25 April 2013
EMA/411229/2013
Committee for Medicinal Products for Human Use (CHMP)

Vivanza

(vardenafil)

Procedure No. EMEA/H/C/000488/X/0043

Bayer Pharma AG

Assessment report for extension of Marketing Authorisation

Assessment report as adopted by the CHMP with all commercially confidential information deleted

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List of abbreviations

ALT	Alanine transaminase
AE	Adverse Events
CHMP	Committee for Medicinal Products for Human Use
ED	Erectile Dysfunction
EMA	European Medicines Agency
FDA	Food and Drugs Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HPLC	High Performance Liquid Chromatography
LOQ	Limit of Quantification
MAH	Marketing Authorisation Holder
NIR	Near-infrared
ODT	Orodispersible tablets
PE	Polyethylene
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
QRD	Quality Review of Documents
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TGA	Thermo-Gravimetric Analysis
TLC	Thin Layer Chromatography
UV	Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

Pursuant to Article 19 and Annex I (point 2d) of Commission Regulation (EC) No 1234/2008, Bayer Pharma AG submitted to the European Medicines Agency (EMA) on 29 November 2012 an application for an extension of Marketing Authorisation.

The extension of the Marketing Authorisation concerns a new pharmaceutical form: orodispersible tablet (10 mg).

In addition, the Marketing Authorisation Holder (MAH) proposed to bring the Product Information in line with the latest QRD template.

Bayer Pharma AG is already the MAH for Vivanza 5 mg, 10 mg and 20 mg film-coated tablets (EU/1/03/249/001-015).

The applicant applied for the same indication as approved for already authorised strengths: "Treatment of erectile dysfunction in adult men. Erectile dysfunction is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance. In order for Vivanza to be effective, sexual stimulation is required."

The application submitted is composed of administrative information, complete quality data, and two pivotal, placebo controlled, randomized Phase III trials (Studies 12093 and 12094; Table 2) with a treatment period of 12 weeks have been conducted to support efficacy and safety of the 10 mg ODT. In addition the clinical program included three Phase I trials (Studies 10021, 12769 and 13396; Table 1) which provided pharmacokinetic results in healthy volunteers as in patients with erectile dysfunction..

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/345/2010 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The MAH did not seek scientific advice at the CHMP.

Licensing status

Vivanza has been given a Marketing Authorisation in the EU on 04 March 2003.

1.2. Manufacturers

Manufacturer responsible for batch release

Bayer Pharma AG

D-51368 Leverkusen

Germany

1.3. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was: Concepcion Prieto Yerro

- The application was received by the EMA on 29 November 2012.
- The procedure started on 26 December 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 March 2013.
- During the meeting on 11 April 2013, the PRAC agreed on an RMP Advice and assessment overview to the CHMP.
- During the meeting on 22-25 April 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for an extension of the Marketing Authorisation for Vivanza, 10 mg orodispersible tablets on 25 April 2013.

2. Scientific discussion

2.1. Introduction

Vivanza film-coated tablet contain vardenafil as the active substance and is indicated in the treatment of erectile dysfunction in adult men. Vardenafil is a selective inhibitor of phosphodiesterase type 5 (PDE5), the most prominent PDE in the human corpus cavernosum. During sexual stimulation nitric oxide is released resulting in an increased level of cyclic guanosine monophosphate (cGMP) in the corpus cavernosum, smooth muscle relaxation and induction of penile erection. Inhibiting PDE5 vardenafil increases the level of cGMP enhancing relaxation of smooth muscle, which increases blood flow to the penis and induces penile erection.

Currently Vivanza is available as film-coated tablets containing 5 mg, 10 mg or 20 mg of vardenafil.

The present application supports a line extension for new tablet formulation developed as single oral dose for the treatment of erectile dysfunction. The orodispersible tablet disintegrates rapidly in the mouth in the presence of saliva and permits a convenient mode of intake without water. Patients who have difficulty swallowing tablets or who prefer a more discreet mode of administration of the product can benefit from using this form.

The additional pharmaceutical form applied for is orodispersible containing 10 mg of vardenafil. There are no changes in the route of administration or indications compared to the currently approved film-coated tablets. The same orodispersible tablet formulation has already been approved in September 2010 for the product Levitra, of which Vivanza is a duplicate license. The principle data package is therefore identical.

With this line extension application the entire product information was brought in line with the latest QRD template.

2.2. Quality aspects

2.2.1. Introduction

The new pharmaceutical form is presented as orodispersible tablets containing 10 mg of vardenafil (active substance) in form of the hydrochloride salt. Tablets are round and white, and are provided in aluminium (alu/alu) blister packs. Excipients used in the preparation of orodispersible tablets are well known excipients such as magnesium stearate, aspartame (E951), peppermint flavour, mannitol (E421), sorbitol (E420), crospovidone and hydrated colloidal silica.

2.2.2. Active Substance

Vivanza 10 mg orodispersible tablets contain the same active substance as the one authorised for film-coated tablets. The substance is sourced from the same manufacturers, is manufactured with the same manufacturing process and released in accordance with the same approved active substance specification. The active substance specifications were found to be suitable for use in orodispersible tablets. Hence the applicant referred to the dossier of the already authorised film-coated tablets of Vivanza for information on the active substance.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The objective of the pharmaceutical development was to provide an immediate release dosage form of vardenafil with high convenience and patient compliance. Orodispersible tablets have been selected as dosage form which may be taken without water in a discreet manner.

The selected tablet size was considered small enough to support convenient intake and to prevent gastrointestinal problems in sensitive patients caused by high doses of polyols. However the tablet size is large enough to allow easy handling also by elderly patients.

Apart from flavour, sweetener and lubricant, the formulation is solely composed of the direct compression excipient Pharmaburst B2 which is commercially available mixture of crospovidone, mannitol, hydrated colloidal silica and sorbitol. The ratio between the active substance and the filler Pharmaburst B2 was determined by the size of the orodispersible tablet. A slightly bitter taste of vardenafil hydrochloride was compensated by addition of aspartame as sweetener and peppermint flavour.

Compatibility of the active substance with standard tablet excipients such as crospovidone, magnesium stearate or silica colloidal anhydrous has already been known from the previous development of the film-coated tablets. Compatibility with specific excipients needed for the formulation of orodispersible tablets was investigated in a separate study. It has been demonstrated that excipients chosen did not affect the appearance, assay or degradation products, there was no sign of significant degradation of the active substance. Compatibility was further demonstrated by the finished product stability studies.

Vivanza orodispersible tablets are manufactured in a direct-compression process. The components are blended and compressed into final tablets on a standard rotary press. During development and scale-up the impact of manufacturing conditions on key quality attributes were investigated. As rapid disintegration of orodispersible tablets based on Pharmaburst B2 is only achieved if addition of any binder is avoided, the powder blend is not granulated. Thus, a direct compression process has been selected.

Adventitious agents

None of the excipients present in the formulation is of animal or human origin.

Magnesium stearate is of vegetal origin.

Manufacture of the product

The manufacturing process is sufficiently described with clearly defined critical steps. A flow diagram and detailed description of the process have been provided. The manufacturing process comprises the following steps: (1) premixing, (2) final blending, (3) tablet compression and (4) packaging.

Standard in-process controls are routinely performed during the manufacturing process to control the product quality. Acceptance criteria and specification limits have been set-up. The proposed in-process control tests are adequate to control critical steps of the manufacturing process.

The validation was performed with 3 consecutive batches at commercial scale. All manufacturing steps, in-process controls and quality tests were performed in accordance to the requirements and complied with the specification. The evaluation of these batches was based on manufacturing process parameters, in process control data that accompanied every production batch, and additional tests that were carried out only in the validation phase. Each validation batch was tested for compliance with the release specification.

It was demonstrated that the process is capable of producing the finished product of the intended quality.

Product specification

The product specification is standard for tablets and contains tests with suitable limits for appearance, identification (HPLC, TLC or NIR), friability, water content, disintegration, uniformity of dosage units, assay (HPLC), degradation products (HPLC) and microbial limits.

Full details of all analytical methods were provided. All non pharmacopoeial methods have been satisfactory validated.

The same HPLC method is used for identification, assay and degradation products. The method has been appropriately validated. It has been demonstrated that the method is suitable for the identification and determination of vardenafil and its degradation products in orodispersible tablets.

Batch analysis data was provided on three commercial scale batches. Batches met the proposed specification limits. Results showed that orodispersible tablets can be manufactured reproducibly according to the finished product specifications.

Stability of the product

Long-term stability data were provided for 3 commercial scale batches stored at 30°C/75 % relative humidity (RH) in order to prove that the product is stable in climatic zones I - IV.

Additionally, 18 months stability data were provided for one laboratory scale batch packed in the same primary packaging after storage at 25°C/60 % RH and at 30°C/75 % RH. The stability data were evaluated against the proposed shelf life specification.

Accelerated studies at 40°C/75 % RH have been performed over a period of 6 months. Test parameters, methods and specification were the same as described for the long-term stability studies. The tablets were stable under accelerated storage conditions over the test period of 6 months.

The applicant also performed stressed stability testing. For stress stability testing, the samples were exposed to heat, humidity and light.

In order to investigate the stability of the product under moist conditions (humidity stress) tablets were stored in open containers at 25°C/60 % RH, 30°C/75 % RH and 40°C/75 % RH for 8 weeks. It has been demonstrated that the formulation is humidity sensitive and need to be stored in the original water-tight package to prevent exposure to high ambient humidity.

Unprotected tablets exposed to light showed signs of decomposition of the active substance however, the assay results and the amount of degradation products still remained within the specification limits. Only the discoloration proceeded rapidly.

