulations are interchangeable. These risks can be mitigated by suitable precautionary statements in the PI and CMI.

Safety Specification

There are no efficacy or safety data on ODT strengths higher or lower than 10 mg. Consequently, no more than 10 mg of the vardenafil ODT formulation should be taken to treat ED. Patients requiring a greater response than that obtained from ODT 10 mg should take 20 mg FCT and not 2 x 10 mg ODT. This should be clearly stated in both the PI and the CMI. However, the lack of ODT strengths other than 10 mg should not preclude registration of the 10 mg ODT formulation. Confusion between the two formulations would best be

avoided by having two separate PIs (one for the 10 mg ODT formulation and one for the 5, 10, and 20 mg FCT formulations).

Balance

It was considered that the benefit-risk assessment of vardenafil 10 mg ODT for the treatment of ED is favourable.

Conclusions

Approval of the Levitra ODT 10 mg formulation was recommended for the "treatment of erectile dysfunction in adult males (inability to achieve penile erection sufficient for sexual performance)".

Recommended Conditions for Registration and Product Information

It was recommended that that there be separate PIs and CMIs for the ODT and FCT formulations.

Amendments to Product Information

Amendment Relating to the Starting Dose in the Elderly

Overview

The current *Dosage and Administration* section of the PI includes the following statement relating to elderly patients: "A starting dose of 5 mg should be considered for patients aged≥ 65 years old". The sponsor proposes to replace this with the following: "Dose adjustment is not required in elderly patients". In support of this amendment the submission included three integrated analyses and four expert statements of the safety of vardenafil in the elderly. These documents are summarised in Table 29.

Table 29: Provided expert reports and integrated analyses of the safety of vardenafil in the elderly.

Expert Statement	Safety and tolerability of vardenafil in elderly subjects: a review of clinical-pharmacological studies conducted after submission of the initial dossier and reported in Periodic Safety Update Reports. Bayer HealthCare AG, August 2008.
Integrated Analysis	Integrated analysis of safety in elderly subjects – PH-35483. Bayer HealthCare AG, July 2008.
Integrated Analysis	Safety of Vardenafil by patients' age and initial dose – Results from the Real-Life Safety and Efficacy of Vardenafil (REALISE): Europe & Overseas Post-Marketing Surveillance Integrated analysis of safety in elderly subjects – LV0301EO-PH- 35158 A, Bayer HealthCare, May 2008.
Expert Statement	Expert Statement: age dependence of systemic exposure of vardenafil; a review of clinical-pharmacological studies and pharmacokinetic analyses, Bayer HealthCare, August 2008.
Integrated Analysis	Safety of Vardenafil by patients' age and initial dose – Results from the Real-Life Safety and Efficacy of Vardenafil (REALISE): USA Post-Marketing Surveillance Integrated analysis of safety in elderly subjects – LV0301US-Update, MRR-00263 A, Bayer HealthCare, May 2008.
Expert Statement	Expert Statement: Safety data of vardenafil in elderly from published literature, Bayer HealthCare AG, 06-June-2008.
Expert Statement	Expert statement: Report on the clinical pharmacology of vardenafil: age effect on dose normalized AUC and Cmax. Bayer HealthCare AG 22-Apr-2008

Integrated Analysis PH-35483 – Bayer HealthCare July 2008.

The objective of this integrated analysis was to describe the safety profile of vardenafil in elderly subjects (aged≥ 65 years) in order to show that a 10 mg starting dose is as safe as a 5 mg starting dose. The main analysis was based on 16 of 58 Phase II-IV studies which were in the sponsor's vardenafil Global Integrated Analyses Database (GIAD) on 1 March 2008. The 16 studies included 4294 subjects treated with vardenafil of the total 16905 subjects included

in the 58 studies. The 16 studies were divided into two pools [Pool 1 and 3 (no Pool 2)]. *Pool 1* included five placebo-controlled, fixed-dose studies comparing vardenafil 5 mg, 10 mg and 20 mg with placebo. *Pool 3* included 11 placebo-controlled, flexible-dose studies comparing placebo with vardenafil initiated with a 10 mg dose and allowing the first titration at Week 4. The remaining 42 of the 58 studies including 12611 patients treated with vardenafil were considered to be supportive. The discussion in this report focuses on the main analyses in the Pool 1 and 3 populations. The distribution of subjects in the analyses are summarised in Table 30.

Table 30: Summary of the number of subjects treated with vardenafil by pooled population.

Phase II to IV	Number of studies	Total number of patients	Number of patients ≥ 65 year-of-age
Pool 1 ED fixed dose placebo controlled	5	2160	390
Pool 3 ED flexible dose placebo controlled	11	2134	372
ED protocol violators (by age) Or daily dosing ED plus other	12* 5*	2418 454	3 7
ED other	26	9739	1774
Phase II to IV total	58	16905	2546

one study present in two categories

Subjects and Exposure

Main Analysis Pool 1 (5 fixed-dose studies): Pool 1 included 713 subjects treated with placebo, 716 subjects treated with vardenafil 5 mg, 724 subjects treated with vardenafil 10 mg and 720 subjects treated with vardenafil 20 mg. The total number of subjects was 2873, with 530 (18.5%) aged ≥ 65 years and 2343 (81.5%) aged < 65 years. Co-morbidities increased with age regardless of treatment. The fixed-dose analysis is considered to be the most relevant for comparing the AE profiles of vardenafil 5 mg and 10 mg.

Main Analysis Pool 3 (11 flexible-dose studies): Pool 3 included 1698 subjects treated with placebo and 2134 subjects treated with vardenafil. Subjects were started on vardenafil 10 mg and could be titrated at Week 4. The total number of subjects was 3832, with 695 (18.1%) aged ≥ 65 years and 3137 (81.9%) aged < 65 years. Co-morbidities increased with age regardless of treatment. The majority of subjects (54.7%, n=2096) were treated with vardenafil 10 mg (334 aged≥ 65 years, 1762 aged < 65 years). There were only 38 elderly subjects treated with vardenafil 5 mg. Around 70% of patients were up-titrated to vardenafil 20 mg at least once, including 244 elderly patients who started with 10 mg.

Supportive Analysis: The remaining 42 studies included 12611/16905 (74.6%) subjects treated with vardenafil and these studies were considered supportive.

Exposure: All ED studies lasted at least 4 weeks, most of them 3 months, and maximum duration was about 2 years. Study medication was given as needed, except in 3 studies where daily dosing was used. In two studies for other indications, twice daily dosing for 4 months was used to treat benign prostatic hypertrophy and twice daily dosing for 4 months was used to treat tinnitus.

Adverse Events

The variables for the safety evaluation included AEs, standardized MedDRA queries (SMQ) for AEs of special interest, and predefined laboratory investigations (AST, ALT, and CK).[9] ECG findings and vital signs were not reported as the timing of these measurements was considered not to adequately correspond to the timing of drug intake. The frequency of AEs, ADRs, serious AEs, and AEs leading to discontinuation of the study drug, as well as the incidence rates of laboratory abnormalities were compared between the placebo and vardenafil treatment groups.

Adverse Events in the Fixed-Dose Studies (Pool 1)

The incidence of TEAEs or ADRs in the fixed-dose studies occurring within the first 4 weeks of treatment are summarised in Table 31. The results showed that the frequency of TEAEs /

[9] MedDRA: Medical Dictionary for Regulatory Activities.

ADRs increased with dose in both age groups. There was no significant difference in the TEAE / ADR frequency between 5 mg and 10 mg doses in subjects aged≥ 65 years. Comparison of the 5 mg with the 10 mg dose in subjects aged≥ 65 years showed that the incidence of all TEAEs was lower in the 10 mg dose group compared with the 5 mg dose group while the reverse was seen for all ADRs. The placebo response rate for all AE was more than twice that in subjects aged < 65 years compared with subjects aged≥ 65 years. The placebo-subtracted all AE rates for subjects aged < 65 compared with subjects aged≤ 65 years were, respectively: 5 mg (8.9% vs 19.8%); 10 mg (16.2% vs 17.9%); and 20 mg (20.8% vs 33.3%).

Table 31: Fixed-Dose Studies - incidence rates occurring within the first 4 weeks of treatment.

	Age group	Placebo	5mg vardenafil	10mg vardenafil	20mg vardenafil
No. of subjects	**< 65 y**	573	582	604	584
	>= 65 y	140	134	120	136
All AE	**< 65 y**	16.4%	25.3%	32.6%	37.2%
	>= 65 y	7.1%	26.9%	25.0%	40.4%
All ADR	**< 65 y**	5.4%	16.7%	24.3%	29.6%
	>= 65 y	4.3%	12.7%	15.0%	32.4%
All serious AE*	**< 65 y**	0.7%	0.3%	0.5%	0.5%
	>= 65 y	0	1.5%	0.8%	1.5%

The placebo-subtracted rates suggests that all AEs occurred less frequently in younger compared with older subjects for 5 mg and 20 mg doses, while frequencies were comparable in both age groups for the 10 mg dose. The all AE rates were similar for the 5 mg and 10 mg doses in patients aged ≥ 65 years. The placebo-subtracted ADR rates suggested that ADRs occurred less commonly in the older subjects than younger subjects or at comparable rates. The all ADR rated were similar for the 5 mg and 10 doses in patients aged ≥ 65 years.

The most frequently occurring TEAEs are summarised in Table 32. The incidence of most commonly occurring events was lower in subjects aged≥ 65 years compared with subjects aged < 65 years. In the older age group there was no evidence that the 10 mg dose is consistently associated with a higher incidence of common AEs compared with the 5 mg dose. The most significant TEAE difference in older subjects between the 5 mg and 10 mg doses was dizziness (0.7% and 4.2%, respectively).

Table 32: Frequently reported TEAEs within the first 4 weeks of treatment (MedDRA Preferred Term).

Patients < 65 years	Placebo (N=573)		5 mg (N=582)		10 mg (N=604)		20 mg (N=584)	
	n	%	n	%	n	%	n	%
Headache	12	2.1	35	6.0	54	8.9	69	11.8
Flushing	4	0.7	33	5.7	52	8.6	58	9.9
Hot Flush	3	0.5	9	1.5	13	2.2	11	1.9
Dizziness	3	0.5	7	1.2	7	1.2	4	0.7
Nasal congestion	2	0.3	12	2.1	19	3.1	26	4.5
Dyspepsia	0	0	6	1.0	12	2.0	17	2.9

Patients ≥ 65 years	Placebo (N=140)		5 mg (N=134)		10 mg (N=120)		20 mg (N=136)	
	n	%	n	%	n	%	n	%
Headache	2	1.4	9	6.7	4	3.3	22	16.2
Flushing	0	0	6	4.5	5	4.2	14	10.3
Hot Flush	0	0	1	0.7	2	1.7	3	2.2
Dizziness	0	0	1	0.7	5	4.2	5	3.7
Nasal congestion	1	0.7	3	2.2	2	1.7	4	2.9
Dyspepsia	0	0	0	0	2	1.7	3	2.2

The incidence of serious TEAEs was higher in subjects aged≥ 65 years than in subjects aged < 65 years for all doses of vardenafil. No serious TEAEs occurred in subjects aged≥ 65 years treated with placebo. In subjects < 65 years, the incidence of serious TEAEs in each of the treatment groups was: placebo 0.7%, 4/573 (one case each of umbilical hernia, femoral neck fracture, colon cancer with liver metastases and arthritis); vardenafil 5 mg 0.3%, 2/582 (one case each of 1petit mal epilepsy and syncope); vardenafil 10 mg 0.5%, 3/604 (one case each of chest pain, road traffic accident and abnormal liver function tests); and vardenafil 20 mg 0.5%, 3/584 (one case each of coronary artery occlusion, tachycardia and epistaxis). In subjects aged ≥ 65 years, the incidence of serious TEAEs in each of the treatment groups was: placebo 0%, 0/140; vardenafil 5 mg 1.5%, 2/134 (one case each of arthritis and aortic aneurysm); vardenafil 10 mg 0.8%, 1/120 (abdominal hernia); and vardenafil 20 mg 1.5%, 2/136 (one case each of prostate cancer and cholecystectomy). The between treatment and between age group differences in serious TEAEs do not give rise to concern. The serious TEAEs reported with vardenafil in subjects aged≥ 65 years appear to be unrelated to treatment.

Discontinuations due to TEAEs during the first 4 weeks of treatment in subjects aged ≥ 65 years (vs subjects aged < 65 years) were: placebo 0% (vs 0.2%, 1/573); vardenafil 5 mg 3.0%, 4/134 (vs 1.0%, 6/582); vardenafil 10 mg 1.7%, 2/120 (vs 1.2%, 7/604); and vardenafil 20 mg 2.2%, 3/136 (vs 2.1%, 12/584). TEAEs leading to discontinuation in the four elderly patients receiving vardenafil 5 mg included aortic aneurysm, dizziness, anxiety plus depression plus headache, and conjunctivitis plus flushing plus nasal congestion. In the two elderly patients receiving vardenafil 10 mg, TEAEs leading to discontinuation included flushing, and asthenia plus dizziness. In the vardenafil 20 mg group, the three elderly patients discontinuing reported asthenia plus choking sensation, headache plus increased lacrimation plus skin tightness plus nausea, and nephrolithiasis.

The AEs / SMQs of special interest were “central serous retinopathy”, “cerebrovascular accident”, “myocardial infarction”, “Nonarteritic Anterior Ischemic Optic Neuropathy (NAION)”, “priapism”, “QT prolongation”, “seizures”, “syncope”, and “hypotension”. The incidence of TEAEs of special interest within the first 4 weeks of treatment in subjects aged≥ 65 years (vs subjects aged < 65 years) were: placebo 1.4%, 2/140 (vs 3.3%, 21/573); vardenafil 5 mg 1.5%, 2/134 (vs 4.3%, 25/582); vardenafil 10 mg 3.3%, 4/120 (vs 4.3%, 26/604); and vardenafil 20 mg 3.7%, 5/136 (vs 5.3%, 31/584). The placebo-subtracted incidence of TEAEs of special interest in subjects aged ≥ 65 years (vs subjects aged < 65

years) for each of the vardenafil treatments was: vardenafil 5 mg 0.1% (vs 0.6%); vardenafil 10 mg 1.9% (vs 0.6%); and vardenafil 10 mg 2.3% (vs 1.6%). The placebo-subtracted TEAE of special incidence rates for vardenafil 10 mg and 20 mg were lower in subjects aged < 65 years than subjects aged ≥ 65 years. In subjects aged ≥ 65 years, the incidence of TEAEs of special interest in subjects aged≥ 65 years was two -fold higher in the vardenafil 10 mg group compared with the vardenafil 5 mg group, but absolute subject numbers were small (4 and 2, respectively).

The TEAEs / SMQs of special interest for SMQ defined “myocardial infarction” are summarised in Table 33. The results showed that most of the events defined as SMQ “myocardial infarction” were non-MB CK increases. The only other TEAE of special interest occurring in ≥ 1% of vardenafil-treated subjects was visual disturbance occurring in 6 (1.0%) subjects treated with vardenafil 20 mg in the < 65 years group (vs 0% placebo).

Table 33: SMQ defined "Myocardial Infarction".

	Group	Placebo	Vardenafil 5 mg	Vardenafil 10 mg	Vardenafil 20 mg
SMQ "Myocardial Infarction" Any	< 65 yrs	2.3% (13/573)	2.4% (14/582)	2.8% (17/604)	5.3% (31/584)
CK increased		*2.1% (12/573)*	*1.9% (11/582)*	*2.6% (16/604)*	*2.2% (13/584)*
CK-MB increased		*0%*	*0%*	*1 (0.2%)*	*1 (0.2%)*
CK abnormal		*0%*	*0.2% (1/582)*	*0%*	*0%*
ST-segment elevation		*0%*	*0.2% (1/582)*	*0%*	*0%*
Coronary artery occlusion		*0%*	*0%*	*0%*	*0.2% (1/584)*
Myocardial Infarction		*0.2% (1/573)*	*0.2% (1/582)*	*0%*	*0%*
SMQ "Myocardial Infarction" Any	≥ 65 yrs	0.7% (1/140)	0	0.8% (1/120)	1.5% (2/136)
CK increased		*0.7% (1/140)*	*0%*	*0.8% (1/120)*	*1.5% (2/136)*
CK-MB increased		*0%*	*0%*	*0%*	*0%*
CK abnormal		*0%*	*0%*	*0%*	*0%*
ST-segment elevation		*0%*	*0%*	*0%*	*0%*
Coronary artery occlusion		*0%*	*0%*	*0%*	*0%*
Myocardial Infarction		*0%*	*0%*	*0%*	*0%*

Adverse Events in the Flexible Dose Studies (Pool 3)

The overall incidence rates for TEAES or ADRs and serious TEAEs in the flexible-dose studies with vardenafil starting at a dose of 10 mg are summarised in Table 34. The incidence rates for all AE, ADR, or serious AEs were comparable in the two age groups. Incidence rates of AE leading to dose reduction were 1.4% in the younger subjects and 0.6% for the elderly subjects.

Table 34: Overall incidence rates in flexible dose studies within the first 4 weeks of treatment.

	Age group	Placebo	Vardenafil flexible dose, starting with 10 mg*
No. of patients	**< 65 y**	1375	1762
	≥ 65 y	323	334
All AE	**< 65 y**	11.1%	24.4%
	≥ 65 y	10.2%	21.3%
All ADR	**< 65 y**	3.0%	17.7%
	≥ 65 y	1.9%	15.9%
All serious AE	**< 65 y**	0.1%	0.6%
	≥ 65 y	0	0.3%

The incidence rates of TEAEs of special interest occurring in the first 4 weeks of treatment in subjects aged ≥ 65 years (vs subjects aged < 65 years) were: placebo 0.3%. 1/1357 (vs 0.7%, 9/1375); initial vardenafil 5 mg 0%, 0/38 (vs not assessed); initial vardenafil 10 mg 0.6% 2/334 (vs 1.5%, 26/1762). The results indicated that the incidence of TEAEs of special interest were lower in older subjects compared with younger subjects when vardenafil was

initiated at a dose of 10 mg. The most commonly occurring TEAE of special interest in younger subjects was increased CK with the incidence being 0.3% (6/1762) in the initial vardenafil 10 mg group compared with 0.1% (1/1375) with placebo. In the younger subjects, the incidence of increased CK-MB in the initial vardenafil 10 mg group (vs placebo) was < 0.1%, 1/1762 (vs 0%, 0/1375), and the respective incidence rates for MI were 0.2% (3/1762) and 0% (1/1375). In the elderly subjects there were no reported increases in CK, CK-MB, or MI in any of the treatment groups.

Clinical Laboratory

The *Pool 1 and Pool 3* data included a comparison between vardenafil and placebo for selected treatment emergent laboratory abnormalities (AST, ALT, and CK). The results for the fixed-dose (Pool 1) studies are provided in Table 37. The incidence of the three parameters in subjects aged ≥ 65 years increased with dose. The placebo-subtracted incidence rates in subjects ≥ 65 years (vs < 65 years) for AST were: vardenafil 5 mg -0.2% (vs -1.4%); vardenafil 10 mg 3.2% (vs 0.5%); and vardenafil 20 mg 5.7% (vs -1.6%). The corresponding placebo-subtracted comparisons for ALT were: minus 0.3% (vs -0.4%); 5.8% (vs 2.1%); and 8.2% (vs -1.2%). The corresponding placebo-subtracted comparisons for CPK were: 6.3% (vs 4.1%); 8.0% (vs 2.2%); and 5.5% (vs 3.1%). The results showed that although the incidence rates for the vardenafil 5 mg and 10 mg doses in the elderly subjects for the three parameters of interest were lower than those for the younger subjects, the placebo-subtracted rates were reversed. The placebo incidence rates in the younger age group were particularly high. In the elderly group, the incidence rates for each of the three parameters of interest were higher in subjects treated with vardenafil 10 mg than with vardenafil 5 mg.

Table 35: Fixed-dose studies – overall incidence rates in selected treatment emergent laboratory abnormalities.

	Age group	Placebo n/N (%)	5 mg vardenafil n/N (%)	10 mg vardenafil n/N (%)	20 mg vardenafil n/N (%)
SGOT/AST > ULN	**< 65 y**	37/455 (8.1%)	33/491 (6.7%)	45/526 (8.6%)	33/506 (6.5%)
	>= 65 y	5/114 (4.4%)	5/118 (4.2%)	8/105 (7.6%)	12/119 (10.1%)
SGPT/ALT > ULN	**< 65 y**	40/426 (9.4%)	42/469 (9.0%)	57/497 (11.5%)	39/475 (8.2%)
	>= 65 y	3/105 (2.9%)	3/115 (2.6%)	9/104 (8.7%)	13/117 (11.1%)
CPK > ULN	**< 65 y**	53/370 (14.3%)	73/397 (18.4%)	70/424 (16.5%)	71/409 (17.4%)
	>= 65 y	4/84 (4.8%)	11/99 (11.1%)	11/86 (12.8%)	10/97 (10.3%)

The overall incidence rates in the flexible dose studies for the three laboratory parameters of interest are summarised in Table 36. The results showed that for AST and ALT the ULN incidence rates in subjects aged < 65 years were lower in the treatment group than the placebo group, while the reverse was seen in subjects aged≥ 65 years. The results for the CK showed that the ULN incidence rate in subjects aged < 65 years was greater in the vardenafil treatment group than the placebo group, while the reverse was seen in subjects aged≥ 65 years.

Table 36: Flexible dose studies – overall incidence rates in selected treatment emergent laboratory abnormalities.

	Age group	Placebo n/N (%)	Vardenafil flexible dose, starting with 10 mg n/N (%)
SGOT/AST > ULN	< 65 y	43/857 (5.0%)	33/1275 (2.6%)
	>= 65 y	2/220 (0.9%)	8/253 (3.2%)
SGPT/ALT > ULN	< 65 y	46/760 (6.1%)	68/1174 (5.8%)
	>= 65 y	6/214 (2.8%)	11/243 (4.5%)
CPK > ULN	< 65 y	81/712 (11.4%)	132/1069 (12.3%)
	>= 65 y	19/202 (9.4%)	20/231 (8.7%)

Examination of the data from the flexible-dose studies showed that the majority of the ULN results for AST and ALT were ≤ 3x ULN. In these studies there were no subjects aged ≥ 65 years with a treatment emergent AST or AST > 3x ULN in the placebo, vardenafil initiated at 5 mg or 10 mg groups. In subjects aged < 65 years, treatment emergent AST > 3x ULN occurred in 1/901 (0.1%) subject in the placebo group and 2/1354 (0.1%) in the vardenafil initiated at 10 mg group. The corresponding figures for ALT > 3x ULN in the < 65 year age group were 4/901 (0.4%) for placebo and 3/1354 (0.2%) for vardenafil initiated at 10 mg group.

Clinical Evaluator's Overall Comments

This was a reasonable study given the difficulties associated with undertaking large retrospective database cross-comparisons of multiple studies. Overall, the data suggest that the TEAE profiles are similar in subjects aged < 65 years and≥ 65 years. In a ddition, the safety profiles of vardenafil 5 mg and 10 mg are generally comparable in subjects aged≥65 years. However, it is considered that the reporters tended to over interpret the significance of lower incidence rates observed with vardenafil in elderly subjects compared with younger subjects in a number of the analyses by not accounting for the high placebo rates seen in younger subjects. In a number of analyses the placebo rates were markedly higher in younger subjects compared with elderly subjects. The imbalance was seen in objective reporting such as laboratory testing as well as more subjective reporting such as TEAEs. The reasons for the higher placebo rates observed in this study in younger patients are not known.

Integrated Analyses - REALISE [Europe and Overseas] and [USA]

These two analyses reported results from the Real-Life Safety and Efficacy Study (REALISE). REALISE was a prospective, international, company-sponsored, non-interventional, post-marketing surveillance (PMS) study in which men with ED who were prescribed vardenafil (prn) in routine clinical practice were followed for a period of 2 months. The study population was stratified by age (< 65 years and≥ 65 years). The data were reported in separate analyses for "Regions of Europe and Overseas", and the "USA".

All treatment-emergent adverse events (TEAEs) were recorded, irrespective of possible causal relationship to vardenafil. The severity of TEAEs, possible relationship to treatment, action taken and outcome were also assessed. AEs with a relationship to vardenafil or missing relationship assessment were defined as adverse drug reactions (ADRs) or serious adverse drug reactions (SADRs). In addition, the overall incidence of ADRs from nine Standardised MedDRA Queries (SMQs) were analysed

Study Population [Europe and Overseas]

Data were analysed from a total of 73946 patients from 26 countries or regions collected from March 2003 to November 2005. Of the analysed patients, 20.1 % (14861) were aged ≥ 65 years and 79.4% (58700) were aged < 65 years, with missing age information for 385 (0.5%) patients. The most frequently prescribed initial vardenafil dose was 10 mg, 74.9% in younger patients and 72.1% in elderly patients. The least frequently prescribed vardenafil dose was 5 mg, 6.2 % in younger patients and 6.1 % in elderly patients. The maximum approved vardenafil dose of 20 mg was initially prescribed to 18.4% of younger patients and 21.3% of elderly patients. Regardless of age or starting dose, ED in most patients in the study population was reported to be either organic (27.4%) or mixed organic/psychogenic (47.6%).

Patients received a wide range of different concomitant medications. The most frequently prescribed of these were renin-angiotensin antagonists (18.0%), diabetes medications (16.3%), agents for the treatment of lipid disorders (10.0%), beta blockers (9.5%) and topical products for joint and muscular pain (9.3%). Elderly patients generally used more concomitant medications than younger patients. Only 21.4% of elderly patients taking vardenafil 5 mg received no concomitant medication compared with 42.5% of younger patients. The respective figures for 10 mg were 31.3% and 49.4%, and for 20 mg were 35.1% and 51.5%. Not surprisingly, the reported prevalence of concomitant diseases in elderly patients was higher than in younger patients. Overall, about 25%-27% of younger patients reported no concomitant diseases compared with only 8%-13% of elderly patients. The most frequently reported concomitant diseases were cardiovascular (about 39.6% of all patients with the difference in prevalence in the younger and elderly patients being nearly 20%).

Study Population [USA]

Data were analysed from a total of 30010 patients from the USA collected from October 2003 to September 2004. Of these patients, 7178 (23.9%) were aged ≥ 65 years and 22604 (75.3%) were aged < 65 years, with missing age data for 228 (0.8%) patients. The most frequently prescribed initial vardenafil dose was 10 mg, 67.6% in younger patients and 60.7% in elderly patients. The least frequently prescribed vardenafil dose was 5 mg, 6.0% in younger patients and 6.3% in elderly patients. The maximum approved vardenafil dose of 20 mg was initially prescribed to 23.2% of the younger, and 29.5% of the elderly patients. Several patients received multiple initial prescriptions for different doses and could not be assigned to a specific initial dosing group. Regardless of age or starting dose, ED in most patients in the study was reported to be organic (49.4%) or mixed organic/psychogenic (39.0%). The most frequently prescribed medications were renin-angiotensin antagonists (24.4%), agents to treat lipid disorders (21.8%), diabetes medications (13.3%), beta blockers (9.2%) and drugs to treat acid-related disorders (8.1%). Elderly patients generally used more concomitant medications than younger patients. Only 37.1% of elderly patients taking vardenafil 5 mg received no concomitant medication compared with 52.7% of younger patients. The respective figures for 10 mg were 35.2% and 45.2% and for 20 mg were 38.4% and 44.7%.

The most frequently reported diseases associated with ED were hypertension (44.7%), lipid metabolism disorders (25.0%) and diabetes (20.5%). Not surprisingly, the prevalence of most associated diseases was higher in elderly patients than in younger patients. However, the associated conditions of spinal cord injury, multiple sclerosis and depression had a higher prevalence in younger patients. The reported prevalence of concomitant diseases in elderly patients was higher than in younger patients. Overall, about 15-24% of younger patients reported no concomitant diseases compared with only 6-7% of elderly patients. The most

frequently reported concomitant diseases were cardiovascular (51.1% of all patients). The absolute difference in the prevalence between younger and elderly patients was 15%.

Safety Results

In REALISE [Europe and Other Regions], the overall incidence of AEs with vardenafil in all age groups was 3.6%, and the overall incidence of ADRs was 3.3%. There were no notable differences in the frequency of AEs for younger or elderly patients at each of the starting doses. For the 5 mg dose, the frequency of AEs was 2.7% in younger patients and 3.3% in elderly patients. For the 10 mg dose, the frequency of AEs was 3.9% in younger patients and 3.6% in elderly patients. For the 20 mg dose, the frequency of AEs was 2.5% in younger patients and 2.7% in elderly patients. Similarly, no marked differences due to age in the different dose groups were seen with respect to the frequency of ADRs, SAEs, or SADRs (Table 37).

In REALISE [USA], the overall incidence of AEs with vardenafil in all age groups was 8.7%, and the overall incidence of ADRs was 7.2%. There were no notable differences in the frequency of AEs in younger or elderly patients at each of the starting doses. For the 5 mg dose, the frequency of AEs was 8.2% in younger patients and 7.7% in elderly patients. For the 10 mg dose, the frequency of AEs was 8.5% in younger patients and 9.4% for elderly patients. For the 20 mg dose, the frequency of AEs was 8.8% in younger patients and 10.7% in elderly patients. Similarly, no marked differences due to age in the different dose groups were seen with respect to the frequency of ADRs, SAEs, or SADRs (Table 37)

Table 37: REALISE [Europe/Other Regions] and [USA] - Frequency of AEs and ADRs.

European and overseas patients*

	Total (N=73946)		< 65 years 5 mg (N =3660)		≥ 65 years 5 mg (N =900)		< 65 years 10 mg (N=43945)		≥ 65 years 10 mg (N=10709)		< 65 years 20 mg (N=10787)		≥65 years 20 mg (N=3169)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
AE	2656	3.6	100	2.7	30	3.3	1732	3.9	389	3.6	273	2.5	84	2.7
ADR	2472	3.3	86	2.3	27	3.0	1624	3.7	360	3.4	257	2.4	74	2.3
SAE	45	0.1	2	0.1	2	0.2	23	0.1	9	0.1	3	0.0	2	0.1
SADR	26	0.0	2	0.1	2	0.2	12	0.0	6	0.1	1	0.0	0	0.0

USA patients**

	Total (N=30010)		< 65 years 5 mg (N=1348)		≥ 65 years 5 mg (N=455)		< 65 years 10 mg (N=15274)		≥ 65 years 10 mg (N=4355)		< 65 years 20 mg (N=5247)		≥ 65 years 20 mg (N=2121)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
AE	2624	8.7	111	8.2	35	7.7	1300	8.5	408	9.4	460	8.8	226	10.7
ADR	2150	7.2	90	6.7	27	5.9	1058	6.9	327	7.5	393	7.5	180	8.5
SAE	113	0.4	4	0.3	3	0.7	50	0.3	22	0.5	19	0.4	14	0.7
SADR	16	0.1	1	0.1	1	0.2	6	0.0	4	0.1	2	0.0	1	0.0

AE= adverse events, ADR= adverse drug reactions, SAE= serious adverse events, SADR= serious adverse drug reactions
*Data on age or dose was incomplete for 776 patients; n=48 (6.2%) with AEs, n=44 (5.7%) with ADR, n=4 (0.5%) with SAE, and n=3 (0.4%) with SADR
**Data on age or dose was incomplete for 1210 patients; n=84 (6.9%) with AEs, n=75 (6.2%) with ADR, n=1 (0.1%) with SAE, and n=1 (0.1%) with SADR

In REALISE [Europe and Overseas], the most frequently reported ADRs were: headache (1.68%), flushing (0.46%), erythema/reddening (0.34%) and nasal congestion (0.27%). Except for the 5 mg dose of vardenafil there were no notable differences between younger and older patients with regard to the frequency of headache, flushing, erythema, and nasal congestions. For the 5 mg dose, the incidence of headache was higher in elderly patients compared with younger patients. The ADR results are summarised in Table 38.

In REALISE [USA], the most frequently reported ADRs were: headache (3.62%), flushing (1.52%), nasal congestion (0.82%), and dizziness (0.38%). Dizziness occurred more

frequently in the US population (0.38%) than in the European and Overseas population (0.19%). In the US population, erythema occurred less frequently than in the European and Overseas population (0.09% vs 0.34%, respectively). There were no notable differences between younger and older patients with regard to the frequency of headache, flushing, nasal congestions and dizziness. The ADR results are summarised in Table 38.

Table 38: REALISE [Europe/Other Regions] and [USA] – Most commonly occurring ADRs.

European and overseas patients

	Total (N=73946)		< 65 years 5 mg (N=3660)		≥ 65 years 5 mg (N=900)		< 65 years 10 mg (N=43945)		≥ 65 years 10 mg (N=10709)		< 65 years 20 mg (N=10787)		≥ 65 years 20 mg (N=3169)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Headache	1242	1.68	32	0.87	14	1.56	853	1.94	172	1.61	129	1.20	32	1.01
Flushing	342	0.46	12	0.33	7	0.78	200	0.46	54	0.50	47	0.44	17	0.54
Erythema	252	0.34	11	0.30	2	0.22	181	0.41	33	0.31	20	0.19	3	0.09
Nasal congestion	202	0.27	6	0.16	1	0.11	139	0.32	33	0.31	19	0.18	0	0

USA patients**

	Total (N=30010)		< 65 years 5 mg (N=1348)		≥ 65 years 5 mg (N=455)		< 65 years 10 mg (N=15274)		≥ 65 years 10 mg (N=4355)		< 65 years 20 mg (N=5247)		≥ 65 years 20 mg (N=2121)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Headache	1085	3.62	38	2.82	10	2.20	554	3.63	151	3.47	203	3.87	85	4.01
Flushing	456	1.52	21	1.56	9	1.98	227	1.49	82	1.88	67	1.28	38	1.79
Nasal congestion	246	0.82	12	0.89	0	0	132	0.86	29	0.67	51	0.97	15	0.71
Dizziness	113	0.38	3	0.22	5	1.10	43	0.28	33	0.76	13	0.25	7	0.33

Serious ADRs were very infrequently reported in both populations. In the European and Overseas population, 26 (0.04%) patients were reported as experiencing a serious ADR compared with 16 (0.05%) patients in the US population. There were no relevant differences in ADR rates between the two age groups in the two populations. In addition, there were no significant differences in ADR rates among the doses in either the younger or elderly subjects in the two populations. Similarly, analysis of the nine special groups of adverse events (SMQ) showed only small incidence rates in both populations.