Although tablets were shown to be sensitive to humidity and slightly sensitive to light it shows good chemical and physical stability when adequately protected by a hermetic primary container. This confirms that aluminium blisters which have been chosen as the packaging material for clinical trial and commercial supply are appropriate.

In addition to the blistered samples one commercial scale tablet batch was tested as bulk material and stored in the chosen container material at 25°C/60 % RH, 30°C/75 % RH and 40°C/75 % RH. Data were available for a storage period of 12 months at 25 °C/60 % RH and for 1 month storage at 30°C/75 % RH and 40°C/75 % RH. All parameters remained unchanged under the storage conditions tested and it was possible to conclude that the bulk packaging offers sufficient protection for the tablets.

In accordance with EU GMP guidelines the stability studies will be continued following the stability protocol and any out-of-specification result will be reported to the authorities.

Based on available stability data, the proposed shelf-life as stated in section 6.3 of the SmPC are acceptable.

In summary the stability data provided support the proposed shelf-life and storage conditions.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The 10 mg orodispersible tablets have been developed to be a more convenient dosage form in comparison with the approved film-coated tablets because it can be administered without water. Orodispersible tablets contain different excipients than the film-coated tablets, however none of the excipients is considered a concern. The active substance is identical to the one used in the film-coated tablets.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform clinical performance.

At the time of the CHMP opinion, there were no unresolved quality issues having no impact on the Benefit-Risk balance of the product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3. Non-clinical aspects

No further studies are required and the applicant has justified why no such data was provided, which was considered acceptable by the CHMP.

Regarding the environmental risk assessment, no significant increase in environmental exposure is anticipated. The Applicant has submitted a statement on non-significant increase of environmental exposure to vardenafil exposing that the introduction of Vivanza 10 mg orodispersible tablets is not assumed to increase the overall environmental concentration of vardenafil as active ingredient significantly, since this new formulation is administered at the same dose regime as the already marketed tablets, but allows for the uptake of just 1 tablet (10 mg) instead of 2 (5 mg) in the previous formulation. Hence, Vivanza 10 mg orodispersible tablets does not increase the number of overall doses of vardenafil significantly.

Accordingly, it can be expected that no additional significant increase in use will occur. Therefore no further environmental risk assessment is required, following the EMEA guideline CPMP/SWP/4447/00, where it is stated that an environmental risk assessment is not required, when the proposed line extension does not result in a significant increase in the environmental exposure. This is not assumed for Vivanza 10 mg orodispersible tablets.

2.4. Clinical aspects

2.4.1. Introduction

To support this application two pivotal, placebo controlled, randomized Phase III trials (Studies 12093 and 12094; Table 2) with a treatment period of 12 weeks have been conducted to support efficacy and safety of the 10 mg ODT. In addition the clinical program included three Phase I trials (Studies 10021, 12769 and 13396; Table 1) which provided pharmacokinetic results in healthy volunteers as in patients with erectile dysfunction.

The initial development strategy was aimed to demonstrate bioequivalence of the orodispersable tablets (ODTs) with the approved film-coated tablets (FCTs). As the orodispersable formulation showed suprabioavailability, clinical studies to demonstrate efficacy and efficacy in patients with erectile dysfunctions were performed.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1 Clinical pharmacokinetic development for the ODT formulation

Study Number	Study 10021	Study 12769	Study 13396
Objective(s) of the Study	Mechanistic study to investigate absorption in the oral cavity compared to absorption in the GIT (swallowed intake)	Compare PK of ODT to FCT; investigate effect of food and water, resp. on PK of ODT	Compare PK of ODT to FCT; investigate multiple once-daily administration of ODT and effect of age on ODT
Study Design and Type of Control	Randomized, non-blind, 2-fold crossover. Fasting intake, 1 week wash out.	Randomized, non-blind, 4-fold crossover. Single dose administration.	Non-blind, age-stratified, group comparison Day 1: 10 mg FCT Day 4-13: 10 mg ODT
Test Product(s) Dosage Regimen Route of Administration	10 mg Vardenafil HCL solution 0.1% single dose i. kept in the mouth for 15 min, then mouth was emptied and rinsed ii. swallowed with water	10 mg ODT w/o water fasting, w/o water fed, with water fasting 10 mg 10 mg FCT, fasting with water	10 mg ODT w/o water, 10 x once-daily, fasting on PK profile days 10 mg FCT single dose
Number of Subjects	10 valid for safety and PK	16 valid for safety, 13 valid for PK	36 valid for safety. Valid for PK: 14 (18 to ≤45) 6 (>45 to <65) 7 (<70) and 7 (≥70)
Healthy Subjects or Diagnosis of Patients	Healthy male subjects aged 26-43 years	Healthy male subjects aged 29-49	ED patients stratified by age 18 to ≤45, >45 to <65, ≥65 to<70 and ≥70 years; overall range 26-80 years

Table 2 Clinical efficacy-safety development for the ODT formulation

Study ID	No. of study centres / locations	Design	Study treat-ment	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
12093	40 active investigational centres in Belgium, France, Germany, Spain, South Africa, and The Netherlands	Double-blind, multicentre, randomized, parallel-group, placebo controlled study	10 mg ODT vs. placebo	to compare the efficacy and safety of vardenafil ODT 10 mg (PRN) after 12 weeks of treatment or LOCF with placebo in a general population of men with erectile dysfunction.	409 male subjects were screened, 362 subjects randomized (186 vardenafil 10 mg ODT, and 176 placebo)	4 week run in period without study medication + 12 week 10 mg vardenafil (PRN) or placebo.	Male < 65 years ODT 52.8±9.0 placebo 52.7±8.5 ≥ 65 years ODT 69.7±4.2 placebo 69.8±4.9	A history of ED for at least 6 months	- IIEF-EF Domain score at Week 12 or LOCF - SEP 2 (success rates of penetration) at Week 12 overall - SEP 3 (success rates of maintenance of erection) at Week 12 overall
12094	35 active investigational centres in the US, Canada,	Fixed dose, double-blind, randomized	10 mg ODT vs. placebo	to compare the efficacy and safety of vardenafil ODT 10 mg	473 male subjects were screened subjects, 339	4 week run in period without study + 12 week	Male < 65 years ODT 52.5±8.	A history of ED for at least 6 months	- IIEF-EF Domain score at Week 12 or LOCF - SEP 2

	Mexico, and Australia			(PRN) after 12 weeks of treatment or LOCF with placebo in a general population of men with erectile dysfunction	subjects randomized (172 subjects given vardenafil 10 mg ODT, and 167 placebo)	10 mg vardenafil (PRN) or placebo.	6 placebo 53.5±7.8 ≥ 65 years ODT 70.3±4.9 placebo 70.5±5.3		(success rates of penetration) at Week 12 overall - SEP 3 (success rates of maintenance of erection) at Week 12 overall

2.4.2. Pharmacokinetics

Methods

Analytical Methods

Sampling Scheme

On the Pharmacokinetic (PK) profile days as defined in the studies, venous blood samples were taken for the determination of plasma concentrations of vardenafil. A typical schedule was comprised of a pre-dose sample and 17 sampling time points after administration as detailed in the following: 10*, 20, 30 and 45 minutes and 1, 1.5, 2, 2.5*, 3, 4, 5, 6, 8, 10, 12, 15 and 24 hours (h) (* not used in study 12093).

Determination of vardenafil concentrations in human plasma

Vardenafil (in free base equivalents) plasma concentrations were measured using fully validated high-performance liquid chromatography assays with tandem mass spectrometric detection (HPLC-MS/MS). Deuterated analogues of vardenafil (i.e. [$^2H_5$]-vardenafil) were used as internal standard (ISTD) for the respective analyte. Monitored ion transitions (m/z) were 489 → 151 (312) for vardenafil and 494 → 151 (312) for the [$^2H_5$]-labelled ISTD. The applied calibration range of the procedure reached from the lower limit of quantification (LLOQ; 0.1 – 0.123 µg/l) to 50 – 52.5 µg/l. The concentrations were validated by assaying quality control samples of blank plasma spiked with known concentrations of the analytes. Concentrations above LLOQ were determined with a precision of better than 15% and accuracy within 85 – 115% in accordance with internal SOPs and pertinent guidelines on method validation

Determination of vardenafil concentrations in human saliva

Vardenafil concentrations in saliva were determined after dilution employing HPLC with gradient elution and ultraviolet (UV) absorbance detection at 230 nm wavelength. The working range comprised concentrations in the range 0.0206 to 8.23 µg/l. Accuracy / precision in calibrators were 92.8% / 9.4% at the LLOQ and 98.1-100.6% / 0.25-1.5% above LLOQ. The QC samples were determined with 98.4% accuracy and 2.5% precision.

Pharmacokinetic data analysis

The linear-logarithmic trapezoidal method was used to calculate AUC, and $t_{1/2}$ was estimated by linear least squares regression after logarithmic transformation of the terminal concentrations. Based on the plasma concentration time data the following parameters were calculated using non-compartmental methods.

C_{max} and AUC values were dose- and body weight normalized ([$C_{max,norm}$] and [AUC_{norm}]), according to the dose in milligram per kilogram body weight. Plasma concentration–time courses (calculated if two thirds or more of individual values were greater than the LLOQ, at the scheduled time) are presented as geometric mean values with or without geometric standard deviations. Pharmacokinetic parameters (except t_{max}) are presented as geometric mean values including geometric coefficient of variation [%CV] and range. Results for t_{max} are presented as median [range].