Clinical Evaluator's Overall Comments

The two large PMS populations showed that vardenafil was generally well tolerated at initial doses ranging from 5 mg to 20 mg. There appeared to be no notable differences in the AE or ADR profile between patients aged < 65 years and patients aged≥ 65 years. In addition, AEs and ADRs in patients aged≥ 65 years were generally comparable in patients initiated on vardenafil 5 mg, 10 mg or 20 mg. Vardenafil appeared to be generally well tolerated in elderly subjects at the three initiating doses. In both PMS populations, treatment was most frequently initiated with vardenafil 10 mg in both younger and elderly patients despite "prescribing information" recommending an initial dose of 5 mg in elderly patients.

Expert Statement - Bayer HealthCare August 2008

This expert statement summarised pharmacokinetic data from one study in healthy subjects and population-pharmacokinetic (popPK) studies combining data from healthy subjects and

patients with ED. The PK analyses were undertaken to investigate the effect of age on the PKs pharmacokinetics of vardenafil.

Study 100195 compared PKs in healthy elderly men (mean age 72 [range 66 to 78] years) with healthy young men (mean age 28 [range 18 to 45] years) who received a single 40 mg dose of vardenafil. The results showed that elderly subjects (n=9) had higher mean vardenafil C_{max} and AUC values (34% and 52%, respectively) than younger subjects (n=8). The ratios [elderly:young] and 90% CIs were: C_{max} = 1.34 [0.84-2.14]; and AUC = 1.52 [1.01-2.28]. The 90% CIs for both ratios were not within the accepted bioequivalence interval of 0.80-1.25. The terminal half life in elderly subjects was 6.0 hours and 4.8 hours in young subjects.

In *pop-PK study I*, data from 247 subjects were analysed from 11 studies in healthy volunteers and 2 studies in subjects with ED. Of the 247 subjects, 23 were aged≥ 65 years and 5 were aged ≥ 75 years. The analysed population had a mean age of 39 (range 18-84) years. Based on the final pop-PK model and the covariate analysis, vardenafil exposure (AUC) was estimated in subjects in the lowest and highest 10 percentile. The model predicted a mean AUC increase of 32% in subjects aged ≥ 57 years compared with subjects aged ≤ 24 years. The AUC in subjects at the extremes of age (18 years and 84 years) differed by 43%. Age was not identified as a relevant covariate for C_{max} or terminal half-life.

In *pop-PK study II*, data from 1028 patients with ED from three Phase III studies were analysed. The analysed population had a mean age of 56.6 (range 20-81) years. Based on the final pop-PK model and the covariate analysis, the AUC and C_{max} of vardenafil were estimated in 800 patients aged < 65 years and 228 patients aged ≥ 65 years (with 26 patients being aged ≥ 75 years). The model predicted mean AUC and C_{max} increases of 20 % in patients aged ≥ 65 years compared with patients aged < 65 years. The ratios [elderly:young] and 90% CIs were: C_{max} = 1.202 [90%CI: 1.23-1.286]; and AUC = 1.202 [90%CI: 1.119-1.293]. The 90% CIs for both the C_{max} and AUC were not within the accepted bioequivalence interval of 0.80-1.25. The model predicted that AUC and C_{max} exposures were 31-32% higher in a patient aged 81 (representing patients age ≥ 65 year) compared with a patient aged 56.6 years (representing patients aged < 65 years). At the extremes of age, the model predicted that AUC and C_{max} exposure was about 80% higher in a patient aged 81 compared with a patient aged 20.

Comment

The studies included in the expert statement showed that age consistently increased vardenafil exposure in elderly subjects compared with younger subjects in both men with ED and healthy volunteers. The size of the increased exposure varied among the studies probably due to differences in the age groups and populations assessed. In the large pop-PK II study of data from Phase III studies, the model predicted mean AUC and C_{max} increases of 20 % in patients aged ≥ 65 years compared with patients aged < 65 years. The data from this study showed that the more extreme the difference in age, the greater the exposure to vardenafil in the older compared with the younger patient.

Expert Statement - Boettcher 2008

This was a review of those clinical pharmacological studies reported after submission of the initial vardenafil dossier which had been summarised in the Periodic Safety Update Reports (PSURs). The review identified four studies with safety and tolerability data on healthy subjects and patients aged ≥ 65 years treated with vardenafil alone. These four studies included 6 healthy elderly Japanese subjects aged≥ 65 years treated with a single oral 10 mg dose, and 30 elderly patients aged ≥ 65 years treated with a single oral 20 mg dose. The review concluded that, based on a small number of subjects, it did not indicate a different

vardenafil safety and tolerability pattern in subjects aged≥ 65 years compared with subjects < 65 years of age.

Comment

This review included only a small number of subjects administered one dose of vardenafil. There was no detailed reporting of safety with the data being reported briefly and descriptively. Those adverse events which were described are known to be associated with vardenafil (headache, hot flushes, facial flushing, nausea, and nasal stuffiness). The review stated that no clinically relevant changes were observed in clinical laboratory parameters, vital signs, ECG or eye examinations.

Expert Statement - Nagel 2008

This expert statement reported on a literature search using the Product Literature Information Database. The objective of the literature search was to identify publications on the use of vardenafil in the elderly population (aged >65 years) and reported side effects in order to evaluate whether this population is at increased risk. The search identified a total of 134 publications from which 46 relevant publications were selected. The expert statement concluded that there was no evidence from the literature that side-effects to vardenafil in the elderly occurred due to age alone. Co-morbidities and co-medication in the elderly were identified as primary preconditions for side-effects in the elderly treated with vardenafil.

Comment

This expert statement listed the selected studies but did not provide any other information on individual studies. The overall results of the literature search were briefly presented in summary statements.

Clinical Evaluator's Overall Comment

The data submitted in support of the proposed amendment to the PI relating to the initial dose in elderly patients was comprehensive. The PK data showed that although exposure to vardenafil increased in older compared with younger subjects, this did not translate into an increased risk of adverse events in the older subjects. The data also showed that vardenafil safety profiles in elderly subjects aged≥ 65 years were similar irrespective of whether treatment was initiated with 5 mg or 10 mg. Interestingly, the PMS data from REALISE for both the "European and Overseas" and "USA" populations indicated that most elderly patients being treated with vardenafil in these populations had treatment initiated with a 10 mg dose rather than a 5 mg dose. This is despite the recommendation in the prescribing information that vardenafil should be initiated in the elderly with a 5 mg dose. In addition to the integrated analyses and expert reports submitted to support the PI amendment, the data from the two pivotal studies (POTENT I and II) submitted to support registration of the vardenafil 10 mg ODT formulation demonstrated that treatment in elderly patients aged≥ 65 years can be safely initiated with this dose and formulation. In conclusion, the submitted data are considered to support the proposed PI amendment relating to no dosage adjustment being required in the elderly based on age alone.

Amendment Relating to Addition of Clarithromycin Interaction to PI Precautions

It was initially considered that there would a PI for both vardenafil products but during the course of the evaluation it was decided that separate PIs would be drafted. This particular proposed amendment applies only to the PI for the film-coated tablet and is not now relevant to this AusPAR. In the proposed PI for the oral dispersible tablet (ODT), concomitant use with moderate inhibitors (e.g. erythromycin) and potent inhibitors (e.g. clarithromycin, ketoconazole etc) of CYP3A4 is contraindicated.

Proposal to Update the Adverse Effects Section in the PI.

The sponsor proposed a number of amendments to update the *Adverse Effects* section of the PI. In support of these amendments the sponsor provided a justification document - "*Update of Section Undesirable Effects (4.8). Changes from CCDS 12 to CCDS 13"*, dated 14 August 2009. Comments are provided below on selected specific changes. If no comment is provided for a specific change then it can be assumed that the proposed change is acceptable.

a. The introductory paragraph includes a new statement regarding exposure in the controlled and un-controlled clinical trials with vardenafil. The sponsor has been requested to provide information relating to this data.

b. Where the abbreviation CPK appears change to CK, and refer to creatine kinase rather the creatine phosphokinase.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Medicines Safety Monitoring (OMSM). The ongoing safety concerns which have been identified by the sponsor are shown in Table 39:

Table 39: Ongoing Safety Concerns for Levitra

Important identified risks	Hypersensitivity Decrease in blood pressure Effects on QT-interval and cardiac rhythm Prolonged erection, priapism Counterfeit drug product Access to drug product without prescription CCM CYP3A4 inhibitors CCM alpha-blockers CCM nitrates and NO donors
Important potential risks	NAION, transient and permanent vision loss Transient Global Amnesia Epilepsy/Seizure/Convulsion Central Serous Retinopathy
Important missing information	-

The submission included routine pharmacovigilance (PhV) activities and the following additional pharmacovigilance activities (not specifically relating to the ODT formulation or the elderly starting dose adjustment):[10]

A drug utilisation survey for the use of concomitant alpha-blockers.
NAION (NonArteritic Ischaemic Optic Neuropathy) study.
Targeted follow-up questionnaires for spontaneous case reports of NAION, transient global amnesia, seizures and central serious retinopathy.

An assessment of the requirement to provide a risk minimisation plan concluded that routine risk minimisation activities were sufficient for the clinical safety concerns.[11] Regarding the risk of counterfeit medication and medication access without prescription, the sponsor proposed risk minimisation activities including a linked website called "Beware of counterfeits", support of the EFPIA coding and identification initiative and working in close cooperation with the corresponding authorities.

[10] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

[11] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

The OMSM reviewer noted that while there have not been any new safety related concerns from the Levitra ODT clinical trials or trials on the safety of varied Levitra doses (5, 10 or 20 mg) in the elderly, there is the potential for dose-related ADRs, drug interactions and medication errors with the new ODT in terms of the differing dosing and bioavailability. As such, certain recommendations for Product Information (PI) changes were made including the sponsor providing separate PIs for each drug form.

The RMP (Version1.0, July 2009) was evaluated as acceptable with the addition of the following recommendations that need to be addressed by the sponsor:

- Projected post-authorisation usage data for the ODT preparation is required.
- An overview on the potential for the Levitra ODT preparation to be counterfeited.
- Provision of any data/reports of paediatric off-label use for pulmonary hypertension.
- Clarifications on whether the pharmacoepidemiology studies (drug utilisation study and the NAION study) have included patients taking the ODT formulation.
- An update on the progress and analysis of the pharmacoepidemiology studies should be provided and will be expected in future PSURs. The sponsor was also expected to present a comparative evaluation of the two Levitra formulations in the PSUR.
- Sudden decrease or loss of hearing with PDE5 inhibitors have been reported in the post-marketing setting. This should be included in the important potential risks and addressed in the pharmacovigilance and risk management plans, and reported in the PSUR.
- The following are considered important missing information. The sponsor should include these items in the PhV action plan, or justify their exclusion, and report on these in a separate section of the PSUR. The sponsor was also required to provide an assessment of the need for risk minimisation activities to mitigate these potential safety concerns and to describe how the effectiveness of any proposed activities will be assessed:
  - Off-label use.
  - Potential for medication errors. With the introduction of the supra-bioavailable Levitra ODT preparation there is the possible risk of medication errors from interchanging between the film-coated and ODT forms, assumption of dose equivalence between the preparations, prescription errors from the pharmaceutical form not being identified and the use of the ODT formulation in dose titration with interacting medications or in patients with hepatic impairment.
- With respect to the additional risk minimisation activities for counterfeit drug products, the sponsor was asked to outline the relevance of the EFPIA (European Federation of Pharmaceutical Industries and Associations) coding initiative in terms of the Australian product and what procedures are in place to address the risk of counterfeit vardenafil in Australia.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Approval of this submission was recommended with respect to chemistry and quality. With regard to bioavailability, the submission included one bioavailability study to compare the bioavailability of the proposed orodispersible tablets (ODT) to that of the registered immediate-release film-coated tablet. This study, Study 12769, also determined the effect of

food and water on the bioavailability of the ODT. The results were that the proposed 10 mg ODT, administered without food or water, was not bioequivalent to the registered Levitra 10 mg immediate-release tablet which is administered with water. AUC was 44% higher, C_{max} was 15% higher and T_{max} was 45 minutes longer. When administered with water, the bioavailability of the 10 mg ODT was decreased by 29% compared to when administered without water. There were no significant changes to either T_{max} or to C_{max} in this situation. When administered with food (high fat meal), the bioavailability of the 10 mg ODT was not affected compared to when administered without food although C_{max} was decreased by 35%. T_{max} was unaffected by food. Regardless of the mode of administration (without water, with water or with food), the 10 mg ODT returned results for inter-subject variability in exposure which were very similar to those recorded for the registered 10 mg Levitra immediate release tablet. These comparative bioavailability issues were drawn to the attention of the Delegate by the pharmaceutical chemistry evaluator. This issue was also considered comprehensively by the clinical evaluator.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical evaluator has recommended approval of the Levitra ODT 10 mg formulation and of the PI change related to the recommendation concerning the starting dose in elderly males.

Pharmacology

Pharmacokinetic studies in healthy subjects

Study 10021 was designed to investigate whether absorption of a vardenafil solution was faster after sublingual (non-swallowed) than after oral (swallowed administration). The study was only briefly discussed as neither the vardenafil solution nor sublingual administration is being proposed for approval. Based on the $AUC_{0\text{-}inf}$ ratio, the vardenafil relative bioavailability of the sublingual, non-swallowed 10 mg solution was 24.6%, 90% CI [17.0, 35.6] of that of the oral, swallowed solution. Only about 8% of a sublingual dose was absorbed through the oral mucosa.

Study 12769 was a Phase I, randomised, open-label, single-dose, four-way crossover study in healthy young male volunteers. The primary objectives were to compare the pharmacokinetics (fed vs fasting) of the vardenafil 10 mg ODT formulation taken with a high-fat, high-calorie breakfast (without water) and taken fasting (with water). The secondary objectives were to compare the pharmacokinetics of the 10 mg ODT formulation taken fasting (without water) and the 10 mg film-coated tablet formulation taken fasting (with water). The point estimate of the ratio and 90% confidence intervals for the primary vardenafil PK parameters of C_{max} and AUC are summarised in Table 3.

Vardenafil was “suprabioavailable” following single dose ODT 10 mg (fasting without water) compared with a single dose of the film-coated tablet 10 mg (fasting with water). Under these conditions, the AUC was 44% higher and the C_{max} was 15% higher and the 90% CI for each ratio was outside the standard bioequivalence range. The bioavailability of the ODT taken fasting with water was reduced compared with that of the ODT taken fasting without water. Accordingly, when a single dose ODT 10 mg was taken fasting with water, it was no longer “suprabioavailable” when compared with a single dose of film-coated tablet taken fasting with water. A high fat, high calorie breakfast had little effect on the bioavailability, as measured by AUC, of vardenafil following single dose ODT 10 mg, with the 90% CI for the fed/fasted ratio being within the standard bioequivalence range. However,

food reduced the vardenafil C_{max} in this situation by about 35%. As noted by the clinical evaluator, the fed/fasted data suggest that ODT 10 mg can be taken with or without food.

Pharmacokinetics in males with erectile dysfunction

Study 13396 was a Phase I, non-randomised, non-blinded, non-controlled, age-stratified, single-centre PK study which enrolled 36 males aged at least 18 years (14 subjects aged 18-45, 6 aged 46-64, 7 aged 65-69 and 9 aged 70 years and over) and with a history of erectile dysfunction for at least 6 months. The point estimates and 90% CIs of vardenafil AUC and C_{max} following single doses of the film-coated tablet (FCT) 10 mg and the orodispersible tablet (ODT) in the $\leq$ 45 years & $\geq$ 65 years age groups are shown in Table 5.

Following single dose ODT 10 mg, the vardenafil AUC and C_{max} were 39% and 21% higher, respectively, in subjects aged at least 65 years compared with those aged 45 and below. Following single dose FCT 10 mg, the vardenafil AUC and C_{max} were 48% and 39%, higher, respectively, in the older compared with the younger age group. The single dose vardenafil AUC, that is, bioavailability, was 29% higher with the ODT compared with the FCT in the younger age group and 21% higher for the same comparison in the older age group. By contrast, the single dose vardenafil C_{max} was lower for the ODT than for the FCT in both age groups.

The point estimates and 90% CIs of vardenafil AUC and C_{max} following multiple doses of the ODT 10 mg in the $\leq$ 45 years & $\geq$ 65 years age groups are shown in Table 6. Following multiple dose ODT 10 mg once daily for 10 days, the vardenafil AUC_{ss} and $C_{max, ss}$ were 31% and 16%, higher, respectively, in the older compared with the younger age group. Comparison between single and multiple dose ODT 10 mg administrations showed that vardenafil, as assessed by the relevant AUC ratios, did not significantly accumulate in either age group.

Study 12093 was a sub-group PK study stratified by age. The pivotal efficacy and safety study, Study 12093 or POTENT I, included a PK analysis in 25 patients (n = 12 for those aged 18-64 years, n = 13 for those aged 65 years and over). The PK parameters for vardenafil and M-1 (metabolite 1 of vardenafil) are summarised in Table 7.

The AUC and C_{max} were higher in patients aged 65 years and over compared with patients aged 18-64 years. The 90% CIs of both the mean AUC and C_{max} ratios were not within the accepted bioequivalence interval. The clinical evaluator does make a comment that the similarity of the terminal half-lives in the two age groups (5.4 hours in the younger age group and 5.9 hours in the older) is at odds with the statement made in the study report that the higher AUC and C_{max} values seen in the older age group "*appears to be due to a decrease in systemic clearance as evidenced by an increased terminal half-life...in the elderly compared with the younger patients*". The sponsor was requested to comment on this observation in its response prior to the meeting of the Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC) (pre-ACPM response). The sponsor noted that the increased half-life parallels the increased AUC/decreased CL/f. Both effects on $t_{1/2}$ and AUC are small (9% and 17%) and there is no contradiction.