Absorption

Vardenafil hydrochloride (HCl) is highly soluble in aqueous media at pH 1, however, due to the strong decrease in solubility with increasing pH a dose of 10 mg (vardenafil) is not completely soluble at pH values above 4.5 (250 ml of aqueous medium; 37 °C). Vardenafil is a highly permeable drug in vitro in the Caco-2-cell model. Due to the low solubility at neutral pH vardenafil HCl is a BCS class 2 drugs. This condition makes that a small amount of vardenafil is bioavailable in the oral cavity as it was studied in the mechanistic study 10021.

o **Study 10021: Study to investigate local oral absorption**

Randomized, unblinded, two fold crossover study was performed in 10 healthy male subjects (aged 33.8 (26 – 43) years; mean (range)) in order to investigate the local bioavailability of vardenafil in the oral cavity. Fasted subjects received a solution of 10 mg vardenafil as HCl salt which they either swallowed with water or rested into the oral cavity, respectively. Subjects remained in a sitting position while they kept the solution in their mouth for 15 minutes and were instructed not to swallow. Subsequently they emptied their mouth and rinsed it with 5 x 20 ml water. The mouth rinses were collected, combined and subject to analysis of vardenafil concentrations in order to estimate the amount of drug absorbed in the oral cavity.

The relative bioavailability f_{rel} (ratio of AUC values) after local administration was 24.6 (17.0 - 35.6) % (point estimate (90% CI)) compared to oral (swallowed) intake of a solution containing 10 mg vardenafil as HCl. A pronounced lag time (t_{lag}) of about 30 minutes was noted and the rate of absorption was slower after local oral compared to gastrointestinal absorption resulting in a delay in median t_{max} of 2 h (see Figure 1). The terminal elimination half-lives (3.5 and 3.6 h) were independent of formulation. The pharmacokinetic parameters are shown in Table 3.

92 (48 – 113)% (arithmetic mean (range)) of the sublingually administered dose was recovered in saliva and water collected after rinsing the oral cavity. Assuming a negligible portion of vardenafil swallowed after local oral administration it can be inferred that about 8% of the dose (0.8 mg vardenafil) was absorbed in the oral cavity. The vardenafil AUC after administration to the oral cavity (4.904 µg*h/l) resulting from this small dose compares to an AUC of 19.91 µg*h/l after gastrointestinal absorption of a 10 mg dose. The relative bioavailability f_{rel}* of vardenafil after local oral absorption based on the actual absorbed dose (ratio of [AUC/Dose]) is estimated at 308%. This study indicates that a small amount of vardenafil is absorbed in the oral cavity with increased bioavailability.

Figure 1: Plasma concentrations (µg/l) of vardenafil after a single dose of 10 mg vardenafil oral solution and 10 mg (nominal dose) sublingual solution, respectively (geometric means and geometric SD, linear scale, all subjects valid for pharmacokinetics, n =10) (Study 10021)

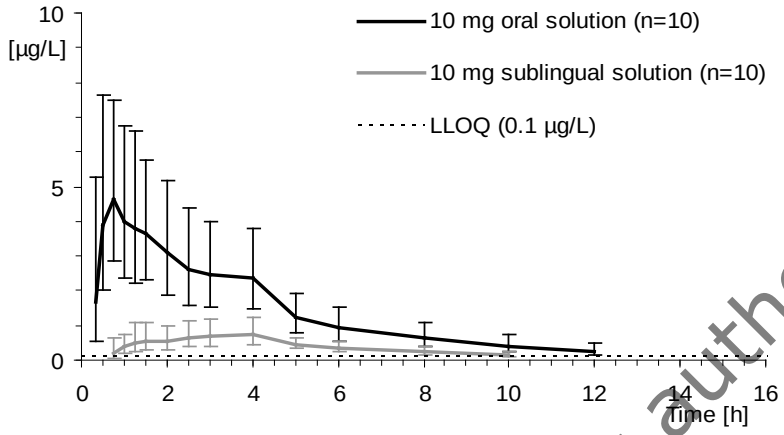


Table 3: Pharmacokinetic parameters of vardenafil in plasma following single dose administration of 10 mg vardenafil oral (swallowed) solution and sublingual solution, respectively (geometric mean / %CV (range), all subjects valid for PK, n=10) (Study 10021)

Parameter	Unit	Vardenafil oral (swallowed) solution (n=10)	Vardenafil sublingual solution (n=10)
AUC	µg*h/l	19.91/32.4	4.904/32.8
		(10.4 – 39.1)	(2.40 – 10.6)
AUC_{norm}	kg*h/l	0.1533/38.3	0.03774/37.8
		(0.0804 – 0.391)	(0.0163 – 0.0743)
C_{max}	µg/l	5.254/39.3	0.879/43.9
		(1.97 – 10.4)	(0.371 – 2.16)
$C_{max,norm}$	kg/l	0.04046/43.8	0.006757/49.3
		(0.0152 – 0.0727)	(0.00289 – 0.0194)
$t_{½}$	h	3.636/12.5	3.529/22.3
		(2.70 – 4.50)	(2.29-6.75)
MRT	h	4.610/14.7	6.282/16.3
		(3.05 - 5.84)	(4.89 – 9.79)
CL/f	l/h	501.9/32.4	2038/32.9
		(256 - 957)	(942 - 4160)
t_{max}[a]	h	0.75	2.75
		(0.33 – 1.25)	(1.25 – 4.00)

a) median range

Bioavailability

Study 12769: Relative bioavailability, effect of food and effect of water

This was a randomized, open-label, four-fold crossover study in healthy young male subjects (mean age and range: 37.8 (29 – 49) years, n=13 valid for pharmacokinetics). The study compared the pharmacokinetics of 10 mg vardenafil as ODT (fasting, w/o water) and film-coated tablet (fasting, with 180 mL water), and investigated the effect of a high fat, high calorie breakfast on ODT taken w/o water. The ODT was administered 30 minutes after start of the meal. A fourth treatment arm investigated the effect of water (180 ml) administered together with the 10 mg ODT in the fasting condition in order to assess the pharmacokinetic changes in subjects who are non-compliant with the recommended mode of administration (i.e. w/o water).

When administered w/o water the ODT demonstrated suprabioavailability in comparison to film-coated tablet i.e. its mean bioavailability (AUC) was increased by 44% (point estimate and 90% CI of ratio [ODT fasted w/o water vs. film-coated tablet]: 144 (132-158) %). The AUC increase was observed from about 1 h post administration onwards and is attributed to the local absorption of vardenafil in the oral cavity with increased bioavailability. The change in shape of plasma-concentration vs. time profile translated into a small increase in mean residence time (MRT) from 4.6 h (film-coated tablet) to 5.0 h (ODT). With the rate of absorption through the oral mucosa being slow, C_{max} was less affected with the 90% CI of the ratio including unity (point estimate and 90% CI of ratio [ODT fasted w/o water vs. film-coated tablet]: 115 (94-140) %). ODT intake w/o water also resulted in an increase in median t_{max} of 0.75 h compared to film-coated tablet. In the treatment '10 mg ODT w/o water' the geometric CV% as a measure of inter-subject variability was numerically smaller for AUC compared to film-coated tablet (42 vs. 55%), while C_{max} demonstrated similar variability (51 vs. 50%).

If taken with water (180 ml) the concentration vs. time profiles of ODT and film-coated tablet were similar and the ODT was no longer suprabioavailable in comparison to film-coated tablet, with the AUC ratio and 90% CI ([ODT fasted with water / film-coated tablet] of 103 (94.0 – 113)%) complying with bioequivalence criteria. Under these conditions of intake with water, C_{max} demonstrated a 10% increase (point estimate and 90% CI [ODT with water / film-coated tablet]: 110 (90 – 135) %) and median t_{max} was reduced by 0.25 h compared to 10 mg film-coated tablet (0.75 to 0.5 h). If the ODT is taken with water, vardenafil is completely swallowed and its residence time in the oral cavity is not sufficient to allow permeation of the oral mucosa. When comparing 'ODT with water' to 'ODT w/o water' these effects of intake with water translate into a decrease in AUC by 29%, essentially unchanged C_{max} (- 4%) and a decrease in median t_{max} by 1 h (1.5 to 0.5 h).

Administration of the ODT with a high fat/high calorie meal had no effect on vardenafil AUC (point estimate and 90% CI of ratio [fed / fasting]: 98 (89 – 107) %) while C_{max} was reduced by 35% (C_{max} ratio [fed / fasting]: 65 (53 – 79) %). Food had no effect on the time to reach C_{max}. Geometric CV % values for exposure parameters were numerically smaller if the ODT was taken with food (36 vs. 42% (AUC) and 34 vs. 51% (C_{max}), fed vs. fasted condition). Given the lack of food effect on extent of bioavailability, slight reduction in C_{max} and unchanged t_{max} with food, it can be concluded that the ODT can be administered without regard to food intake.