There were no PK studies with vardenafil 10 mg ODT in patients with hepatic impairment. The PI currently states that patients with moderate hepatic impairment should be started on one 5 mg film-coated tablet which may be subsequently increased to 10 mg based on tolerability and efficacy. The clinical evaluator has recommended that it should be clearly stated that patients with moderate hepatic impairment should be advised not to use the 10 mg ODT tablet to up-titrate from the 5 mg film-coated tablet. If patients with moderate hepatic impairment up-titrate from the 5 mg film-coated tablet then the 10 mg film-coated tablet

should be used. The proposed PI includes a precautionary statement that the 10 mg ODT should not be used in patients with moderate hepatic impairment. The clinical evaluator has further recommended that this precautionary statement should be upgraded to a contraindication for the 10 mg ODT formulation. The 10 mg ODT formulation should not be used in patients with hepatic impairment due to the risks associated with suprabioavailability of the 10 mg ODT formulation compared with the 10 mg FCT formulation. The sponsor noted that it had made both moderate and severe hepatic impairment a contraindication but there was no contraindication for use in mild hepatic impairment.

There were no PK studies with vardenafil 10 mg ODT in patients with renal impairment. The PI indicates that no dose adjustment is required in patients with renal impairment. Consequently, the clinical evaluator considered that the proposed dose of 10 mg ODT can be used in patients with renal impairment with the same precautions as currently in the PI relating to vardenafil not being used in patients requiring dialysis.

Efficacy in Erectile Dysfunction

The submission included two pivotal, Phase III, efficacy and safety studies of identical design, Study 12093, POTENT I and Study 12094, POTENT II. The studies were reviewed and evaluated together. Their primary objectives were to compare the efficacy and safety of vardenafil ODT 10 mg with placebo over a 12-week treatment period in a general population of men with erectile dysfunction. Both studies required approximately 50% on active treatment to be aged at least 65 years. Both studies were multi-national, multi-centre, randomised, placebo-controlled and parallel-group in design. There were 3 co-primary efficacy variables:

- The change from baseline to Week 12 in the International Index of Erectile Function-Erectile Function (IIEF-EF) Domain scores
- SEP 2 (success rates of penetration) on questioning at visit 4 (Week 12) overall
- SEP 3 (maintenance of erection) on questioning at visit 4 (Week 12) overall.

There were a number of secondary efficacy variables including the percentage of subjects achieving "back to normal" erectile function at visit 4 (Week 12). Efficacy of drug treatment was claimed if the primary efficacy variables of IIEF-EF and the overall success rates of the diary questions SEP 2 (penetration) and SEP 3 (maintenance) were simultaneously significant ($p < 0.05$).

Treatment with vardenafil 10 mg ODT was statistically significantly superior to placebo in both pivotal studies for the three primary endpoints. Furthermore, there was consistency between the results of each of the studies. While there were no formal analyses of the primary efficacy endpoints comparing treatments in men stratified by age (< 65 years and ≥ 65 years), there was a consistent trend for the changes in the measured parameters to be not so great in the older age group compared with the younger. However, the changes in both age groups were all consistently positive and the difference between the two groups not substantial.

In both pivotal studies, analyses of all secondary efficacy variables were nominally statistically significant in favour of vardenafil 10 mg ODT compared with placebo. For example, in POTENT I, vardenafil 10 mg ODT resulted in a higher percentage of patients reporting "back to normal" erectile function (40% vardenafil vs 12% placebo). Similarly in POTENT II, vardenafil 10 mg ODT resulted in a higher percentage of patients reporting "back to normal" erectile function (46% vardenafil vs 9% placebo).

The submission included an integrated analysis (PH-35849) of the two pivotal studies. A secondary objective was the confirmation of the efficacy of vardenafil 10 mg ODT as assessed by the three main efficacy variables, IIEF-EF, SEP 2 and SEP 3, overall and in pre-defined subgroups. The integrated efficacy analysis showed that treatment with vardenafil 10 mg ODT was nominally statistically significantly superior to placebo for each of the three efficacy variables ($p < 0.0001$). In addition, sub-group analysis showed that vardenafil 10 mg ODT was nominally statistically significantly superior to placebo for each of the three primary efficacy variables in patients aged less than 65 years and in those aged at least 65 years.

Safety

Integrated Analysis PH-35849: The review of safety focused on the Integrated Analysis (PH-35849) of the data from the two pivotal, randomised, placebo-controlled studies, POTENT I and POTENT II. The *Integrated Safety Analysis* of the two studies included information on a total of 695 patients of whom 355 (51.1%) had been exposed to vardenafil 10 mg ODT and 340 (48.9%) to placebo. In the safety population, 173 patients aged < 65 years had been exposed to vardenafil 10 mg ODT compared with 165 exposed to placebo and 182 patients aged ≥ 65 years had been exposed to vardenafil compared with 175 exposed to placebo. The overall mean exposure time to vardenafil 10 mg ODT was 75.7 days (range 1.0-117.0) and 71.7 days (range 1.0-111.0) for placebo.

The most frequently reported TEAEs in all patients treated with vardenafil ODT 10 mg (vs placebo) were: headache 14.4% (vs 1.8%), flushing 7.6% (vs 0.6%), nasal congestion 3.1% (vs 0.3%), dyspepsia 2.8% (vs 0%), dizziness 2.3% (vs 0%) and back pain 2.0% (vs 1.2%). In the vardenafil ODT 10 mg group, most of the reported TEAEs were rated as mild in intensity and nearly all resolved by study end with most requiring no action.

The most frequently reported TEAEs in vardenafil 10 mg ODT treated patients aged < 65 years (vs ≥ 65 years) were: headache 16% (vs 13%), flushing 9% (vs 6%), nasal congestion 5% (vs 1%), dyspepsia 3% (vs 3%), dizziness 3% (vs 2%), diarrhoea 2% (vs 1%) and back pain 2% (vs 2%).

The *Integrated Safety Analysis* included a treatment comparison of TEAEs of special interest. The incidence rates of TEAEs ≥ 1% in vardenafil 10 mg ODT total treated patients (vs placebo) were: immediate type hypersensitivity reactions 10.7% (vs 1.8%), vasodilatation 8.2% (vs 0.6%), cardiac arrhythmias 2.5% (vs 3.5%), dizziness 2.3% (vs 0%) and oral irritation 1.4% (vs 0.9%). In the age group < 65 years (vs the age group ≥ 65 years), the incidence of immediate type hypersensitivity reactions was 13% (vs 8%) and for vasodilatation was 10% (vs 6%).

There were no treatment emergent deaths. Serious TEAEs were reported in 6 (0.9%) of patients in the total safety population of 695 patients, 2 (0.6%) in the placebo group (neurosensory deafness in a 68 year old male, prostate cancer in a 49 year old male) and 4 (1.7%) in the vardenafil 10 mg ODT group (acute coronary syndrome in a 68 year old male, gastrointestinal haemorrhage in a 65 year old male, syncope in a 72 year old male and hypertension/chest pain in a 55 year old male).

Overall, there were no notable differences in "high" and "low" laboratory abnormalities between the active and placebo groups. Inspection of the laboratory results for vardenafil 10 mg ODT compared with placebo in the < 65 years and ≥ 65 years sub-groups showed them to be similar. The most notable difference between vardenafil (vs placebo) stratified by age was high glucose 13.1% in the < 65 years group (vs 6.6%). There were no notable signals from the assessment of vital signs or from the ECG readings. Patients aged < 65 years and ≥ 65

years had similar safety profiles and no special precautions appear to be required for elderly patients treated with vardenafil 10 mg ODT.

There were no safety data on patients exposed to vardenafil 10 mg ODT for more than 6 months and there were no data on how long patients are likely to continue to take vardenafil 10 mg ODT. The ICH guidelines on the extent of population exposure to assess the safety of medicines intended for long-term treatment of non life threatening conditions suggests 300-600 patients treated for 6 months. These numbers are higher than those observed in the safety population for vardenafil 10 mg ODT. However, as noted by the clinical evaluator, the relatively small exposure numbers in this submission should be interpreted in the context of the known safety data for the film-coated tablet and the likely intermittent use of vardenafil. Furthermore, the clinical evaluator commented that one of the strengths of the two pivotal studies was the high proportion of included patients aged at least 65 years.

Integrated analysis PH-35483: The objective of this integrated analysis was to describe the safety profile of vardenafil in elderly subjects (aged≥ 65 years) in order to show that a 10 mg starting dose was as safe as a 5 mg starting dose. The main analysis was based on 16 of 58 Phase II-IV studies which were in the sponsor's vardenafil Global Integrated Analyses Database (GIAD) on 1 March 2008. The 16 studies included 4294 subjects treated with vardenafil of the total 16905 subjects included in the 58 studies. The 16 studies were divided into two pools (Pools 1 & 3, no Pool 2). Pool 1 included 5 placebo-controlled, fixed-dose studies comparing vardenafil 5, 10 & 20 mg with placebo. Pool 3 included 11 placebo-controlled, flexible-dose studies comparing placebo with vardenafil initiated with a 10 mg dose and allowing the first titration at Week 4. The remaining 42 of the 58 studies including 12611 patients treated with vardenafil were considered supportive. The sponsor was requested to outline, in its pre-ACPM response, the principal characteristics distinguishing the supportive studies from those in the Main Analysis.

Pool 1 (five fixed-dose studies) included 713 subjects treated with placebo, 716 with vardenafil 5 mg, 724 treated with vardenafil 10 mg and 720 treated with vardenafil 20 mg. The total number of subjects was 2873 with 530 (18.5%) aged ≥ 65 years and 2343 (81.5%) aged < 65 years. Pool 3 (11 flexible-dose studies) included 1698 patients treated with placebo and 2134 with vardenafil. The total number of subjects was 3832 with 695 (18.1%) aged ≥ 65 years and 3137 (81.9%) aged < 65 years.

The incidence of TEAEs or ADRs in the Pool 1, fixed-dose studies occurring within the first 4 weeks of treatment was examined and the results showed that the frequency of these events increased with dose in both age groups. There was no significant difference in the TEAE/ADR frequency between the 5 mg and 10 mg doses in subjects aged≥ 65 years. Comparison of the 5 mg with the 10 mg dose in subjects aged≥ 65 years showed that the incidence of all TEAEs was lower in the 10 mg dose group compared with the 5 mg dose group while the reverse was true for all ADRs. The most significant TEAE difference in older subjects between the 5 mg and the 10 mg doses was dizziness (0.7% and 4.2%, respectively). This represents a six-fold increase in the rate of dizziness and was of some concern to the Delegate.

The incidence of serious TEAEs in Pool 1 was higher in subjects aged≥ 65 years than in subjects aged < 65 years. The between treatment and between age group differences in serious TEAEs did not give rise to concern. The serious TEAEs reported with vardenafil in subjects ≥ 65 years appeared to be unrelated to treatment.

In subjects aged ≥ 65 years, the incidence of TEAEs of special interest (for example, central serious retinopathy, CVA, MI, NAION, priapism, QT prolongation, seizures, syncope and

hypotension) was two-fold higher in the vardenafil 10 mg group compared with the vardenafil 5 mg group. However, absolute subject numbers were small (4 and 2, respectively).

The overall incidence rates for TEAEs or ADRs and serious TEAEs in the Pool 3, flexible-dose studies with vardenafil starting at a dose of 10 mg were examined. The incidence rates for all AE, ADR or serious AEs were comparable in the two age groups. Incidence rates of AEs leading to dose reduction were 1.4% in the younger subjects and 0.6% for the elderly subjects.

Regarding the incidence rates of TEAEs of special interest occurring in the first 4 weeks of treatment, the results indicated that they were lower in older subjects compared with younger subjects when vardenafil was initiated at a dose of 10 mg.

The Pool 1 and Pool 3 data included a comparison between vardenafil and placebo for selected treatment emergent laboratory abnormalities (AST, ALT and CK). The results showed that, although the incidence rates for the vardenafil 5 mg and 10 mg doses in the elderly subjects for the three parameters of interest were lower than for the younger subjects, the reverse was the case for the placebo-subtracted rates. The incidence rates on placebo in the younger age group were particularly high. In the elderly group, the incidence rates for each of the three parameters of interest were higher in subjects treated with vardenafil 10 mg than with vardenafil 5 mg. The clinical evaluator was critical of the reporters in the analysis for their tendency to over interpret the significance of the lower incidence rates observed with vardenafil in the elderly compared with the younger by not accounting for the high placebo rates seen in younger subjects. The sponsor was requested to respond to this comment by the clinical evaluator.

Integrated Analyses, REALISE [Europe and Overseas] and REALISE [USA]: These two analyses reported results from the Real-Life Safety and Efficacy Study (REALISE) which was a prospective, international, company-sponsored, non-interventional, post-marketing surveillance study in which men with erectile dysfunction who were prescribed vardenafil prn in routine clinical practice were followed for a period of 2 months. The study population was stratified by age (< 65 years and ≥ 65 years). The data were reported in separate analyses for "Regions of Europe and Overseas" and for the "USA".

Europe and Overseas: Data were analysed from a total of 73,946 patients from 26 countries between March 2003 and November 2005. Of the analysed patients, 20.1% (14,861) were aged ≥ 65 years and 79.4% (58,700) were aged < 65 years. The most frequently prescribed initial vardenafil dose was 10 mg, 74.9% in younger patients and 72.1% in elderly patients.

USA: Data were analysed from a total of 30,010 patients between October 2003 and September 2004. Of these patients, 7,178 (23.9%) were aged ≥ 65 years and 22,604 (75.3%) were aged < 65 years. Again, the most frequently prescribed initial vardenafil dose was 10 mg, 67.6% in younger patients and 60.7% in elderly patients.

In both analyses, REALISE [Europe and Other Regions] and REALISE [US], there were no notable differences in the frequency of AEs for younger or elderly patients at any of the starting doses. Similarly, no marked differences due to age in the different dose groups were seen with respect to the frequency of ADRs, SAEs or SADRs. Serious ADRs were very infrequently reported in both populations.

Expert statement – Bayer HealthCare August 2008: This expert statement summarised PK data from one study in healthy subjects and population PK studies combining data from healthy subjects and patients with erectile dysfunction. The studies included in the expert statement showed that age consistently increased vardenafil exposure in elderly subjects

compared with younger subjects in both men with erectile dysfunction and healthy volunteers.

Clinical evaluator's overall comment regarding the proposed amendment to the PI about the initial dose in elderly patients: The data submitted in support of the proposal was judged to be comprehensive. The PK data showed that, although exposure to vardenafil increased in older compared with younger subjects, this did not translate into an increased risk of adverse events in the older subjects. The data also showed that vardenafil safety profiles in elderly subjects aged ≥ 65 years were similar irrespective of whether treatment was initiated with 5 mg or 10 mg. Post-marketing surveillance data from REALISE indicated that most elderly patients being treated with vardenafil in these large populations had treatment initiated with a 10 mg dose rather than a 5 mg dose – despite the PI recommendation for the latter.

Response by the sponsor to the Clinical Evaluation Report

The sponsor was requested by the clinical evaluator to provide data supporting the statement that "*Levitra ODT disintegrates on the tongue within a few seconds*". The sponsor replied that this statement is based on the *in vitro* disintegration test performed according to the European Pharmacopoeia. In this test orodispersible tablets were shown to have disintegration times of 9 seconds. The sponsor went on to state that throughout the clinical studies a consistent mode of administration was used for the ODT formulation, that is, it was administered without water. Subjects had to place it on the tongue and were instructed not to chew the tablet but to manipulate it with the tongue against the palate once every second and swallow once the ODT had disintegrated. Subjects were also instructed not to bite on the particles present after disintegration. The sponsor also provided an assurance that it does not intend to make a quantitative claim that the tablet disintegrates on the tongue within a few seconds. Such a statement is not to be included in either the PI or the CMI.

The Delegate reviewed the instructions for taking the tablet and even in the CMI, they are quite vague. The Delegate requested that the specific set of instructions given to subjects in the clinical trials be reproduced in both the PI and the CMI. In the latter, a more easily understandable term than 'palate' will have to be used.

The sponsor replied to the request of the clinical evaluator that the precautionary statement recommending against the use of the 10 mg ODT formulation in patients with hepatic impairment should be upgraded to a contraindication for the 10 mg ODT formulation. The sponsor argued that, based on the demonstrated small increases in AUC (+17%) and C_{max} (+22%) for vardenafil FCT in Child-Pugh A subjects, similar relative changes would be expected for vardenafil ODT. A table showing the relevant data for the 10 mg FCT tablet is reproduced below:

Mean ratios of vardenafil AUC and C_{max} and corresponding 90% confidence intervals (hepatically impaired subjects vs healthy subjects) following administration of 10 mg vardenafil FCT

Parameter	Child-Pugh A vs healthy	Child-Pugh B vs healthy
AUC	1.17 (0.66 – 2.07)	2.60 (1.47 – 4.61)
C_{max}	1.22 (0.76 – 1.97)	2.33 (1.45 – 3.77)

The sponsor went on to argue that, given that the 10 mg ODT formulation has up to 1.44-fold higher AUC compared with the 10 mg FCT, subjects with mild hepatic impairment (Child-Pugh A) would be expected to show up to 1.7-fold (1.17 x 1.44 = 1.68) higher AUC with the

10 mg ODT in comparison with that when the 10 mg FCT is taken by healthy subjects. With vardenafil AUC and C_{max} increasing more than dose proportionally from 10 mg FCT to 20 mg FCT, the AUC and C_{max} of 10 mg ODT in Child-Pugh A subjects would fall below the corresponding values for the 20 mg FCT which is the highest approved and marketed dose. Thus the sponsor argued that a contraindication for vardenafil 10 mg ODT in subjects with mild hepatic impairment (Child-Pugh A) appears not to be warranted.