Figure 2: Plasma concentrations (µg/l) of vardenafil after a single dose of 10 mg vardenafil, geometric means, linear scale, all subjects valid for pharmacokinetics, n = 13 (Study 12769)

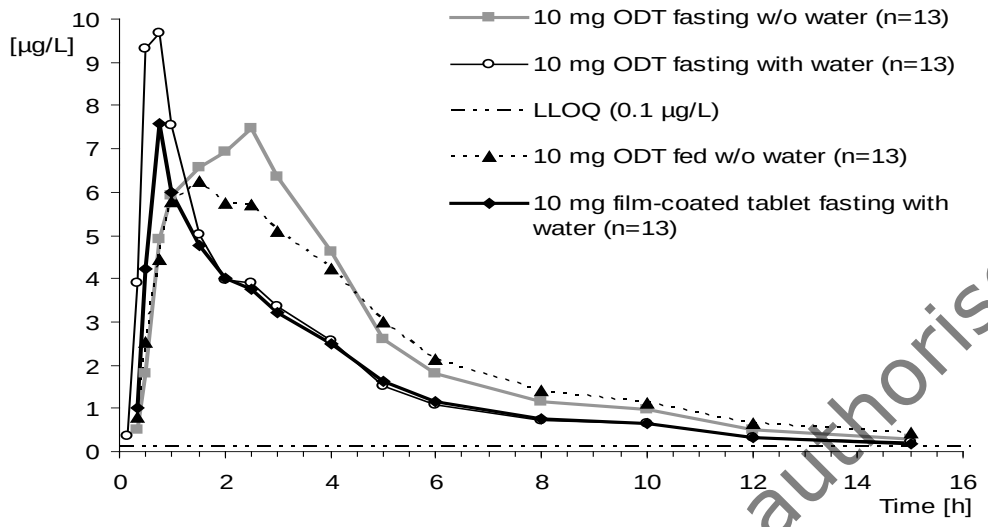


Table 4: Pharmacokinetic parameters of vardenafil in plasma following a single oral dose of 10 mg vardenafil (geometric mean / %CV (range), all subjects valid for PK, n=13) (Study 12769)

Parameter	Unit	ODT fasting, w/o water (n=13)	ODT with breakfast, w/o water (n=13)	ODT fasting, with water (n=13)	Film-coated tablet, fasting with water (n=13)
AUC	µg*h/L	39.38/41.7 (19.80-78.13)	38.47/35.6 (21.17-64.20)	28.14/43.7 (15.46-55.66)	26.95/54.7 (11.73-65.12)
AUC_{norm}	kg*h/L	0.3253/43.0 (0.1762-0.6094)	0.3178/37.3 (0.1884-0.5843)	0.2325/45.8 (0.1342-0.4341)	0.2226/54.4 (0.1032-0.5405)
C_{max}	µg/L	10.94/51.3 (4.997-22.42)	7.179/33.6 (3.668-11.02)	10.68/40.8 (6.343-23.31)	9.586/49.9 (5.559-28.76)
$C_{max,norm}$	kg/L	0.09037/51.4 (0.04448-0.2040)	0.05930/35.7 (0.03264-0.09809)	0.08820/42.4 (0.05011-0.2121)	0.07918/47.3 (0.04892-0.2387)
$t_{½}$	h	4.145/26.7 (2.713-5.454)	4.676/25.1 (2.752-6.155)	3.793/29.7 (2.386-7.263)	3.849/29.1 (2.280-6.476)
MRT	h	4.964/17.9 (3.433-6.296)	6.045/15.6 (4.824-7.694)	4.336/18.7 (3.114-6.296)	4.562/28.8 (3.020-8.851)
CL/f	L/h	253.9/41.7 (128.0-505.1)	259.9/35.6 (155.8-472.4)	355.3/43.7 (179.7-646.6)	371.0/54.7 (153.6-852.8)
t_{max}[a]	h	1.50 (0.75-3.00)	1.50 (0.75-2.50)	0.50 (0.50-1.00)	0.75 (0.50-2.00)

Table 5: Point estimates (LS-means) and two-sided 90 % confidence intervals for the ratios of the primary parameters AUC and C_{max} of vardenafil (results of ANOVA, all subjects valid for PK, n=13) (Study 12769)

Ratio	Parameter	n	Estimated ratio (%)	90% confidence interval (%)
ODT fasting with water / ODT fasting w/o water	AUC	13	71.39	[65.29-78.05]
	C_{max}	13	96.23	[79.11-117.05]
ODT with breakfast / ODT fasting w/o water	AUC	13	97.94	[89.48-107.20]
	C_{max}	13	64.66	[53.03-78.83]
ODT fasting w/o water / Film-coated tablet fasting with water	AUC	13	144.12	[131.67-157.75]
	C_{max}	13	114.66	[94.04-139.80]
ODT fasting with water / Film-coated tablet fasting with water	AUC	13	102.88	[93.99-112.61]
	C_{max}	13	110.33	[90.49-134.53]
ODT with breakfast / Film-coated tablet fasting with water	AUC	13	141.15	[129.10-154.33]
	C_{max}	13	74.13	[60.95-90.17]

Distribution

No additional studies to investigate distribution following administration of the ODT were performed. The distribution of vardenafil after absorption from the ODT is considered to be no different from that of the film-coated tablet.

Elimination

No additional studies to investigate excretion or metabolism following administration of the ODT were performed. The excretion and metabolism of vardenafil after absorption from the ODT is considered to be no different from that of the film-coated tablet.

Dose proportionality and time dependencies

Not applicable

Special populations

Impaired renal function

Renal impairment was already investigated in detail with the film-coated tablet and the results are considered to apply to the ODT.

Vardenafil pharmacokinetics was similar in subjects with mild to moderate renal impairment compared with a normal renal function control group. No statistically significant correlation was observed between creatinine clearance and vardenafil plasma exposure. Subjects with severe renal impairment showed a 21% increase in mean vardenafil AUC and a decrease in mean C_{max} of 23% compared with subjects with normal renal function.

Impaired hepatic function

Hepatic impairment was already investigated in detail with the film-coated tablet and the results are considered to apply to the ODT.

Vardenafil clearance was reduced in subjects with moderate hepatic impairment (Child-Pugh B) resulting in 2.6-fold and 2.3-fold increased AUC and C_{max}, compared with healthy controls. Subjects

with mild hepatic impairment (Child-Pugh A) demonstrated 1.2-fold increased AUC and C_{max}, compared with the control group.

Gender

Vivanza orodispersable tablets are not indicated for use by women.

Race

Race was already investigated in detail with the film-coated tablet and exposure has been shown to be comparable in subjects of different ethnic origin.

Elderly

The covariate "age" was specifically investigated for Vivanza ODT in view of the possibility of local absorption in the oral cavity being age-dependent.

The age-effect was investigated in the Study 13396.

- **Study 13396: Multiple-dose study to investigate the effect of age in male patients with erectile dysfunction**

Male ED patients were stratified by age according to the categories 18 to ≤45 years (n=14), >45 to <65 years (n=6), ≥65 to <70 years (n=7) and ≥70 years (n = 7). The primary comparison to evaluate the effect of age was performed between subjects ≥65 years (actual mean (range): 70.5 (65 – 80) years; n=14) and ≤45 years (actual mean (range): 39.9 (31 – 45) years; n=14). The subjects received a single dose of 10 mg film-coated tablet with water on study day 1 followed by a wash-out of 2 days duration. Subsequently, 10 repeated once-daily doses of 10 mg ODT were administered w/o water with pharmacokinetic profiles being collected after the first dose (study day 4) and last dose (study day 13). Drug intake on day 1, 4 and 13 was in the fasting condition while administrations on days 5-12 were performed after a standardized Continental breakfast. Study 13396 showed that age has similar effects on the systemic vardenafil exposure of the ODT and film-coated tablet.

Following the first 10 mg ODT dose vardenafil AUC and Cmax were increased by 39 % and 21 %, respectively, in subjects aged ⩾65 years compared to subjects aged ⩽45 years. On the last day of the multiple-dose regimen, vardenafil $AUC_{\tau,ss}$ [AUC(288-312)ss] and Cmax,ss were greater by 31 % and 16 %, respectively, in subjects aged ⩾65 years. These effects of age on systemic drug exposure of the 10 mg ODT formulation were numerically smaller compared to 10 mg vardenafil IR tablet where AUC and Cmax were increased by 48 % and 39 %, respectively, in subjects aged ⩾65 years. However the relative suprabioavailability of the ODT compared to 10 mg film-coated tablet was decreased in the elderly. The relative bioavailability of the 10 mg ODT compared to

the 10 mg IR tablet was slightly decreased in subjects aged ⩾65 years (frel: 129 %; BAY BAY 38-9456 / 13396 / 28 May 2009 123 of 1395 subjects aged ⩽45 years vs 121 %; subjects aged ⩾65 years). Regardless of age, a once-daily dosing regimen of vardenafil ODT did not result in accumulation in plasma.

Children

Vivanza orodispersable tablets are not indicated for individuals below 18 years of age.

Pharmacokinetic interaction studies

The effects of CYP3A4 inhibitor comedication on the metabolism of vardenafil have been investigated in detail with the marketed Vivanza film-coated tablet and are also considered to apply to the ODT.

Pharmacokinetics using human biomaterials

No specific studies have been conducted in support of this application.

2.4.3. Pharmacodynamics

Not applicable as no new pharmacodynamics data was required.

2.4.4. Discussion on clinical pharmacology

The applicant calculated that about 8% (0.8 mg) of the dose is absorbed from the oral cavity. However, considering that the amount of drug recovered in saliva and water collected after rinsing the oral cavity showed a high variability in the amount of drug recovered (48 – 113)% (arithmetic mean (range)) and also taking into account that the sample used (10 subjects) seems to be small, the 8% of dose absorbed can be considered as an approximation. Nevertheless, the important issue is that part of the dose is absorbed in the oral cavity, which would avoid to some extent the hepatic first pass effect leading to an increase of bioavailability.

In a relative bioavailability study it was demonstrated that the ODT shows suprabioavailability in comparison to the film coated tablet. It means bioavailability was increased by 44% point estimate and 90% CI of ratio [ODT fasted w/o water vs. film-coated tablet]: 144 (132-158) %, which is attributed to the local absorption of vardenafil in the oral cavity. This information is clearly reflected in the SPC to allow prescribers knowing that the ODT 10 mg and the film coated tablet are not bioequivalent.