The Delegate agreed. The Delegate also pointed out that he does not think it was the intention of the clinical evaluator to recommend a blanket contraindication in patients with hepatic impairment of any grade but rather to recommend a contraindication in those with moderate (and worse) hepatic impairment. The Delegate noted that the sponsor has in fact upgraded the precaution about moderate hepatic impairment to a contraindication. The RMP evaluator also recommended this latter upgrading of the hepatic impairment precaution. The Delegate sought specific comment from the ACPM about the situation of those with mild hepatic impairment. Given the fact that the vardenafil AUC and C_{max} do increase more than dose proportionally from 10 mg FCT to 20 mg FCT, there is a case for imposing a maximum FCT dose of 10 mg in subjects with mild hepatic impairment. There is currently a ceiling dose of 10 mg FCT for those with moderate hepatic impairment. The sponsor was asked to comment on this issue and the Delegate also asked for specific comment from the ACPM.

The sponsor accepted all the other recommendations of the clinical evaluator regarding the PI, in particular the recommendation that the orodispersible tablet formulation should have its own PI and CMI.

Risk Management Plan

The RMP (Version 1.0, July 2009) was evaluated by the Office of Product Review (formerly OMSM). It was evaluated as acceptable by the RMP evaluator who made a number of recommendations regarding issues which needed to be addressed by the sponsor (see *Section V*).

The sponsor responded to the RMP evaluation and the response was considered acceptable by the Office of Product Review. The sponsor outlined anti-counterfeit mechanisms and agreed to the inclusion of sudden decrease or loss of hearing to the RMP pharmacovigilance plan and to provide updates on the progress and analysis of safety relevant pharmacoepidemiological studies in future PSURs. There were no outstanding issues from the RMP review.

Risk-Benefit Analysis

Delegate Considerations

The pharmacokinetics of vardenafil 10 mg ODT have been adequately characterised following single dosing in healthy young men and single and multiple once daily dosing in men with erectile dysfunction aged < 65 years and≥ 65 years. The bioavailability of vardenafil following single dose ODT 10 mg (fasting, without water), as assessed by the AUC, was higher than that of single dose FCT 10 mg (fasting, with water) in healthy young men (by 44%) and in young (by 29%) and elderly (by 21%) men with erectile dysfunction. The data showed that the ODT 10 mg (fasting, without water) and the FCT 10 mg (fasting, with water) were not bioequivalent in any of the populations studied. Food (high fat, high calorie breakfast) reduced the vardenafil AUC by 2% and the C_{max} by 35%, in comparison with fasting, following single dose vardenafil ODT 10 mg. Overall the data suggest that the clinical effects of ODT 10 mg are unlikely to be different either with or without food. Overall, the comparative data showed that vardenafil AUC and C_{max} values were higher in

elderly men with erectile dysfunction compared with younger men with erectile dysfunction. This might be due to reduced vardenafil clearance in elderly compared with younger men, although the clinical evaluator has questioned this and the sponsor has been asked to comment. The multiple once daily ODT 10 mg data showed that accumulation of vardenafil was not marked. The AUC was 8.6% (≤ 45 years) and 2.7% (≥ 65 years) higher following multiple dose compared with single dose in men with erectile dysfunction and the corresponding values for C_{max} were 16% and 11%.

There were no PK studies with vardenafil 10 mg ODT in patients with hepatic impairment. However, it has been contraindicated in those with either moderate or severe degrees of hepatic impairment (Child-Pugh B and C, respectively). The sponsor has outlined data to show that, in subjects with mild hepatic impairment (Child-Pugh A), the AUC with the ODT 10 mg could be expected to be up to 1.7-fold higher than the AUC for the FCT 10 mg in healthy subjects. Such a level of AUC in subjects with mild hepatic impairment would then fall below the AUC associated with the FCT 20 mg, the highest approved and marketed dose. The Delegate regarded the sponsor's argument as reasonable. Also the Delegate was of the opinion that there is a case for imposing a ceiling dose of 10 mg (either ODT or FCT) in those with mild hepatic impairment.

The submission has satisfactorily established the benefits of vardenafil 10 mg ODT taken 1 hour before sexual intercourse on an as needed basis for the treatment of erectile dysfunction in men aged < 65 years and ≥ 65 years. Based on the IIEF-EF LS mean scores in the integrated efficacy analysis it can be inferred that ED clinically improved from moderate intensity at baseline to mild intensity after 12 weeks treatment with vardenafil 10 mg ODT. By contrast, in the placebo-treated patients there was no meaningful improvement in erectile dysfunction with intensity being moderate both before and after treatment. Furthermore, erectile function success rates as measured by vaginal penetration (SEP 2) and maintenance of erection (SEP 3) were both higher in vardenafil 10 mg ODT treated patients compared with placebo and the differences were clinically meaningful.

The safety profile of the vardenafil 10 mg ODT formulation appears to be similar to that of the vardenafil FCT formulations and raises no new safety concerns or signals. There were no significant differences between the vardenafil 10 mg ODT safety profiles for patients aged < 65 years and for those aged ≥ 65 years. There were no safety data on patients exposed to vardenafil 10 mg ODT for more than 6 months and there were no data on how long patients are likely to continue to take vardenafil 10 mg ODT. However, as noted by the clinical evaluator, the relatively small exposure numbers in the two pivotal trials, POTENT I and POTENT II, should be interpreted in the context of the known safety data for the FCT formulation and the likely intermittent use of vardenafil. Furthermore, as again noted by the clinical evaluator, one of the strengths of the pivotal studies was the significant number of patients studied who were aged ≥ 65 years. There are good comparative safety data on patients aged ≥ 65 years and on patients aged < 65 years. The most commonly occurring TEAEs reported with vardenafil were headache 14.4%, flushing 7.6%, nasal congestion 3.1%, dyspepsia 2.8%, dizziness 2.3% and back pain 2.0%. The difference between vardenafil and placebo in the rates of serious TEAEs did not give rise to concern. There were no treatment emergent deaths reported in the two pivotal studies. Discontinuations due to AEs occurred in 1.4% (n = 5) of vardenafil-treated patients and in 0.6% (n = 2) of placebo-treated patients. The interpretation of laboratory and ECG findings were limited by the lack of a meaningful temporal relationship between study medication and measurements.

The data submitted in support of the proposed amendment to the PI relating to the initial dose in elderly patients was comprehensive, being from a number of sources. The PK data showed

that, although exposure to vardenafil increased in older compared with younger subjects, this generally did not translate into an increased risk of adverse events in the older subjects. The data also showed that vardenafil safety profiles in elderly subjects aged ≥ 65 years were similar regardless of whether treatment was initiated with 5 mg or with 10 mg. As noted by the clinical evaluator, the post-marketing surveillance data from both populations for the REALISE analysis indicated that most elderly subjects being treated with vardenafil had treatment initiated with a 10 mg dose rather than a 5 mg dose despite the PI recommendation for the latter. In addition to the integrated analyses and expert reports submitted to support the PI amendment, the data from the two pivotal studies, POTENT I and POTENT II, provided as evidence for the registration of the 10 mg ODT formulation, demonstrated that treatment in elderly patients aged ≥ 65 years can be safely administered with this dose and formulation. Each of these pivotal studies had approximately 50% of participants who were at least 65 years of age. The Delegate expressed one concern and this was the observation of a six-fold increase in the rate of dizziness in older subjects between doses of 5 mg and 10 mg in the Pool 1 fixed-dose studies of the Integrated Analysis PH-35483 (comparative rates of 0.7% in the 5 mg dose group vs 4.2% in the 10 mg dose group). Dizziness, particularly in the elderly, can have serious consequences. The recommendation of the clinical evaluator was that the submitted data support the proposed PI amendment relating to no dosage adjustment being required in the elderly based on age alone, that is, the usual recommendation will apply, a starting dose of 10 mg, whether ODT or FCT. Before the Delegate could agree to this recommendation, there would have to be some minimum level of appropriate amendment of the PI, for example, a specific precautionary paragraph in the Precautions section on dizziness together with cross-references between this new precaution and the dosage recommendation concerning the elderly.

Efficacy has been satisfactorily established on the basis of the positive changes from baseline to Week 12 in all of the three co-primary endpoints. Benefit was consistently established in both age groups, those under the age of 65 years and those at least 65 years of age. The safety profile of the vardenafil 10 mg ODT formulation appears to be similar to that of the vardenafil FCT formulations and raises no new specific safety concerns or signals. The Delegate therefore was proposing approval of the submission in this regard.

The data submitted in support of the proposed amendment to the PI relating to the initial dose in elderly patients was comprehensive. It not only included data from the two pivotal studies but from two large integrated analyses from the sponsor's global safety database and was generally positive. The effect of the proposed amendment will be to remove the recommendation about the need for a starting dose of 5 mg in elderly patients which, it would appear, is already largely ignored in clinical practice. However, the Delegate was concerned about the differential rates of dizziness reported in the elderly on doses of 5 mg and 10 mg – data in fact from a large integrated source. At this stage, the Delegate regarded the proposed amendment as approvable provided certain minimum changes to the PIs for both the ODT and the FCT are undertaken.

The Delegate proposed approval of the submission for the indication of:

For the treatment of erectile dysfunction in adult males (inability to achieve or maintain penile erection sufficient for satisfactory sexual performance).

Levitra is not indicated for use by women.

The sponsor should address the following issues in their pre-ACPM response:

- The sponsor was requested to provide a summary of what more has been learned in the period since registration of Levitra in Australia about the issues of nitrate

interaction and the interaction with anti-hypertensive agents, the two issues which the ACPM (as ADEC) identified, at the time of the original submission, as not having been comprehensively and definitively addressed.

- The sponsor was requested to comment on the similarity of the terminal half-lives of vardenafil for the younger and older age groups in the PK sub-study of Study 12093 and how this appears to be at odds with the claim that the higher AUC and C_{max} values seen in the older age group may be due to a decrease in systemic clearance.
- The sponsor was requested to detail the main characteristics distinguishing the supportive studies from those in the Main Analysis of PH-35483. In other words what, chiefly, disallowed a supportive study from being included in the Main Analysis?
- In the Pool 1 fixed-dose studies of the Integrated Analysis PH-35483, the most significant TEAE difference in older subjects between the 5 mg and the 10 mg doses was dizziness (0.7% and 4.2%, respectively). This represents a six-fold difference and is of some concern. The sponsor was asked to implement some amendments to the PIs of both the FCT and ODT products to address this concern. If the sponsor does not agree with these requests, then the sponsor was requested to submit a justification in support.
- The Pool 1 and Pool 3 data of PH-35483 included a comparison between vardenafil and placebo for selected treatment emergent laboratory abnormalities (AST, ALT and CK). The clinical evaluator was critical of the reporters in the analysis for their tendency to over interpret the significance of the lower incidence rates observed with vardenafil in the elderly compared with the younger by not accounting for the high placebo rates seen in younger subjects. The sponsor was requested to respond to this comment by the clinical evaluator.
- The sponsor was requested to justify why there should not be a ceiling dose of 10 mg (either ODT or FCT) for those subjects with mild hepatic impairment.

The Delegate also asked the following questions of ACPM:

- Does the ACPM agree that there is sufficient evidence to support the registration of the new dosage form, the 10 mg vardenafil orodispersible tablet?
- Does the ACPM agree that there is no need to include instructions regarding dosing which are specific to the elderly? In one of the integrated analyses of safety, the most significant TEAE difference in older subjects between the 5 mg FCT and 10 FCT doses was dizziness (0.7% and 4.2%, respectively). Is this finding alone sufficient to maintain the starting dose in the elderly at 5 mg FCT or can the need for the starting dose be dispensed with, as proposed, by suitable amendment of the PI?
- Does the ACPM agree with the instruction regarding the ODT in patients with mild hepatic impairment (start with 5 mg FCT which may be increased to one Levitra 10 mg ODT)?
- What is the ACPM's view on the need for a dosage ceiling in those with mild hepatic impairment? Should there be a ceiling of 10 mg (either ODT or FCT)?
- Does the ACPM agree with the recommendations concerning the dose of vardenafil to be taken concomitantly with clarithromycin?

Response from Sponsor

Dosage recommendation for elderly

Prevalence of erectile dysfunction is age-related, with the proportion of patients experiencing the disorder increasing significantly with age. The Massachusetts Male Ageing Study suggests combined prevalence of minimal, moderate and complete impotence of 52% between 40 and 70 years-of-age and complete ED in over 15% of men by the age of 70 years.[12]

As observed in previous PK studies, elderly males (≥ 65 years of age) have higher vardenafil plasma concentrations than younger subjects (18 – 64 years of age). Abundant clinical experience has been accumulated in clinical trials and post-marketing studies since registration in 2003 including usage in elderly population with robust efficacy demonstrated in the general ED population when given 10 mg vardenafil. The overall safety profile of vardenafil administered at a starting dose of 5 mg or 10 mg is comparable in otherwise healthy elderly ED patients to that of the younger patients.

Data presented from two placebo controlled Phase III studies (10128 and 100249) investigates whether elderly patients treated for ED at the recommended starting dose of 5 mg vardenafil are receiving a less efficacious treatment than younger patients (< 65 years-of-age) who routinely start at the higher standard dose of 10 mg. Although the PI for Levitra film-coated tablet currently recommends a starting dose of 5 mg in elderly patients, data from post-marketing studies supports safety and efficacy in elderly patients initiated on vardenafil therapy with a 10 mg dose.

Criteria of main and supportive studies in integrated analysis PH-35483

In support of the removal of 5 mg starting dose restriction in elderly; 58 Phase II-IV studies were integrated and analysed. With reference to PH-35483, the main analysis was based on 16 of 58 Phase II-IV studies, the remaining 42 of 58 studies were considered supportive. The Delegate requested detail on the main characteristics distinguishing the supportive studies from those in the Main Analysis of PH-35483.

The purpose of the safety overview by means of an integrated analysis (PH-35483) was to cover all available data to enable assessment of the safety profile of vardenafil in elderly patients. Due to the different study designs, the studies were categorised into 4 populations according to the appropriateness for comparing the safety profile of different vardenafil doses in the elderly.

The 16 studies for the main analysis are randomised placebo-controlled double-blinded studies testing on-demand treatment for a general population of subjects with erectile dysfunction with at least one group having a starting dose of 10 mg and without a restriction to subjects younger than 65 years. Based on these characteristics it was seen that it provides the most relevant comparison of safety findings between doses and age groups.

Supportive studies comprised additional Phase II – IV studies with vardenafil included in the company data base at the time of the analysis. These studies focussed on special populations (for example, diabetes, post radical prostatectomy, spinal cord injury) provided daily dosing, did not include placebo, used open comparisons with competitors, or had a restriction to younger patients. Due to the differences in design, main objective and included populations these studies were judged to provide only supportive information to the question of the safety of a 10 mg starting dose.

[12] Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, Mckinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts male aging study. J Urol 1994; 151: 54-61.

Drug interactions with nitrate and anti-hypertensive

The Delegate requested a summary of learning in the period since registration of Levitra in Australia on the issues of drug interactions with a focus on nitrate and anti- hypertensive agents. Since registration of Levitra globally, adverse events including events caused by drug interactions have been continuously monitored, with reported cases of drug interactions collected world-wide captured in the PSUR. Clear contraindications and appropriate warning statements regarding drug interactions are provided in the Product Information.

Concomitant use of nitrates is contraindicated and patients are warned repeatedly not to use nitrates while taking Levitra in the CMI; with instructions to seek medical assistance immediately upon angina attack and not to use nitrates to relieve the pain. The small number of cases received post-marketing, reporting a concomitant use of vardenafil with nitrates, can be interpreted as a high level of awareness. Thus, the current label is considered adequate to ensure the safe use of the product.

Furthermore, drug interaction studies have been conducted with agents such as tamsulosin or terazosin to investigate the additive blood pressure lowering effect. The data of these studies have been incorporated in Precautions and demonstrated Interactions section of the PI. Based on the data presented in the PSURs, it can be concluded that this topic is also adequately addressed in the label.

Age-related Pharmacokinetics

In relation to PK study, the Delegate has pointed out that similarity of the terminal half-lives of vardenafil for the younger and older ages groups observed in Study 12093 and the claim that the higher AUC and C_{max} values seen in the two groups may be due to a decrease in systemic clearance appears inconsistent. ED patients in study 12093 showed a relatively small increase of 17% in vardenafil AUC in the age category ≥ 65 years' compared to '18 -64 years'. This was paralleled by a small increase (9.5%) in terminal elimination half-life $t_{1/2}$ (geometric mean value). The mean ages of ED patients in these strata were 70.9 years (n=13) and 53.2 years (n=12).

When comparing the same age categories in a second study conducted to investigate the effect of age on the pharmacokinetics of vardenafil ODT (study 13396), vardenafil AUC and $t_{1/2}$ were increased by 41% and 37%, respectively, in the elderly after the first administration of 10 mg ODT. In this study the mean ages of the strata '≥ 65 years' and '18-64 years' were 70.5 years (n=14) and 44.0 years (n=20).