In this study the 10 mg ODT in the fasted state showed a median time to reach Cmax between 45 to 90 min, which supposes an increase in median Tmax of 0.75h compared to film-coated. When the ODT was taken with a high fat/high calorie meal, no effect on vardenafil AUC was observed, while Cmax was reduced by 35% and food had no effect on the time to reach Cmax. So it can be concluded that the ODT can be administrated without regard to food intake

If the ODT is taken with water, vardenafil is completely swallowed and its residence time in the oral cavity is not sufficient to allow absorption in the oral cavity. This way AUC showed bioavailability equivalence to the film coated tablet. However, Tmax was reduced by 0.25h compared to the 10 mg film coated tablet and Cmax showed a 10% increase. This is addressed in the SPC under section “method of administration”.

The submitted studies have demonstrated time-linear pharmacokinetics and unchanged AUC after multiple once-daily doses.

All special requirements for special population emerged from the studies have been properly included in the SPC.

Overall, what is important to highlight is that the 10 mg orodispersable tablet is not bioequivalent to the 10 mg film coated tablet, and therefore should not be used as an equivalent. The Applicant has included this information in section 4.2 of the SPC, indicating: “Vivanza10 mg orodispersable tablet is not bioequivalent to Vivanza film-coated tablet (see section 5.1). The maximum dose for Vivanza orodispersable is 10 mg/day”.

2.4.5. Conclusions on clinical pharmacology

Pharmacokinetic studies show that the ODT is suprabioavailable when compared to the film coated tablets, so both formulations are not bioequivalent. The submitted documentation showed that vardenafil pharmacokinetic levels are inside the efficacy/safety window considered for the film coated tablets.

Although a direct comparison between the 10 mg ODT and the 10 mg film coated tablets would have been desirable, the information provided with the submitted study is considered acceptable as this new formulation achieves the characteristic flat dose response curved linked to this active substance.

2.5. Clinical efficacy

The pivotal clinical program for the development of Vivanza ODT 10 mg included two Phase-III studies, Study 12093 and Study 12094, with identical study design. These were multi-center, age-stratified, randomized, double-blind, placebo controlled, and fixed-dose studies. Subjects followed a 4-week non-medicated run-in period during which the diagnosis of ED was assessed and verified. Subjects were then randomized to one of the two treatment groups (vardenafil 10 mg ODT, or matching placebo) for a 12-week treatment period, after which there was a 48-hour follow-up period to record any adverse events (AEs).

In order to provide sufficient safety and efficacy data of elderly patients exposed to Vivanza ODT, a stratified randomization procedure guaranteed the inclusion of 50% elderly subjects in each treatment group.

2.5.1. Dose response study

The efficacy was assessed using the same efficacy parameters that those already used in studies investigating the film coated tablets, i.e. IIEF-EF Domain score, SEP 2 (success rates of penetration), and SEP 3 (success rates of maintenance of erection). The clinical efficacy documentation showed that the ODT was significantly superior to placebo in the parameters assessed.

The marketing authorization was granted for 5 mg, 10 mg and 20 mg film coated tablets. The 10 mg is considered the starting dose, however as general precaution a lower starting dose of 5 mg is recommended for subjects ≥ 65 years of age. The MAH considered that since the ODT 10 mg dose is within the EU approved dose range for the film-coated tablets, a higher or lower dose-finding for the ODT was considered unnecessary and a single dose (10 mg) clinical development program was pursued.

2.5.2. Main study

The Applicant has submitted two phase III pivotal studies; 12093 and 12094.

Study 12093: Pivotal phase III trial to investigate the efficacy and safety of an Orodispersible Tablet vardenafil versus placebo in the treatment of men with Erectile dysfunction (ED) – a fixed-dose, double-blind, randomized multi-centre Trial – POTENT I.

Study 12094: Pivotal phase III trial to investigate the efficacy and safety of an Orodispersible Tablet vardenafil versus placebo in the treatment of men with erectile dysfunction (ED) – a fixed-dose, double-blind, randomized multi-centre Trial – POTENT II.

Study 12093 was carried out in 40 centres. Study 12094 was carried out in 35 active centres.

METHODS

The design of both studies was identical and the following is therefore applicable to both studies.

Study Participants

Both studies enrolled men in a stable heterosexual relationship lasting for at least 6 months, 18 years or older, with ED of more than 6 months' duration, as defined by the NIH Consensus Development Panel on Impotence (inability to achieve or maintain an erection of the penis sufficient to permit satisfactory sexual performance).

Subjects were required to make at least 4 attempts at sexual intercourse on separate days during the 1-month untreated baseline period, with at least 50% of these attempts reported to be unsuccessful (inability to get an erection, failed penetration, or maintenance of an erection).

Subject exclusion criteria

The exclusion criteria ensured the correct diagnosis of ED and a population representative of subjects with ED. Subjects who may have had conditions that would have posed a risk during sexual activity according to the National Institutes of Health (NIH) Consensus Panel were excluded to ensure safe conduct of the study. Thus, subjects with clinically significant cardiovascular illnesses within the preceding 6 months such as unstable angina, history of myocardial infarction, stroke, life-threatening arrhythmia were excluded. Subjects with congenital QT prolongation or on drugs known to cause significant prolongation of the QT interval (in particular Type Ia and Type 3 anti-arrhythmics), significant hypo- and hypertension, uncontrolled atrial fibrillation or flutter (defined as a ventricular response rate of ≥100 beats per minute), as well as subjects with a history of syncope or clinically significant postural hypotension within the six months prior to study entry were also excluded.

Concomitant use of nitrates or other nitric oxide donors as well as anti-androgens and alpha-blockers were also exclusion criteria. Any use of potent CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir and indinavir but also of the macrolide antibiotics clarithromycin and erythromycin were excluded from concomitant use with the 10 mg ODT.

Treatments

Vardenafil was supplied as 10 mg orodispersible tablets (ODT) and matching placebo tablets. Both active study drug and placebo had the same peppermint taste.

At Visit 2 (Week 0), subjects were stratified according to their age (18 to 64 and ≥ 65 years-of-age) and randomized in a 1 to 1 ratio to vardenafil or placebo.

Subjects received 1 tablet per day. 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.

The subject was to take the study medication approximately one hour before intended sexual activity. Study medication was to be taken on demand, but no more than one dose of study drug was to be taken per day.

Subjects were instructed that the study medication was not to be swallowed whole. Instead, the study medication tablets were to be placed in the oral cavity where they would quickly disintegrate. The ODT was taken without liquids

In both studies patients were to take the study medication approximately one hour before intended sexual activity. The SPC should recommend to take the medication also one hour before sexual activity.

Objectives

The primary objective of this study is to compare the efficacy and safety of vardenafil ODT 10 mg (PRN) after 12 weeks of treatment or LOCF with placebo in a general population of men with erectile dysfunction.

In these studies, approximately 50% of the men on active treatment have to be 65 years-of-age or older to get information on the safety profile as the 10 mg ODT formulation has a higher bioavailability when compared the 10 mg film coated tablet added to the fact that the elderly patients have higher AUC and Cmax values than younger patients with both formulations.

Outcomes/endpoints

Primary efficacy parameters

The efficacy of the ODT was determined using the International Index of Erectile Function (IIEF), a 15-item questionnaire that has proven a reliable, cross-culturally valid, self-administered measure of erectile function. The 15 items cover five domains: erectile function (6 items), orgasmic function (2 items), sexual desire (2 items), intercourse satisfaction (3 items), and overall sexual satisfaction (2 items).

Apart from the IIEF questionnaire, two event diary questions derived from the Sexual Encounter Profile (SEP), measuring success in penetration and maintenance of successful intercourse, were included as primary co-variables for the evaluation of efficacy.

Primary measures of efficacy for the two studies were:

- The baseline-adjusted erectile function (EF) domain score of the IIEF, calculated as the sum of scores from questions 1 to 5 and 15 at Week 12, using the LOCF method to account for missing data. These 6 questions measure the frequency of achieving erections, the frequency of achieving erections with sufficient rigidity for penetration, the frequency of penetration, the frequency of maintenance of erection after penetration, the ability to maintain erections to completion of intercourse, and confidence in obtaining and maintaining an erection. Depending on the question in the IIEF, the responses were scored either from 0 to 5, or 1 to 5, with 0 for no attempt at sexual intercourse. The responses were evaluated by analysis of covariance (ANCOVA) with baseline as covariate and with the treatment and center as factors, presenting the least squares (LS) means at baseline and post-randomization together with the standard error (SE) for the LS means for each treatment. In agreement with the CPMP recommendations (CPMP/EWP/2863/99, 2003), the stratum variable 'age' was also tentatively included as an additional factor. ED can be classified into five categories based on the EF domain score: severe (6-10), moderate (11-16), mild to moderate (17-21), mild (22-25) and no ED (26-30).

- Success in penetration ("Were you able to insert your penis into your partner's vagina?") according to the subject's diary from randomization to Week 12 (overall) using the per-subject overall success rate.

- Success in maintaining erection during intercourse ("Did your erection last long enough for you to have successful intercourse?") according to the subject's diary from randomization to Week 12 (overall) using the per-subject overall success rate.

The answers to these two questions on penetration and maintenance of erection came from the subject's diary and were collected after every attempt at intercourse during the untreated baseline phase, and capturing each attempt at intercourse over a 24-hour period after every dose of study medication during the double-blind treatment phase.

Per-subject success rates were calculated as the total number of successes divided by the total number of sexual attempts in an interval, and baseline was calculated from the subject's diary completed

during the 4-week baseline phase. The primary time point for assessing efficacy for these two diary questions in both efficacy studies was predefined as the overall interval from randomization to Week 12. No substitution was made for missing values in overall per-subject success rates.

Secondary efficacy parameters

Secondary measures of efficacy included subjects achieving "back to normal" erectile function scores in the IIEF questionnaire, as well as responses on the subject's diary concerning success of intercourse attempts, overall satisfaction with sexual experience, the Treatment Satisfaction Scale (TSS) and the Global Assessment Question (GAQ).

Sample size

The number of subjects required in this study was based on the primary efficacy variables, the EF domain score of the IIEF Questionnaire, and the success rates (coprimaries) of penetration (SEP 2) and maintenance (SEP 3) obtained from the data collected in the Subject Diaries. No alpha adjustment was required under the restriction that the IIEF-EF, the SEP 2, and the SEP 3 had to be simultaneously significant. However, the power of the total test was affected by the presence of coprimary endpoints and consequently, this impacted the sample size.

For the case of the two co-primary efficacy variables, a good lower boundary for the overall power of the analyses was one minus the sum of the probability of the type II error for each variable.

Randomisation

At Visit 2 (Week 0), subjects who met the inclusion and exclusion criteria were stratified according to their age (18 to 64 years-of-age and ≥ 65 years-of-age) and randomly and equally assigned (using a 1 to 1 ratio) to either vardenafil 10 mg ODT or placebo ODT according to a randomization code that was computer generated by the sponsor. The study was randomized in blocks of appropriate size meant to ensure a balance in terms of subjects between treatment groups. In order to achieve the intended allocation of 50% of all subjects older than 65 years-of-age, a forced randomization procedure was used.

Blinding (masking)

In this randomized, double-blind, multicentre, parallel-arm trial, blinding was maintained until completion of the study.

Statistical methods

All quantitative clinical variables were tabulated as descriptive statistics using sample sizes, means, standard deviations, minimum and maximum, and the median per item, domain, visit, LOCF, and treatment group. For the primary and coprimary variables, tables were generated for two samples: ITT (intent-to-treat population) and PP (per protocol population). When possible, means and standard deviations were plotted against time and per treatment group (primary and coprimary).

The two populations analysed for efficacy were defined as follows:

Intent to Treat Population (ITT): Subjects who had taken at least one dose of study medication and who had baseline and any post-baseline efficacy data using the last observation carried forward (LOCF) method to account for dropouts.

Valid-for-efficacy (VfE) population or Per Protocol Analysis (PP): All ITT subjects with the following additional criteria were included in PP analysis:

• Subjects who received 12 weeks of randomized treatment provided they had no additional major protocol violations or if they did not prematurely discontinue the study due to lack of efficacy or due to drug-related adverse events.

• Subjects who had no major protocol violations.

In both studies, the primary efficacy analysis was performed on the ITT population and repeated for the PP population. All three (co-)primary efficacy variables were required to simultaneously show significance ($p<0.05$) so no adjustment to alpha level for multiple endpoints was necessary.

Clinically relevant differences between 10 mg ODT and placebo were predefined for power calculations. A score difference of at least 5 points for the IIEF-EF domain and a percentage response difference of at least 18% for the diary questions in the general population were used for clinical studies on vardenafil. According to pooled data analyses, improvement of ED is generally smaller in elderly subjects (≥65 years) under treatment with PDE5 inhibitors compared with younger subjects. Both studies 12093 and 12094 included 50% elderly subjects, however a score difference of at least 4 points for the IIEF-EF domain and a percentage response difference of at least 15% for the diary questions was assumed, which were interpreted as clinically relevant treatment differences.

RESULTS

Participant flow

Table 6: Study 12093

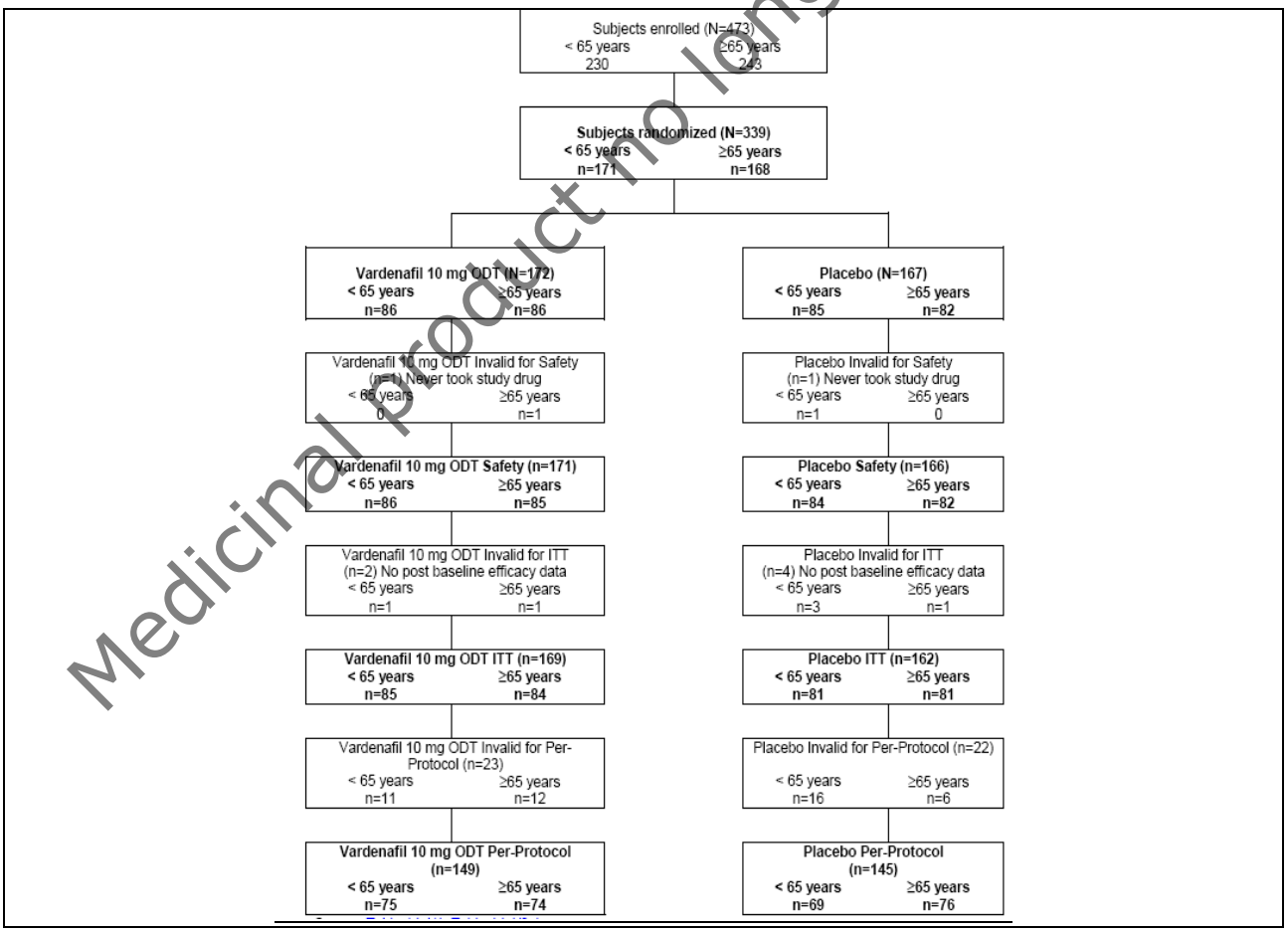
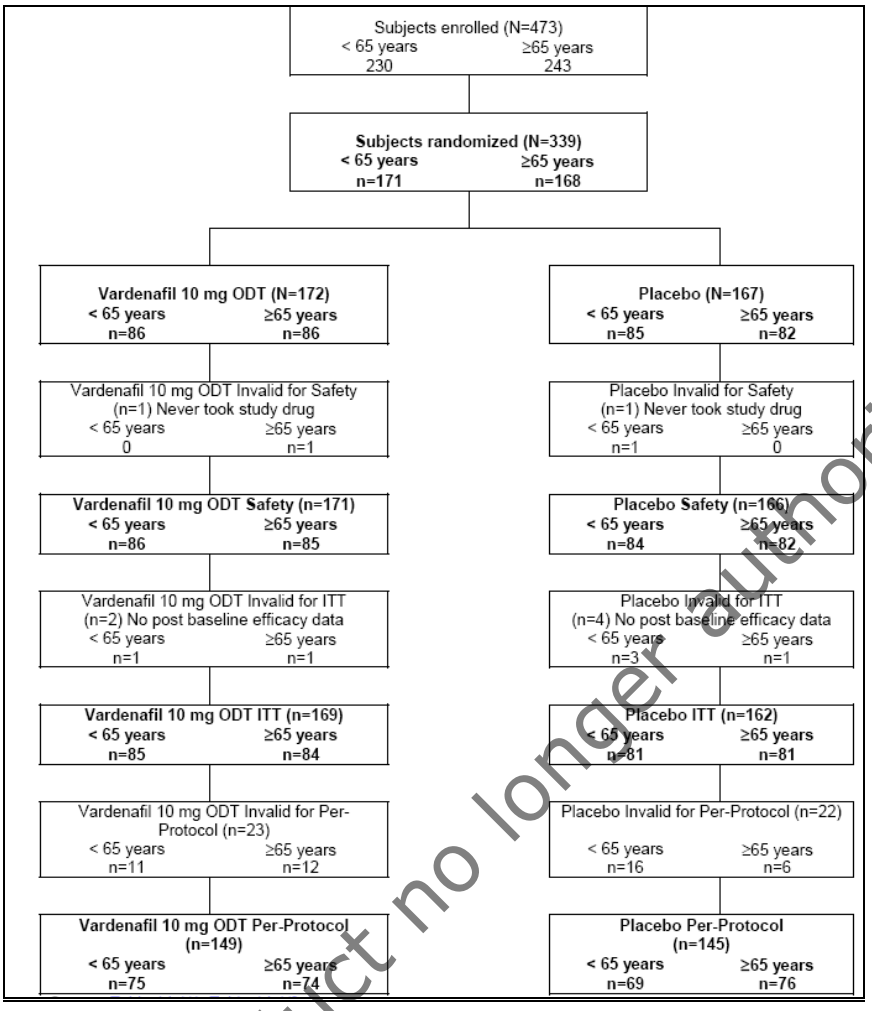


Table 7 : Study 12094



Conduct of the study

Study 12093

Altogether 50 subjects (14% of all randomized patients) had protocol deviations during the study, 29 subjects (16%) in the placebo group and 21 subjects (11%) in the vardenafil group. The most commonly reported protocol deviations in either treatment group were use of erectile dysfunction treatment within 7 days of the selection visit (7% of the placebo subjects and 4% of the vardenafil subjects) and missing follow-up information in all efficacy parameters (6% of the placebo group and 3% of the vardenafil group).