Taking together both studies, the increase in vardenafil AUC, that is, decrease in apparent oral clearance CL/f was always accompanied by an increase in terminal half-life. The effect of age on AUC and $t_{1/2}$ was smaller in study 12093 in comparison to study 13396, most likely as a result of the smaller difference in mean age of the strata ≥ 65 years' and '18 -64 years' in study 12093. In the latter study the mean ages of both strata differed by 18 years whereas the difference in study 13396 was equal to 27 years. In summary, the data demonstrates a consistent effect of age on vardenafil AUC and elimination $t_{1/2}$ which can be explained by a change in systemic clearance. The magnitude of the effect depends on the age distribution of the patients recruited in the respective strata.

Hepatic impairment

Use of vardenafil in patients with various degrees of hepatic impairment has been a topic of interest throughout evaluation of this application. With reference made to previous PK data on 10 mg vardenafil film-coated tablets in patients with hepatic impairment, vardenafil clearance was reduced in proportion to the degree of hepatic impairment and consequently a

higher AUC (1.2-fold and 2.6-fold increase in Child-Pugh A and Child-Pugh B respectively) was observed as compared to healthy control subjects. In light of this finding, the sponsor concurred with the advice recommended by both clinical and RMP evaluators to upgrade use of ODT in moderate hepatic impairment to be contraindicated. In addition, the sponsor has proactively included precautionary measure to recommend a starting dose of 5 mg for patients with mild hepatic impairment. Attention should be paid to the currently approved film-coated PI which has no restriction on dose adjustment for patients with mild-hepatic impairment.

In principle, the sponsor agrees with the Delegate's comment regarding a ceiling dose for mild hepatic impairment for ODT to be 10 mg vardenafil but would like to highlight that 10 mg is the only proposed dose for the ODT formulation. This would therefore make the suggested statement redundant, but the sponsor was agreeable to include such a statement in the PI for Levitra orodispersible tablets.

With respect to a similar statement for Levitra film-coated (FC) tablets, the sponsor would like to draw attention to data previously evaluated by the TGA that supports use of Levitra FC tablets in mild hepatic impairment for 5, 10 and 20 mg doses. The sponsor thus believes that a ceiling dose for mild hepatic impairment is not justified or warranted based on data available for the FC tablet. The sponsor believed that clinical trial data to support safety and efficacy of ODT formulation in patients does not have any impact on the approved dosage recommendation for patients with hepatic impairment in the Levitra film-coated tablets PI.

Incidence of dizziness in Pool 1 of study PH-35483

In the Pool 1 data of the Integrated Analysis PH-35483, dizziness was reported as TEAE in one patient at the 5 mg dose and 5 patients at the 10 mg dose in the elderly population. However, a review of the individual cases showed that in four of the five elderly patients at the 10 mg dose, dizziness was mild and resolved without any further action being taken. In the one remaining patient, moderately severe dizziness was reported that resolved when vardenafil treatment was discontinued.

Dizziness may occur due to the vasodilatory properties of vardenafil. The PI has been updated to include reference to dizziness under Precautions and Dosage and Administration.

Incidence rates of TE lab abnormalities in study PH-35483

The Clinical Evaluator was critical of the reporters in the analysis for their tendency to over interpret the significance of the lower incidence rates observed with vardenafil in the elderly compared with the younger by not accounting for the high placebo rates seen in younger subjects.

In relation to TE lab abnormalities (AST, ALT and CK) in Pool 1 and Pool 3 data of PH-35483, the sponsor asserted that it was not intended to suggest that the numerical lower rate of abnormalities seen under vardenafil in elderly as compared to younger subjects has any significance. It was agreed that taking into account the placebo incidence rates there may be a higher rate in elderly under vardenafil. However, the incidence rates are still within the range which is shown for younger subjects under placebo and the sponsor considered this to be of minor significance.

Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

ACPM recommended approval of the submission for the indication:

For the treatment of erectile dysfunction in adult males (inability to achieve or maintain penile erection sufficient for satisfactory sexual performance).

Levitra is not indicated for use by women.

In making this recommendation, the ACPM considered the comparative bioavailability data for the current and new dosage forms and supported the Delegate in that further consideration should be given to ensuring an improved safety profile by recommending that the lowest effective starting dose is prescribed for patients, particularly in population groups that may have concomitant antihypertensive therapy. The ACPM noted that studies were conducted in a population that generally did not have co-morbidities, however it also recognised the clinical difficulty in defining mild versus moderate or severe reduced hepatic function and the continued lack of pharmacokinetic data in patients with reduced hepatic impairment.

The ACPM also recommended changes to the Product Information (PI) and Consumer Medicines Information (CMI) which should be made prior to approval but these are beyond the scope of this AusPAR.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Levitra orodispersible tablets containing vardenafil 10 mg, indicated for:

For the treatment of erectile dysfunction in adult males (inability to achieve or maintain penile erection sufficient for satisfactory sexual performance).

Levitra is not indicated for use by women.

Included in the specific conditions of registration was the implementation in Australia of the vardenafil Risk Management Plan (RMP), version 1.0, July 2009 and the changes agreed to in the sponsor's response to the RMP evaluation report dated 20 July 2010 and sent to the sponsor on 28 July 2010, included with the submission, and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRODUCT INFORMATION

LEVITRA® 10 mg orodispersible tablets

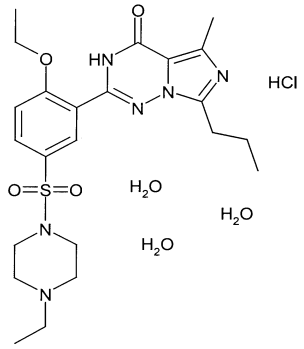
(vardenafil)

NAME OF THE MEDICINE

Vardenafil, as vardenafil hydrochloride trihydrate is 2-[2-ethoxy-5-(4-ethyl-piperazine-1-sulfonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one hydrochloride trihydrate. It is a nearly colourless solid. Vardenafil hydrochloride trihydrate is soluble in 0.1M HCl, very slightly soluble in water, freely soluble in methanol, soluble in ethanol and slightly soluble in acetone.

The empirical formula of vardenafil hydrochloride trihydrate is $C_{23}H_{32}N_6O_4S.HCl.3H_2O$ and its molecular weight is 579.1 g/mol. Its chemical structure is shown in Figure 1. (CAS number: 224785-90-4)

Figure 1.



DESCRIPTION

Levitra orodispersible tablet is a white round tablet without tablet markings. Each tablet contains 10 mg of vardenafil (as 11.852 mg of vardenafil hydrochloride trihydrate).

Levitra orodispersible tablets contain the following excipients: aspartame, peppermint flavour 290017, magnesium stearate, crospovidone, mannitol, silicon dioxide and sorbitol.

PHARMACOLOGY

The pharmacodynamic studies described below were conducted using vardenafil film-coated tablets.

Penile erection is a haemodynamic process based on the relaxation of smooth muscle in the corpus cavernosum and its associated arterioles. During sexual stimulation, from nerve ends in the corpus cavernosum nitric oxide (NO) is released, which activates the enzyme guanylate cyclase resulting in an increased level of cyclic guanosine monophosphate (cGMP) in the corpus cavernosum. This in turn triggers smooth muscle relaxation, allowing increased inflow of blood into the penis resulting in erection. The

actual cGMP level is regulated by the rate of synthesis via the guanylate cyclase on the one hand, and by the rate of degradation via cGMP hydrolyzing phosphodiesterases (PDEs) on the other hand.

The most prominent PDE in the human corpus cavernosum is the cGMP specific phosphodiesterase type 5 (PDE5).

By inhibiting PDE5, the enzyme responsible for cGMP degradation in the corpus cavernosum, vardenafil potently enhances the effect of endogenous NO, locally released in corpus cavernosum upon sexual stimulation. The inhibition of PDE5 by vardenafil leads to increased cGMP levels in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum. Vardenafil thus potentiates the natural response to sexual stimulation.

In vitro assays have shown that vardenafil is a selective inhibitor of PDE5, with an IC_{50} of 0.7 nM for human platelet PDE5.

The inhibitory effect of vardenafil is more potent on PDE5 than on 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). *In vitro*, vardenafil causes an elevation of cGMP in the isolated human corpus cavernosum resulting in muscle relaxation.

In the conscious rabbit, vardenafil causes a penile erection which is dependent upon endogenous nitric oxide synthesis and is potentiated by nitric oxide donors.

Effects on Visual Perception

In a specific clinical trial, evaluation of visual function at a vardenafil dose of 40 mg (twice the maximum recommended daily dose) revealed no effects of vardenafil on visual acuity, visual fields, intraocular pressure, ERG latency, fundoscopic and slit lamp findings. A subset of patients was found to have mild and transient impairment of colour discrimination in the blue/green range and in the purple range 1 hour after dosing. These changes had improved by 6 hours and no changes were present at 24 hours. The majority of these patients had no subjective visual symptoms.

In other trials, daily use of vardenafil at doses of 10 mg to 40 mg for 31 days was not associated with changes in visual acuity, intraocular pressure, or findings on fundoscopic or slit lamp examination.

Effects on Blood Pressure

Vardenafil causes mild and transient decreases in blood pressure which, in the majority of the cases, do not translate into clinical effects. The mean maximum decreases in supine systolic blood pressure following 20 mg and 40 mg vardenafil were -6.9 mmHg with 20 mg and -4.3 mmHg with 40 mg of vardenafil, when compared to placebo.

Effects on Cardiac Parameters

Single oral doses of vardenafil up to 80 mg (four times the maximum recommended daily dose) did not produce clinically relevant effects on the ECGs of healthy volunteers.

Effects on Exercise Performance in Patients with Coronary Artery Disease

In a two-period, placebo-controlled, cross-over trial, 10 mg vardenafil did not alter the total treadmill exercise time compared to placebo in 39 male patients aged 48-77 years with coronary artery disease and exercise induced ischaemia. The total time to angina was not altered compared to placebo; however, the total time to 1 mm or greater ST-segment depression was prolonged 15% in the vardenafil group compared to the placebo group ($p<0.001$). All patients who entered the trial completed the exercise treadmill tests without significant drug-related side effects.

Pharmacokinetics

Absorption

The median time to reach C_{max} in patients receiving Levitra orodispersible tablets in the fasted state varied between 45 and 90 minutes. After administration of Levitra 10 mg orodispersible tablets to patients mean vardenafil AUC was increased by 21 to 29 % while mean C_{max} was 8 to 19% lower in comparison to 10 mg vardenafil film-coated tablet. A high fat meal had no effect on vardenafil AUC and t_{max} while it resulted in a mean reduction in vardenafil C_{max} by 35%. Based on these results Levitra orodispersible tablets can be taken with or without food. If Levitra orodispersible tablet is taken with water, the AUC is reduced by 29% and median t_{max} is shortened by 60 minutes while C_{max} is not affected. Levitra orodispersible tablet should be taken without liquid. If taken with water, the pharmacokinetic profile is expected to be similar to that of vardenafil 10 mg film-coated tablets.

Bioavailability studies have shown that Levitra 10 mg orodispersible tablet is not bioequivalent to Levitra 10 mg film-coated tablet. The bioavailability (AUC) from the 10 mg orodispersible tablet is 21 to 29% higher in patients and 44% higher in healthy subjects than from the Levitra 10 mg film-coated tablet. Therefore, Levitra 10 mg orodispersible tablets should not be used as an equivalent to Levitra 10 mg film-coated tablets.

Distribution

The mean steady state volume of distribution (V_{ss}) for vardenafil is about 2.5 L/kg, indicating distribution into the tissues.

Vardenafil and its major circulating metabolite (M1) are highly bound to plasma proteins (about 95% for parent drug or M1). This protein binding is reversible and independent of total drug concentrations.

Based upon measurements of vardenafil in semen of healthy subjects 90 minutes after dosing, not more than 0.0002% of the administered dose may appear in the semen of patients.

Metabolism

Vardenafil is metabolised predominantly by hepatic enzymes via CYP3A4, with some contribution from CYP3A5 and CYP2C9 isoforms.

In humans, the major circulating metabolite (M1) results from desethylation at the piperazine moiety of vardenafil, and is subject to further metabolism. The terminal plasma elimination half-life of the metabolite M1 is comparable to the parent drug. M1 is also

present in its glucuronide-conjugated (glucuronic acid) form in systemic circulation. The plasma concentration of non-glucuronidated M1 is about 26% that of the parent compound. The metabolite M1 shows a phosphodiesterase selectivity profile similar to that of vardenafil and an *in vitro* inhibitory potency for PDE5 of approximately 28% compared to vardenafil, resulting in an efficacy contribution of about 7%.

The mean terminal half life of vardenafil in patients receiving Levitra orodispersible tablets varied between about 4 – 6 hours. The elimination half life of the metabolite M1 is approximately 3 hours.

Excretion

After oral administration, vardenafil is excreted as metabolites predominantly in the faeces (approximately 91 - 95% of administered oral dose) and to a lesser extent in the urine (approximately 2 - 6% of administered oral dose).

Pharmacokinetics in special populations

Elderly

Vardenafil AUC and C_{max} in elderly patients (65 years or over) taking Levitra orodispersible tablets were increased by 31 to 39% and 16 to 21%, respectively, in comparison to patients aged 45 years and below. Vardenafil was not found to accumulate in the plasma in patients aged 45 years and below or 65 years or over following once-daily dosing of Levitra 10 mg orodispersible tablet over ten days.

Renal insufficiency

In patients with mild (CL_{cr} > 50 – 80 mL/min) to moderate (CL_{cr} > 30 – 50 mL/min) renal impairment vardenafil pharmacokinetics were similar to that of a normal renal function control group following a vardenafil 20 mg film-coated tablet dose. In volunteers with severe renal impairment (CL_{cr} < 30 mL/min) the mean AUC was increased by 21% and the mean C_{max} decreased by 23%, compared to volunteers with no renal impairment. No statistically significant correlation between creatinine clearance and vardenafil plasma exposure (AUC and C_{max}) was observed. Based on this data, no dose adjustment is needed in patients with impaired renal function.

The pharmacokinetics of vardenafil have not been studied in patients requiring dialysis and vardenafil should not be used in this situation.

Hepatic impairment

In patients with mild to moderate hepatic impairment (Child-Pugh A and B), vardenafil clearance was reduced in proportion to the degree of hepatic impairment.

In patients with mild hepatic impairment (Child-Pugh A), vardenafil AUC and C_{max} were increased 1.2-fold (AUC by 17% and C_{max} by 22%) following a vardenafil 10 mg film-coated tablet dose, compared to healthy control subjects. The pharmacokinetics of vardenafil ODT have not been studied in subjects with mild hepatic impairment (Child-Pugh A). An estimated ceiling of 1.7-fold and 1.4-fold increase in AUC and C_{max} respectively can be expected following a vardenafil 10 mg orodispersible tablet dose in subjects with mild hepatic impairment, compared to vardenafil 10 mg film-coated tablet dose in healthy control subject.

In patients with moderate hepatic impairment (Child-Pugh B), vardenafil AUC was increased 2.6-fold (an increase of 160%) and C_{max} was increased 2.3-fold (an increase of 130%), compared to healthy control subjects. Treatment in patients with mild hepatic impairment should not be initiated with Levitra 10 mg orodispersible tablets. In these patients, vardenafil 5 mg film-coated tablet should be used as a starting dose, which may subsequently be increased to vardenafil 10 mg and 20 mg film-coated tablet or Levitra 10 mg orodispersible tablets based on tolerability and efficacy.

Levitra orodispersible tablet 10 mg should not be used in patients with moderate hepatic impairment. The pharmacokinetics of vardenafil have not been studied in patients with severe hepatic impairment (Child-Pugh C). Levitra should not be used in this population (see CONTRAINDICATIONS).

Clinical Studies

Efficacy and safety of Levitra orodispersible tablets was separately demonstrated in a broad population in two studies totalling 701 patients (placebo 343; Levitra orodispersible tablets 358) who were randomised to receive treatment for 12 weeks. Patient subgroups analysed in these studies included elderly patients (51%), patients with history of diabetes mellitus (29%), dyslipidemia (39%) and hypertension (40%).

Primary efficacy assessment was by means of the Erectile Function (EF) Domain score of the International Index of Erectile Function (IIEF) Questionnaire and two questions from the Sexual Encounter Profile (SEP) dealing with the ability to achieve vaginal penetration (SEP2; “Were you able to insert your penis into your partner’s vagina?”), and the ability to maintain an erection long enough for successful intercourse (SEP3, “Did your erection last long enough for you to have successful intercourse?”). The International Index of Erectile Function (IIEF) is a validated self-report instrument assessing male sexual function over a period of 4 weeks. The EF domain is comprised of 6 questions focusing on erection problems.

Pooled data from the two trials demonstrate International Index of Erectile Function – Erectile Function (IIEF-EF) domain scores were significantly higher with Levitra orodispersible tablet compared to placebo.

A percentage of 71% of all sexual attempts reported had successful penetration compared to 44% of all attempts in the placebo group. These results were also reflected in subgroups, in elderly patients (67%), in patients with history of diabetes mellitus (63%), patients with history of dyslipidemia (66%) and hypertension (70%) of all sexual attempts reported had successful penetration.

About 63% of all reported sexual attempts with Levitra orodispersible tablets were successful in terms of erection maintenance compared to about 26% of all placebo-controlled sexual attempts. In the predefined subgroups 57% (elderly patients), 56% (patients with history of diabetes mellitus), 59% (patients with history of dyslipidemia) and 60% (patients with history of hypertension) of all reported attempts with Levitra orodispersible tablet were successful in terms of maintenance of erection.