Study 12094

Altogether 44 subjects (13% of all randomized patients) had protocol deviations during the study; 21 subjects (13%) in the placebo group and 23 subjects (13%) in the vardenafil group. The most commonly reported protocol deviations in either treatment group were also missing follow-up information in all efficacy parameters (8% of the subjects in each of the treatment groups) and the use of erectile dysfunction treatment within 7 days of the selection visit (2% of the subjects in each of the treatment groups).

In study 12093 a total of 11 subjects (3.1% of the safety population) received a sexually enhancing drug after initiation of the study drug (5 subjects in the vardenafil group and 6 subjects in the placebo

group), and in study 12094 a total of 8 subjects (4 in each treatment group; 2.4% of the safety population).

One patient (<65 years) in the placebo group in study 12093 and one more also in the placebo group in study 12094 used a vacuum pump after randomization.

Treatment compliance

The number of doses was based on the difference between dispensed and returned tablets or the number of doses documented in the Case Report Form (CRF).

Study 12093

The average number of doses per week overall for all safety population subjects in the vardenafil group was 2.8 tablets per week compared with 2.2 tablets per week for the placebo group in study 12093. Subjects < 65-years-of-age in the vardenafil took an average of 3.2 tablets per week overall compared with 2.1 tablets per week for the placebo group indicating that the vardenafil subjects made more sexual attempts. Elderly subjects in the vardenafil and placebo groups took an average of 2.4 tablets per week overall. Similar trend were seen in the ITT and PP populations.

Study 12094

The average number of doses per week overall for all safety population subjects in the vardenafil group was 2.7 tablets per week compared with 1.8 tablets per week for the placebo group. Subjects < 65-years-of-age in the vardenafil took an average of 3.0 tablets per week overall compared with 1.9 tablets per week for the placebo group. Elderly subjects in the vardenafil group took an average of 2.3 tablets per week overall compared with 1.7 tablets per week for the placebo group. Similar trend were seen in the ITT and PP populations

Baseline data

Major baseline demographic and clinical characteristic were similar for each group of treatment (placebo vs. vardenafil ODT) in both studies.

Table 8: Subject Demographics – Age, Height and Weight (ITT)

Age mean ± SD (years)			**Height** mean ± SD (cm)			**Body weight** mean ± SD (kg)		
<65 years	**≥65 years**	**Total**	**<65 years**	**≥65 years**	**Total**	**<65 years**	**≥65 years**	**Total**
Study 12093 / report A44851 (N=358)								
52.7 ± 8.8	69.8 ± 4.6	61.8 ± 10.9	177.8 ± 7.5	174.3 ± 7.2	175.9 ± 7.5	87.7 ± 13.4	82.1 ± 11.6	84.7 ± 12.7
Study 12094 / report A45684 (N=337)								
53.0 ± 8.2	70.4 ± 5.1	61.6 ± 11.1	175.5 ± 8.3	173.8 ± 8.7	174.6 ± 8.5	89.3 ± 16.0	86.7 ± 14.2	88.0 ± 15.2

About two-thirds of the safety population were Caucasians, followed by about 22% Hispanic (Study 12094 only) and 4% to 5% black or Asian subjects (see table below). In study 12093, the ethnic origin of about 26% of the subjects was not determined due to country-specific reasons.

Table 9: Subject Demographics – Ethnic Group (ITT)

Number (%) of subjects per stratum

	Study 12093 (Report A44851)			**Study 12094** (Report A45684)		
Ethnic group	**<65 years**	**≥65 years**	**Total**	**<65 years**	**≥65 years**	**Total**
Caucasian (white)	107 (64.5%)	132 (69.8%)	239 (67.3%)	105 (63.3%)	124 (75.2%)	229 (69.2%)
Black	5 (3.0%)	8 (4.2%)	13 (3.7%)	14 (8.4%)	3 (1.8%)	17 (5.1%)
Asian	7 (4.2%)	5 (2.6%)	12 (3.4%)	8 (4.8%)	5 (3.0%)	13 (3.9%)
Hispanic	0	0	0	39 (23.5%)	32 (19.4%)	71 (21.5%)
Non-codable*	7 (4.2%)	11 (5.8%)	18 (5.1%)	0	1 (0.6%)	1 (0.3%)
N.A.	1 (0.6%)	1 (0.5%)	2 (0.6%)	0	0	0
Missing**	39 (23.5%)	32 (16.9%)	71 (20.0%)	0	0	0

* In South Africa, 18 subjects could not be categorized with regard to race (study 12093).
** In France, race was not allowed to be reported (study 12093).

More than 78% of all patients were married.

Altogether 234 subjects (65.4%) (study 12093) and 183 subjects (53.7%) (study 12094) in both age groups reported 'light' alcohol consumption and 200 subjects (55.9% of all subjects in the safety population- study 12093) and 164 subjects (48.7%- study 12094) were past or present smokers. However, approximately 28% (study 12093) and 19% (study 12094) of all subjects were present smokers who continued after terminating the study while the majority of smokers (approximately 72%-study 12093 and 81%- study 12094) already stopped smoking before the end of study.

There were no apparent differences between the ITT and PP populations.

Altogether 266 subjects (74.3% of all subjects valid for safety) of study 12093 and 280 subjects (83.1%) of study 12094 had experience with PDE-V inhibitors such as sildenafil, tadalafil, or the test drug vardenafil.

The ED symptom pattern reported for the total safety population was comparable in both age strata in both treatment groups for both studies.

The average time from onset of ED for the total safety population was about 6 to 7 years in both studies whereas the mean time since diagnosis of ED was about 4 to 5 years. The majority of subjects in both studies were diagnosed with ED with organic aetiology (52.2% and 65.0% in study numbers 12093 and 12094, respectively). The severity of ED symptoms during the last 6 months was comparable between both studies with "Erection is not maintained during intercourse", "Erection too soft to penetrate the vagina" and "Inability to obtain an erection" being the most frequently (≥75%) reported complaints.

Table 10: Baseline characteristics – Erectile dysfunction history and symptoms present in the past 6 months (Safety Population)

	Study 12093 (Report A44851)			Study 12094 (Report A45684)		
	<65 years	**≥65 years**	**Total**	**<65 years**	**≥65 years**	**Total**
ED history						
Time since ED diagnosis (years mean ± SD)	4.1 ± 4.1	4.8 ± 4.4	4.5 ± 4.3	4.6 ± 3.8	5.5 ± 5.0	5.1 ± 4.5
Time since ED onset (years mean ± SD)	5.9 ± 5.4	6.6 ± 4.8	6.3 ± 5.1	6.0 ± 4.8	7.7 ± 5.6	6.8 ± 5.3
Etiology of ED (%)						
Organic	45.8%	57.9%	52.2%	57.6%	72.5%	65.0%
Psychogenic	17.9%	5.8%	11.5%	14.7%	2.4%	8.6%
Mixed	35.7%	35.8%	35.8%	24.1%	22.8%	23.4%
Previous use of oral PDE-5 inhibitors for ED (%)	79.2%	70.0%	74.3%	80.0%	86.2%	83.1%
Satisfied with oral treatment(s) (%)	84.2%	77.4%	80.8%	73.5%	52.8%	62.9%
ED symptoms present in the past 6 months (%)						
No desire for sex	6.0%	5.8%	5.9%	14.1%	8.4%	11.3%
Inability to obtain an erection	70.2%	80.0%	75.4%	81.8%	79.0%	80.4%
Erection too soft to penetrate the vagina	89.3%	92.1%	90.8%	85.9%	89.8%	87.8%
Erection is not maintained during intercourse	96.4%	97.9%	97.2%	94.7%	92.8%	93.8%
Pain during intercourse	1.8%	1.6%	1.7%	0.6%	0.6%	0.6%
Premature ejaculation	16.7%	16.8%	16.8%	20.0%	8.4%	14.2%
Lack of or infrequent orgasm	22.0%	27.4%	24.9%	28.8%	31.7%	30.3%

Apart from erectile dysfunction, subjects in the study reported further concomitant diseases that are frequently associated with ED.

Vascular hypertensive disorders were the most frequently reported abnormalities affecting 148 subjects or 41.3% of all randomized subjects in the safety population-study 12093 and 142 subjects or 42.1% -study 2094.

In both treatment groups, subjects ≥ 65 years-of-age had a higher occurrence of hypertensive disorders than subjects < 65 years-of-age. Elderly subjects also had higher frequencies of gastrointestinal atonic and hypomotility disorders, upper respiratory tract infections, had higher frequencies of diabetes hyperlipidaemia and (osteo) arthropathies than the younger subjects in both treatment groups.

Altogether 78.5% (study 12093) and 82.2% (study 12094) of all subjects in the safety population used concomitant medication post-enrolment.