The efficacy of Levitra orodispersible tablets was demonstrated regardless of baseline erectile dysfunction severity, etiology (organic, psychogenic, and mixed), duration of ED, ethnicity and age.

Table 1. IIEF erectile function domain score (Intention-to-treat population, means). ‡

Study Population	IIEF erectile function domain score							
	Placebo				Levitra ODT 10 mg			
	N	Baseline	Wk 12	change	N	Baseline	Wk 12	change
General	332	12.8	14.2	1.4	348	12.3	20.9	8.6
< 65 years	160	13.3	15.2	1.9	168	13.0	23.0	10.0
≥ 65 years	172	12.4	13.3	1.0	180	11.7	18.9	7.2
Diabetic	84	11.7	13.3	1.6	102	11.5	18.5	7.0
Dyslipidemia	109	12.7	13.3	0.7	136	12.6	19.8	7.3
Hypertension	148	12.0	12.9	1.0	138	12.1	19.9	7.8

‡ Last available observation used in patients with no data at Week 12.

Table 2. Percentage of patients achieving successful penetration (Intention-to-treat population, means). ‡

Study Population	Success rates (%) 'Penetration'							
	Placebo				Levitra ODT 10 mg			
	N	Baseline	Wk 12	change	N	Baseline	Wk 12	change
General	330	38.3	43.8	5.6	347	38.4	71.3	32.9
< 65 years	160	43.6	48.7	5.0	169	43.8	78.3	34.5
≥ 65 years	170	33.3	39.3	6.0	178	33.2	64.7	31.5
Diabetic	84	31.3	39.2	7.9	101	33.2	60.9	27.7
Dyslipidemia	108	40.8	41.9	1.1	135	40.3	67.4	27.1
Hypertension	146	38.6	40.0	1.4	136	32.5	66.5	34.0

‡ overall success rates under treatment up to 12 weeks or last available visit.

Table 3. Percentage of patients achieving successful maintenance of erection (Intention-to-treat population, means). ‡

Study Population	Success rates (%) 'Maintenance'							
	Placebo				Levitra ODT 10 mg			
	N	Baseline	Wk 12	change	N	Baseline	Wk 12	change
General	324	15.0	26.7	11.6	346	13.1	62.0	48.9
< 65 years	159	15.0	30.2	15.2	169	16.4	70.2	53.8
≥ 65 years	165	15.0	23.2	8.2	177	9.9	54.1	44.2
Diabetic	83	12.7	23.1	10.4	101	11.8	54.3	42.4
Dyslipidemia	108	14.7	22.6	7.9	135	12.2	57.7	45.5
Hypertension	144	13.1	23.1	10.0	136	12.2	58.9	46.7

‡ overall success rates under treatment up to 12 weeks or last available visit.

INDICATIONS

Levitra is indicated for the treatment of erectile dysfunction in adult males (inability to achieve or maintain penile erection sufficient for satisfactory sexual performance).

Levitra is not indicated for use by women.

CONTRAINDICATIONS

- Patients with known hypersensitivity to the active substance or to any of the excipients.

- Co-administration with nitrates, nitric oxide donors or organic nitrites in any form either regularly or intermittently. Drugs which must not be used concomitantly include, but are not limited to glyceryl trinitrate (injection, tablets, sprays or patches), isosorbide salts, sodium nitroprusside, amyl nitrite, nicorandil or organic nitrates in any form. Consistent with the effects of PDE inhibition on the nitric oxide/cGMP – pathway, PDE5 inhibitors may potentiate the hypotensive effects of nitrates.

- Concomitant use with moderate inhibitors (e.g. erythromycin) and potent inhibitors (e.g. clarithromycin, ketoconazole, itraconazole and HIV Protease inhibitors such as indinavir or ritonavir) of CYP 3A4

- Patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection with previous exposure to PDE5 inhibitor.

- Known hereditary degenerative retinal disorders such as retinitis pigmentosa.

- Patients in whom sexual intercourse is inadvisable due to cardiovascular risk factors (see PRECAUTIONS). The possibility of undiagnosed cardiovascular

disorders in men with erectile dysfunction should be considered before prescribing the medicine.

- Patients with following cardiac conditions: unstable angina, resting or orthostatic hypotension (systolic blood pressure < 90 mmHg), uncontrolled hypertension, myocardial infarction, stroke, cardiac ischaemia (except stable angina), life-threatening arrhythmia within the previous 6 months and uncontrolled arrhythmia.

- Moderate and severe hepatic impairment.

- End-stage renal disease requiring dialysis.

PRECAUTIONS

Cardiovascular Disease

Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Vardenafil has vasodilator properties which may result in mild and transient decreases in blood pressure. Patients with left ventricular outflow obstruction, e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis, can be sensitive to the action of vasodilators including Type 5 phosphodiesterase inhibitors.

In men for whom sexual activity is not recommendable because of their underlying cardiovascular status, agents for the treatment of erectile dysfunction should generally not be used.

Patients with congenital QT prolongation (long QT syndrome) and those taking Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications should avoid using vardenafil. In a study to elucidate the effect of vardenafil on QT interval in 59 healthy males, therapeutic (10 mg) and supratherapeutic (80 mg) doses of vardenafil produced increases in QTc interval. This observation should be considered in clinical decisions when prescribing vardenafil.

Other Pre-existing Medical Conditions

Agents for the treatment of erectile dysfunction should generally be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease) or in patients who have conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia).

The safety and efficacy of combinations of vardenafil with other treatments for erectile dysfunction (including other PDE5 inhibitors) have not been studied. Therefore the use of such combinations is not recommended.

Vardenafil has not been administered to patients with bleeding disorders or significant active peptic ulceration. Therefore vardenafil should be given to these patients only after careful benefit-risk assessment. In humans, vardenafil has no effect on bleeding time alone or with aspirin. *In vitro* studies with human platelets indicate that vardenafil alone did not inhibit platelet aggregation induced by a variety of platelet agonists. With

supratherapeutic concentrations of vardenafil a small concentration-dependent enhancement of the antiaggregatory effect of sodium nitroprusside, a nitric oxide donor, was observed. The combination of heparin and vardenafil had no effect on bleeding time in rats, but this interaction has not been studied in humans.

Use with alpha-blockers

Patients taking alpha-blockers should not initiate vardenafil therapy with Levitra orodispersible tablets. Patients treated with alpha blockers who have previously used vardenafil film-coated tablets may be switched to Levitra orodispersible tablets. Caution is advised when PDE5 inhibitors are co-administered with alpha blockers. PDE5 inhibitors, including Levitra orodispersible tablets and alpha-adrenergic blocking agents are both vasodilators with blood-pressure lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly (see Interactions with other Medicines) leading to symptomatic hypotension (e.g. fainting). Consideration should be given to the following:

- Patients should be stable on alpha blocker therapy prior to initiating a PDE5 inhibitor. Patients who demonstrate haemodynamic instability on alpha blocker therapy alone are at increased risk of symptomatic hypotension with concomitant use of PDE5 inhibitors.

- Patients treated with alpha blockers should not be initiated on vardenafil therapy with Levitra orodispersible tablets. In those patients who are stable on alpha blocker therapy, vardenafil should be initiated at the lowest recommended starting dose of 5 mg film-coated tablets. Patients may subsequently be switched to Levitra 10 mg orodispersible tablets.

- In those patients already taking an optimised dose of PDE5 inhibitor, alpha blocker therapy should be initiated at the lowest dose. Stepwise increases in alpha blocker dose may be associated with further lowering of blood pressure in patients taking a PDE5 inhibitor.

- Safety of combined use of PDE5 inhibitors and alpha blockers may be affected by other variables, including intravascular volume depletion and other anti-hypertensive drugs.

Use with CYP 3A4 Inhibitors

Concomitant use of moderate (e.g. erythromycin) or potent cytochrome P450 3A4 (CYP 3A4) inhibitors (e.g. clarithromycin, ketoconazole, itraconazole or HIV protease inhibitors such as indinavir or ritonavir) can be expected to produce markedly increased vardenafil plasma levels. Concomitant use with ketoconazole, itraconazole, erythromycin, clarithromycin, indinavir or ritonavir is contraindicated. (See CONTRAINDICATIONS and Interactions with other Medicines).

NAION

Transient vision loss and cases of non-arteritic ischemic optic neuropathy have been reported in connection with the intake of vardenafil and other PDE5 inhibitors. The patient should be advised that in case of sudden vision loss, he should stop taking Levitra orodispersible tablets and consult a physician immediately (see ADVERSE EFFECTS).

Sudden decrease or loss of hearing

Physicians should advise patients to stop taking PDE5 inhibitors, including vardenafil, and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including vardenafil. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors (see ADVERSE EFFECTS).

Other

Aspartame: Levitra orodispersible tablet contains aspartame, a source of phenylalanine which may be harmful for people with phenylketonuria.

Sorbitol: Levitra orodispersible tablet contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take Levitra orodispersible tablets.

Ability to Drive and Use Machines

Patients should be aware of how they react to vardenafil before driving or operating machinery. Due to the vasodilatory properties of PDE 5 inhibitors, concomitant use with alpha-blockers, may contribute to dizziness.

Carcinogenicity

Vardenafil showed no carcinogenic activity when administered orally to rats at doses up to 75 (males) or 25 (females) mg/kg/day or via the drinking water to mice at doses up to 150 (males) or 193 (females) mg/kg/day. The highest doses in these studies were associated with systemic exposure (AUC) to vardenafil >300 (rats) or about 25 (mice) times that expected in men taking 20 mg/day vardenafil.

Genotoxicity

Vardenafil was not genotoxic in assays for gene mutation (reverse mutations in bacterial cells and forward mutations in Chinese hamster V79 cells *in vitro*) or chromosomal damage (Chinese hamster V79 cells *in vitro* and mouse micronucleus assay *in vivo).*

Impairment of Fertility

In a specific clinical trial, single oral doses of 20 mg of vardenafil did not produce any effects on sperm motility or morphology or a variety of parameters indicative for male reproductive function. Based upon measurements of vardenafil in semen of healthy subjects 90 minutes after dosing, not more than 0.0002% of the administered dose appeared in the semen of patients.

Studies in rats showed no effects on fertility, reproductive performance or reproductive organ morphology in males or females given oral doses of vardenafil up to 100 mg/kg/day (systemic exposure > 200 times that expected at the maximum recommended dose of 20 mg, based on AUC).

Other vardenafil formulations

Levitra 10 mg orodispersible tablet is not bioequivalent to Levitra 10 mg film-coated tablets (see DOSAGE AND ADMINISTRATION).

Use in Pregnancy (Category B3)

Vardenafil is not indicated for use by women.

Studies in rats have shown that vardenafil and/or its metabolites cross the placenta and distribute to the fetus. No evidence of embryofetal toxicity or teratogenicity was observed in pregnant rats or rabbits given oral doses of vardenafil up to 18 mg/kg/day. These doses were associated with systemic exposure to vardenafil 125- (rat) or 7- (rabbit) fold greater than that expected at the maximum recommended dose of 20 mg, based on AUC. Higher doses were associated with maternal toxicity, increased embryonic resorptions and delayed fetal development in both species.

Administration of vardenafil 60 mg/kg/day to pregnant rats during late gestation and throughout lactation resulted in increased postnatal pup mortality and delayed physical development. The no-effect-dose of 8 mg/kg/day was associated with systemic exposure approximately 28-fold that expected in humans at the maximum recommended dose of 20 mg vardenafil.

There are no studies of vardenafil in pregnant women.

Use in Lactation

Vardenafil is not indicated for use by women.

Vardenafil and/or its metabolites are excreted in the milk of lactating rats at concentrations up to 19-fold higher that the corresponding maternal plasma concentrations. Increased pre- and post-natal mortality and delayed physical development was observed in offspring from rats treated with oral vardenafil at 60 mg/kg/day during gestation and lactation.

There are no human data on the excretion of vardenafil into breast milk or on the safety of vardenafil exposure in infants.

Interactions with other Medicines

The studies described in this section were conducted using vardenafil film-coated tablets.

Vardenafil is metabolised predominantly by hepatic enzymes via cytochrome P450 (CYP) isoform 3A4, with some contribution from CYP3A5 and CYP2C isoforms. Therefore, inhibitors of these enzymes may reduce vardenafil clearance.

Demonstrated Interactions

Macrolide Antibiotics

Erythromycin (500 mg three times a day), a CYP3A4 inhibitor, caused a 4-fold increase in vardenafil AUC and a 3-fold increase in C_{max} when co-administered with vardenafil (5 mg) to healthy volunteers. Levitra orodispersible tablets should not be used in combination with erythromycin or clarithromycin (see CONTRAINDICATIONS).

Potent CYP 3A4 inhibitors

Ketoconazole

Ketoconazole (200 mg), which is a potent CYP3A4 inhibitor, caused a 10-fold increase in vardenafil AUC and a 4-fold increase in C_{max} when co-administered with vardenafil 5 mg to healthy volunteers. Levitra orodispersible tablets should not be used in combination with ketoconazole (see Dosage and Administration).

Indinavir

Indinavir is a potent CYP3A4 inhibitor. Co-administration of vardenafil film-coated tablet (10 mg) with the HIV protease inhibitor indinavir (800 mg three times a day) resulted in a 16-fold increase in vardenafil AUC and a 7-fold increase in vardenafil C_{max}. At 24 hours after co-administration, the plasma levels of vardenafil were approximately 4% of the maximum vardenafil plasma level (C_{max}). Concomitant use of indinavir and Levitra orodispersible tablets is therefore contraindicated.

Ritonavir

Ritonavir (600 mg twice daily) resulted in a 13-fold increase of vardenafil C_{max} and a 49-fold increase in vardenafil AUC_{0-24} when coadministered with vardenafil 5 mg. The interaction is a consequence of blocking hepatic metabolism of vardenafil by ritonavir, a very potent CYP 3A4 inhibitor, which also inhibits CYP 2C9. Ritonavir significantly prolonged the half-life of vardenafil to 25.7 hours. Concomitant use of Levitra orodispersible tablets with ritonavir is contraindicated.

Potential Interactions

Other CYP 3A4 Inhibitors

Concomitant use of other moderate or potent CYP 3A4 inhibitors (such as clarithromycin, itraconazole, other HIV protease inhibitors) can also be expected to produce markedly increased vardenafil plasma levels (See Demonstrated Interactions). Levitra orodispersible tablets should not be used in combination with other moderate or potent CYP3A4 inhibitors such as clarithromycin, itraconazole and other HIV protease inhibitors.

Nitrates, Nitric Oxide Donors

There is limited information on the potential hypotensive effects of vardenafil when given in combination with nitrates. Based on experience with other PDE5 inhibitors, some patients may experience clinically significant hypotension if vardenafil and nitrates are

coadministered and concomitant use is therefore contraindicated (see CONTRAINDICATIONS).

Nitrates should not be administered for at least 24 hours (approximately 5 half-lives) after the last dose of vardenafil. A longer washout period should be observed if the patient has been taking concomitant drugs, such as CYP3A4 inhibitors, which impair vardenafil metabolism.

Nicorandil is a hybrid of potassium channel opener and nitrate. Due to the nitrate component it has the potential to have serious interaction with vardenafil (see CONTRAINDICATIONS).

Antihypertensive agents

Limited information is available on concomitant use of vardenafil and antihypertensive agents. Population pharmacokinetic investigations of Phase III data revealed no significant effect of ACE-inhibitors, beta-blockers or diuretics on the pharmacokinetics of vardenafil. However, a potential for additive hypotensive effect exists, and until further information is available, caution should be exercised when prescribing vardenafil in combination with antihypertensive agents.

Alpha blockers

Since alpha blocker monotherapy can cause marked lowering of blood pressure, especially postural hypotension and syncope, interaction studies were conducted with vardenafil.

In two interaction studies with healthy normotensive volunteers after forced titration of the alpha-blockers tamsulosin or terazosin to high doses over 14 days or fewer, hypotension (in some cases symptomatic) was reported in a significant number of subjects after co-administration of vardenafil film-coated tablets. Among subjects treated with terazosin, hypotension (standing systolic blood pressure below 85 mmHg) was observed more frequently when vardenafil film-coated tablets and terazosin were given to achieve simultaneous C_{max} than when the dosing was administered to separate C_{max} by 6 hours. Because these studies were conducted using healthy volunteers after forced titration of the alpha blocker to high doses (subjects were not stable on alpha-blocker therapy), these studies may have limited clinical relevance.

Interaction studies were conducted with vardenafil film-coated tablets in patients with benign prostatic hyperplasia (BPH) on stable tamsulosin or terazosin therapy. When vardenafil was given at doses of 5, 10 or 20 mg on a background of stable therapy with tamsulosin, there was no symptomatic reduction in blood pressure. When vardenafil 5 mg was dosed simultaneously with tamsulosin 0.4 mg, 2 of 21 patients experienced a standing systolic blood pressure below 85 mmHg. When vardenafil 5 mg was given with a six hour dose separation from tamsulosin, 2 of 21 patients experienced a standing systolic blood pressure below 85 mmHg. In a subsequent study in patients with BPH, when vardenafil 10 mg and 20 mg was dosed simultaneously with tamsulosin 0.4 or 0.8 mg there were no cases of standing systolic blood pressure below 85 mmHg. When vardenafil 5 mg was given simultaneously with terazosin 5 or 10 mg, one of 21 patients experienced symptomatic postural hypotension. Hypotension was not observed when vardenafil 5 mg

and terazosin administration was separated by 6 hours. This should be considered when deciding about a time separation of dosing.

Figure 2: Mean change from baseline in standing systolic blood pressure (mmHg) over 6 hour interval following simultaneous or 6 hr separation administration of vardenafil 5 mg or placebo with stable dose tamsulosin 0.4 mg in normotensive BPH patients.

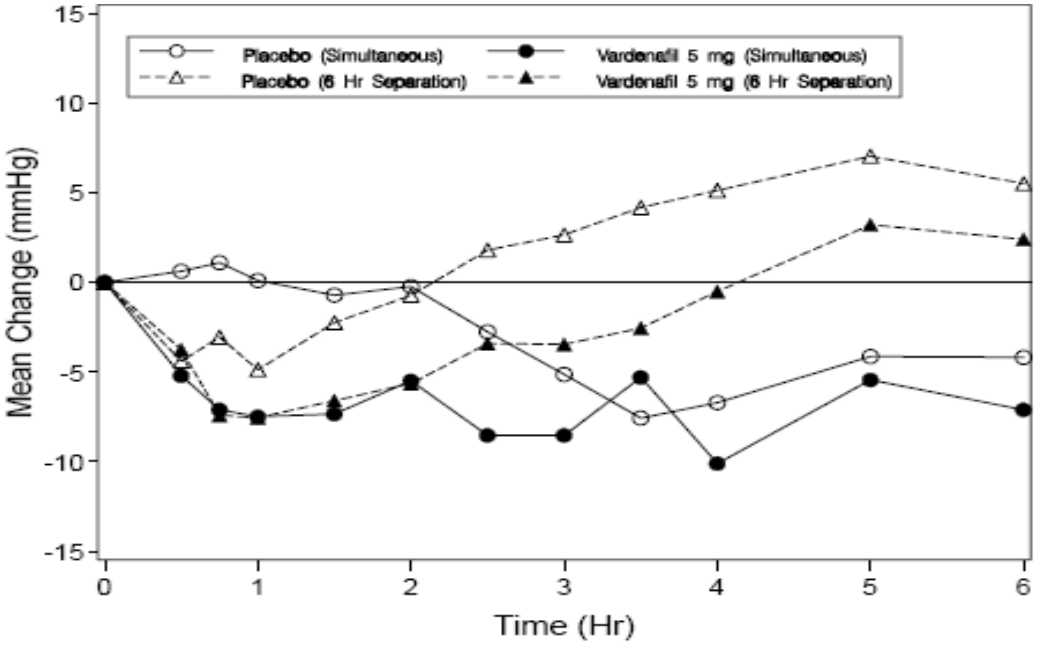
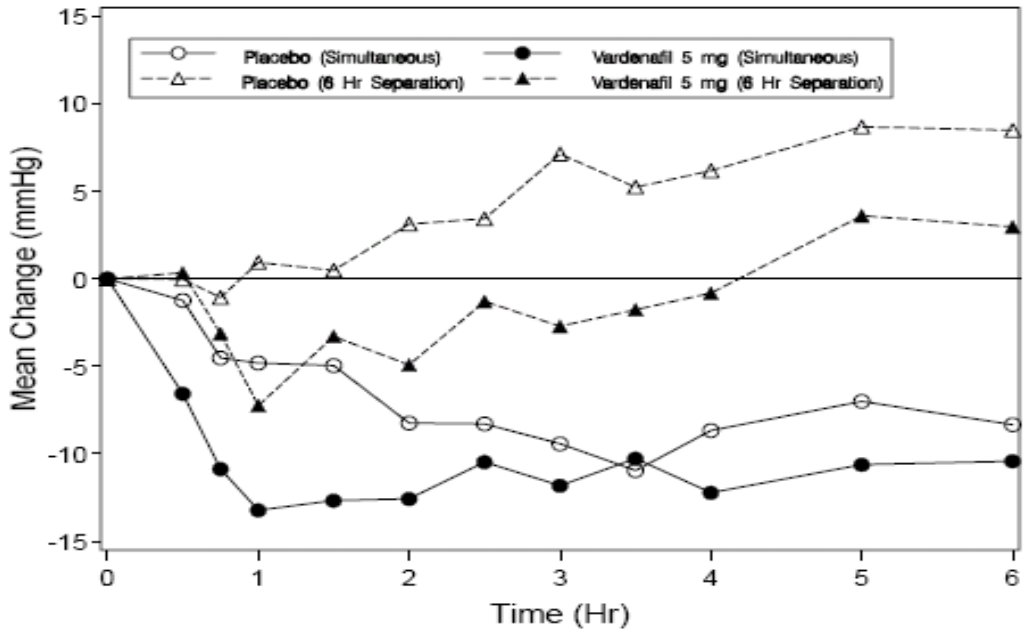


Figure 3: Mean change from baseline in standing systolic blood pressure (mmHg) over 6 hour interval following simultaneous or 6 hr separation administration of vardenafil 5 mg or placebo with stable dose terazosin (5 or 10 mg) in normotensive BPH patients.



Concomitant treatment should be initiated only if the patient is stable on his alpha blocker therapy. In patients who are stable on alpha-blocker therapy, vardenafil should be initiated at a starting dose of 5 mg film-coated tablets.

Levitra may be administered at any time with tamsulosin. With other alpha blockers a time separation of at least 6 hours between dosing is recommended if Levitra is prescribed concomitantly.

Safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and other anti-hypertensive medication.

Interactions shown not to exist

The studies described in this section were conducted using vardenafil film-coated tablets.

Glibenclamide

Vardenafil (20 mg), when co-administered with glibenclamide (3.5 mg), did not affect the relative bioavailability of glibenclamide (no effect on AUC and C_{max} of glibenclamide).

Warfarin

No pharmacokinetic or pharmacodynamic (prothrombin time and clotting Factor II, VII and X) interactions were shown when warfarin (25 mg) was co-administered with vardenafil (20 mg). Vardenafil pharmacokinetics were not affected by co-administration of warfarin.

Nifedipine

Coadministration of vardenafil (20 mg) did not alter the bioavailability (AUC and C_{max}) of nifedipine (30 mg or 60 mg). The combined treatment of vardenafil and nifedipine did not lead to pharmacodynamic interaction (as compared to placebo, vardenafil produced mean additional blood pressure reductions of 5.9 mmHg and 5.2 mmHg for supine systolic and diastolic blood pressure, respectively).

Digoxin

Lack of pharmacokinetic interaction was shown when digoxin (0.375 mg daily) in steady-state was co-administered with vardenafil (20 mg) over 14 days every other day.

Antacids

Single doses of Mylanta (magnesium hydroxide/aluminium hydroxide) did not affect the bioavailability (AUC) or the maximum concentration (C_{max}) of vardenafil.

Ranitidine, Cimetidine

Bioavailability of vardenafil (20 mg) was not affected by co-administration of the H_2-antagonists ranitidine (150 mg twice daily) and cimetidine, a non-specific cytochrome P450 inhibitor (400 mg twice daily).

Aspirin

Vardenafil (10 mg) administered as film-coated tablets did not influence bleeding time when taken alone or in combination with low dose aspirin (2 x 81 mg tablets).

Ethanol

Vardenafil (20 mg) did not potentiate the hypotensive effects of ethanol (0.5 g/kg bodyweight). The pharmacokinetics of ethanol and vardenafil were not significantly altered by coadministration.

Other Drugs

Population pharmacokinetic investigations of Phase III data revealed no significant effect of aspirin, weak CYP 3A4-inhibitors, and medications for the treatment of diabetes (sulfonylureas and metformin) on the pharmacokinetics of vardenafil.

ADVERSE EFFECTS

Safety of Levitra orodispersible tablets was evaluated in two identical multi-national, randomised double-blind, placebo-controlled trials. In both pivotal studies, enrolment was stratified so that approximately 50% of patients were ≥ 65 years old. An integrated analysis of both studies included a total of 335 subjects that received Levitra orodispersible tablets compared to 340 subjects that received placebo (mean age was 61.7, range 21.0 to 88.0. 68% White, 5% Black, 6% Asian, 11% Hispanic and 11% Other). The discontinuation rates due to adverse reactions were 1.4% for Levitra orodispersible tablet compared to 0.4% for placebo.

Table 4: Adverse events reported by ≥ 1% of patients treated with Levitra orodispersible tablet in controlled trials

System organ class	Adverse event Preferred Term (PT)	Levitra ODT (N = 355)	Placebo (N = 340)
Cardiac disorders	Bundle Branch Block Right	0.0%	1.2%
	Supraventricular extrasystoles	1.1%	0.9%
Gastrointestinal disorders	Diarrhoea	1.7%	0.9%
	Dyspepsia	2.8%	0.0%
Infections and Infestations	Nasopharyngitis	0.6%	1.2%
Musculoskeletal and Connective Tissue Disorders	Back pain	2.0%	0.3%
	Muscle spasms	1.1%	0.6%
Nervous system disorders	Dizziness	2.3%	0.0%
	Dysgeusia	1.1%	1.2%
	Headache	14.4%	1.8%
Respiratory, thoracic and mediastinal disorders	Nasal congestion	3.1%	0.3%
Social Circumstances	Pharmaceutical Product Complaint	0.0%	1.2%
Vascular disorders	Flushing	7.6%	0.6%

The number of subjects in all placebo-controlled clinical trials for vardenafil is vardenafil n = 9155; placebo n = 5500. Vardenafil was generally very well tolerated. Adverse events were generally transient and mild to moderate in nature.

All vardenafil clinical trials

Levitra orodispersible tablets and vardenafil film-coated tablets have been administered to 17 748 men during controlled and uncontrolled clinical trials worldwide. The number of patients treated for 6 months or longer was 3357, and 1350 patients were treated for at least 1 year. When vardenafil film-coated tablet or Levitra orodispersible tablet was taken as recommended, the following adverse drug reactions were reported in all clinical trials.

Table 5: Adverse drug reactions reported in patients in all clinical trials for vardenafil world-wide which are either reported as drug-related in ≥ 0.1% of the patients or rare and considered serious in nature.

System Organ Class	Very Common ≥ 10%	Common ≥ 1% to <10%	Uncommon ≥ 0.1% to <1%	Rare ≥ 0.01% to < 0.1%
Immune System Disorders			Allergic oedema and angioedema	Allergic reaction
Infections and Infestations				Conjunctivitis
Psychiatric Disorders			Sleep disorder	
Nervous System Disorders	Headache	Dizziness*	Somnolence Paraesthesia and dysesthesia	Syncope Amnesia Seizure
Eye Disorders incl. related Investigations			Visual disturbance Visual colour distortions Ocular hyperaemia Eye pain and eye discomfort Photophobia	Increase in intraocular pressure
Ear and Labyrinth Disorders			Tinnitus Vertigo	
Cardiac Disorders incl. related Investigations			Palpitations Tachycardia	Angina pectoris Myocardial infarction Ventricular tachyarrhythmias
Vascular Disorders incl. related Investigations		Vasodilatation		Hypotension
Respiratory, Thoracic and Mediastinal Disorders		Nasal congestion	Dyspnoea Sinus congestion	

System Organ Class	Very Common ≥ 10%	Common ≥ 1% to <10%	Uncommon ≥ 0.1% to <1%	Rare ≥ 0.01% to < 0.1%
Gastrointestinal Disorders incl. related Investigations		Dyspepsia	Gastrointestinal and abdominal pain Diarrhoea Dry mouth Gastritis Gastrooesophageal reflux disease Vomiting Nausea	
Hepatobiliary System Disorder			Increase in transaminases	
Skin and Subcutaneous Tissue Disorders			Rash Erythema	
Musculoskeletal and Connective Tissue Disorders incl. related Investigations			Back pain Myalgia Increase in creatine kinase Increased muscle tone and cramping	
Reproductive System and Breast Disorders			Increase in erection	Priapism
General Disorders and Administration Site Conditions			Feeling unwell	Chest pain

*****In a pooled analysis of placebo-controlled fix-dose studies comparing 5 mg, 10 mg and 20 mg of vardenafil film-coated tablets a higher rate of dizziness was seen in elderly subjects (≥ 65 years) with doses of 10 mg or higher than in younger subjects (4.2% vs. 1.2 %). Dizziness was usually mild and resolved without any further action. Due to the vasodilatory properties of PDE 5 inhibitors, concomitant use with alpha-blockers may contribute to dizziness.

Myocardial infarction (MI) has been reported in temporal association with the use of vardenafil and sexual activity, but it was not possible to determine whether MI is related directly to vardenafil, or to sexual activity, to the patient's underlying cardiovascular disease, or to a combination of these factors.

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 PDE inhibitors, including vardenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. 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.

Visual disturbances including vision loss (temporary or permanent) have been reported rarely post-marketing in temporal association with the use of PDE5 inhibitors, including vardenafil. 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 to other factors.

Sudden decrease or loss of hearing has been reported in a small number of post-marketing and clinical trials cases with the use of all PDE5 inhibitors, including vardenafil. It is not possible to determine whether these reported events are related directly to the use of vardenafil, to the underlying risk factors for hearing loss, a combination of these factors or to other factors.

DOSAGE AND ADMINISTRATION

The recommended dose is one Levitra orodispersible tablet, taken orally 60 minutes before sexual activity. Sexual activity can be initiated as soon as 15 minutes and as long as 4 – 5 hours after taking Levitra orodispersible tablet. Sexual stimulation is required for a natural response to treatment.

The maximum recommended dose is one Levitra orodispersible tablet per day.

Levitra orodispersible tablet can be taken with or without food.

Levitra orodispersible tablet should be taken without liquid immediately upon removal from the blister. It should be placed on the tongue. Manipulate the tablet with the tongue against the palate and swallow with saliva once it has disintegrated. Do not chew the tablet. Do not bite on the disintegrated particles.

Dose Range

Based on efficacy and tolerability, the vardenafil dose may be increased to 20 mg (one 20 mg film-coated tablet) or decreased to 5 mg (one 5 mg film-coated tablet). Levitra 10 mg orodispersible tablet is not bioequivalent to Levitra 10 mg film-coated tablet. Levitra 10 mg orodispersible tablets have 21 to 44% higher bioavailability compared to Levitra 10 mg film-coated tablets. For patients requiring a higher or lower dose, vardenafil film-coated tablets should be considered. Depending on co-morbidities and concomitant medications, it may be necessary to commence on a lower dose of 5 mg film-coated tablet.

Elderly (above 65 years)

Dose adjustment is not warranted based on age alone. It should be considered that co-morbidities increase with age.

Children (from birth to 18 years)

Levitra orodispersible tablet is not indicated for use in children.

Hepatic impairment

In patients with mild hepatic impairment (Child-Pugh A), vardenafil 5 mg should be used as a starting dose, which may subsequently be increased to one Levitra orodispersible tablet. Levitra orodispersible tablet is not indicated as a starting dose in patients with mild hepatic impairment. There is limited clinical data in patients with mild hepatic impairment on Levitra orodispersible tablets.

Vardenafil clearance is reduced in patients with moderate hepatic impairment (Child-Pugh B). The pharmacokinetics of vardenafil have not been studied in patients with severe hepatic impairment (Child-Pugh C). Levitra orodispersible tablet should not be used in patients with moderate or severe hepatic impairment (see CONTRAINDICATIONS).

Renal impairment

No dose adjustment is needed in patients with mild (CL_{cr} > 50-80 mL/min), moderate (CL_{cr} > 30-50 mL/min), or severe (CL_{cr} < 30 mL/min) renal impairment.

The pharmacokinetics of vardenafil have not been studied in patients requiring dialysis, therefore vardenafil should not be used in these patients (see Pharmacokinetics).

Concomitant Alpha-blockers

Patients treated with alpha-blockers should not be initiated on vardenafil therapy with Levitra orodispersible tablets.

In those patients who are stable on alpha-blocker therapy, 5 mg vardenafil film-coated tablets should be used as initial therapy. Patients may subsequently be switched to Levitra orodispersible tablets.

In those patients already taking an optimised dose of vardenafil, alpha-blocker therapy should be initiated at the lowest dose. Stepwise increase in alpha-blocker dose may be associated with further lowering of blood pressure in patients taking a PDE5 inhibitor including vardenafil.

OVERDOSAGE

In single dose volunteer studies, vardenafil was tested in doses up to and including 80 mg per day. Even the highest dosage tested (80 mg per day) was generally tolerated without producing serious adverse side effects. This was confirmed in a study with 40 mg once daily doses over 4 weeks.

When 40 mg was administered twice daily, cases of severe back pain were observed. However, no muscle or neurological toxicity was identified.

In cases of overdose, standard supportive measures should be taken as required. Renal dialysis is not expected to accelerate clearance as vardenafil is highly bound to plasma proteins and not significantly eliminated in the urine. Contact Poisons Information Centre 131126 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Levitra orodispersible tablet is available in blister packs of 1 (sample pack), 4 and 8. Each orodispersible tablet contains vardenafil hydrochloride trihydrate equivalent to 10 mg of vardenafil. Store in original container.

Store below 30 °C.

NAME AND ADDRESS OF THE SPONSOR

BAYER AUSTRALIA LIMITED
ABN 22 000 138 714
875 Pacific Highway
PYMBLE NSW 2073

POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE

DATE OF APPROVAL

Date of TGA Approval: 12 January 2011

® Registered trademark of Bayer AG

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au