Numbers analysed

Table 11: Data sets-analyzed- Number of subjects enrolled, discontinued and included in the efficacy analysis:

Study number	Report number	Number of enrolled subjects	Number of randomized subjects	Subjects excluded from any analysis*	EFFICACY ANALYSIS					
					Number of subjects in the ITT population			Number of subjects in the PP population		
					<65 y	≥65 y	Total	<65 y	≥65 y	Total
12093	A44851	409	362	55	166	189	355	146	165	311
12094	A45684	473	339	47	165	166	331	144	150	294

* Number of subjects which were excluded from either the safety, ITT or PP analysis

The number of subjects excluded from the efficacy analyses in the study 12093 was a total of 51 subjects and in study 12094 a total of 45 subjects, and the primary reason for exclusion was that the subjects took prohibited medication/therapy during the study or that there was missing follow-up information in all primary efficacy parameters.

Outcomes and estimation

Table 12: PRIMARY EFFICACY VARIABLES

Study 12093 – EF domain score of the IIEF: Summary statistics			
ITT population		**Placebo**	**10 mg ODT**
Summary statistics			
< 65 years		n = 80	n = 85
(arithmetic mean ± SD)	Baseline	13.4 ± 4.74	13.4 ± 4.78
	Week 12 (LOCF)	15.4 ± 7.64	23.0 ± 6.95
	Change from Baseline	2.1 ± 7.33	9.6 ± 6.28
≥ 65 years		n = 92	n = 96
(arithmetic mean ± SD)	Baseline	12.3 ± 5.44	12.2 ± 4.87
	Week 12 (LOCF)	13.2 ± 7.42	19.9 ± 8.81
	Change from Baseline	0.9 ± 6.42	7.7 ± 8.19
Total		n = 172	n = 181
(arithmetic mean ± SD)	Baseline	12.8 ± 5.14	12.8 ± 4.85
	Week 12 (LOCF)	14.2 ± 7.59	21.4 ± 8.12
	Change from Baseline	1.4 ± 6.86	8.6 ± 7.40
(LS-mean)	Baseline	12.85	12.86
	Week 12 (LOCF)	14.38	21.48
Comparison (LS-mean difference [95% CI]; p-values [ANCOVA])			
	Treatment: Placebo – Vardenafil	-7.11 [-8.56 to -5.66]	
	Age group: < 65 years – ≥ 65 years	2.00 [0.54 to 3.47]	
	Treatment	p < 0.0001	
	Age group	p = 0.0076	

CI: confidence interval; IIEF: International Index of Erectile Function; LS: least squares; SD: standard deviation

A statistically significant age effect can be observed regardless of treatment group.

Table 13

Study 12093 – Success rates for penetration (SEP 2): Summary statistics

ITT population		Placebo	10 mg ODT
Summary statistics			
< 65 years		n = 79	n = 85
(arithmetic mean ± SD)	Baseline	43.1% ± 36.86%	44.7% ± 36.68%
	Week 12 (LOCF)	48.6% ± 39.55%	80.5% ± 26.84%
	Change from Baseline	5.5% ± 42.82%	35.8% ± 33.63%
≥ 65 years		n = 90	n = 94
(arithmetic mean ± SD)	Baseline	32.5% ± 34.77%	34.6% ± 33.85%
	Week 12 (LOCF)	41.2% ± 37.22%	69.8% ± 35.87%
	Change from Baseline	8.7% ± 28.41%	35.2% ± 38.06%
Total		n = 169	n = 179
(arithmetic mean ± SD)	Baseline	37.5% ± 36.04%	39.4% ± 35.48%
	Week 12 (LOCF)	44.7% ± 38.38%	74.9% ± 32.26%
	Change from Baseline	7.2% ± 35.79%	35.5% ± 35.93%
(LS-mean)	Baseline	38.76	40.38
	Week 12 (LOCF)	46.68	73.73
Comparison (LS-mean difference [95% CI]; p-values [ANCOVA])			
	Treatment: Placebo – Vardenafil	-27.04% [-33.66% to -20.43%]	
	Age group: < 65 years – ≥ 65 years	3.78% [-2.79% to 10.35%]	
	Treatment	p < 0.0001	
	Age group	p = 0.2591	

CI: confidence interval; IIEF: International Index of Erectile Function; LS: least squares; SD: standard deviation

Again, there was a treatment-independent statistically significant age effect for this endpoint.

Table 14

Study 12093 – Success rates for maintenance (SEP 3): Summary statistics

ITT population		Placebo	10 mg ODT
Summary statistics			
< 65 years		n = 78	n = 85
(arithmetic mean ± SD)	Baseline	14.5% ± 21.63%	16.3% ± 21.95%
	Week 12 (LOCF)	29.7% ± 35.05%	70.8% ± 33.33%
	Change from Baseline	15.2% ± 31.30%	54.5% ± 32.72%
≥ 65 years		n = 86	n = 93
(arithmetic mean ± SD)	Baseline	14.5% ± 20.27%	10.4% ± 18.89%
	Week 12 (LOCF)	22.3% ± 28.94%	59.6% ± 38.71%
	Change from Baseline	7.7% ± 25.72%	49.2% ± 37.28%
Total		n = 164	n = 178
(arithmetic mean ± SD)	Baseline	14.5% ± 20.86%	13.2% ± 20.56%
	Week 12 (LOCF)	25.8% ± 32.11%	65.0% ± 36.57%

	Change from Baseline	11.3% ± 28.67%	51.7% ± 35.18%
(LS-mean)	Baseline	15.16	13.60
	Week 12 (LOCF)	26.70	64.89

Comparison (LS-mean difference [95% CI]; p-values [ANCOVA])

Treatment: Placebo – Vardenafil	-38.19% [-45.02% to -31.37%]
Age group: < 65 years – ≥ 65 years	7.10% [0.37% to 13.83%]
Treatment	p < 0.0001
Age group	p = 0.0386

CI: confidence interval; IIEF: International Index of Erectile Function; LS: least squares; SD: standard deviation

Again, there was a treatment-independent statistically significant age effect for this endpoint.

Table 15

Study 12094 – EF domain score of the IIEF: Summary statistics

ITT population		**Placebo**	**10 mg ODT**
Summary statistics			
< 65 years		n = 80	n = 83
(arithmetic mean ± SD)	Baseline	13.3 ± 5.08	12.6 ± 5.57
	Week 12 (LOCF)	15.0 ± 7.58	22.9 ± 8.43
	Change from Baseline	1.7 ± 6.28	10.3 ± 7.78
≥ 65 years		n = 80	n = 84
(arithmetic mean ± SD)	Baseline	12.5 ± 6.35	11.1 ± 5.79
	Week 12 (LOCF)	13.6 ± 7.82	17.8 ± 9.08
	Change from Baseline	1.1 ± 6.01	6.7 ± 8.06
Total		n = 160	n = 167
(arithmetic mean ± SD)	Baseline	12.9 ± 5.75	11.8 ± 5.72
	Week 12 (LOCF)	14.3 ± 7.71	20.4 ± 9.11
	Change from Baseline	1.4 ± 6.14	8.5 ± 8.11
(LS-mean)	Baseline	12.76	11.70
	Week 12 (LOCF)	13.88	20.80

Comparison (LS-mean difference [95% CI]; p-values [ANCOVA])

Treatment: Placebo – Vardenafil	-6.92 [-8.46 to -5.38]
Age group: < 65 years – ≥ 65 years	2.35 [0.81 to 3.89]
Treatment	p < 0.0001
Age group	p = 0.0029

CI: confidence interval; IIEF: International Index of Erectile Function; LS: least squares; SD: standard deviation

A statistically significant age effect can be observed regardless of treatment group.

Table 16

Study 12094 – Success rates for penetration (SEP 2): Summary statistics			
ITT population		**Placebo**	**10 mg ODT**
Summary statistics			
< 65 years		n = 81	n = 84
(arithmetic mean ± SD)	Baseline	44.2% ± 33.53%	42.9% ± 35.61%
	Week 12 (LOCF)	48.8% ± 38.83%	76.1% ± 33.85%
	Change from Baseline	4.6% ± 34.12%	33.2% ± 33.27%
≥ 65 years		n = 80	n = 84
(arithmetic mean ± SD)	Baseline	34.1% ± 36.11%	31.6% ± 36.11%
	Week 12 (LOCF)	37.1% ± 37.18%	58.9% ± 39.33%
	Change from Baseline	3.0% ± 33.33%	27.3% ± 37.39%
Total		n = 161	n = 168
(arithmetic mean ± SD)	Baseline	39.2% ± 35.10%	37.2% ± 36.20%
	Week 12 (LOCF)	43.0% ± 38.35%	67.5% ± 37.59%
	Change from Baseline	3.8% ± 33.63%	30.2% ± 35.40%
(LS-mean)	Baseline	38.33	36.37
	Week 12 (LOCF)	43.02	68.99
Comparison (LS-mean difference [95% CI]; p-values [ANCOVA])			
	Treatment: Placebo – Vardenafil	-25.97% [-32.69% to -19.26%]	
	Age group: < 65 years – ≥ 65 years	7.68% [0.88% to 14.48%]	
	Treatment	p < 0.0001	
	Age group	p = 0.0270	

CI: confidence interval; IIEF: International Index of Erectile Function; LS: least squares; SD: standard deviation

Again, there was a treatment-independent statistically significant age effect.

Table 17

Study 12094 – Success rates for maintenance (SEP 3): Summary statistics			
ITT population		**Placebo**	**10 mg ODT**
Summary statistics			
< 65 years		n = 81	n = 84
(arithmetic mean ± SD)	Baseline	15.5% ± 19.68%	16.4% ± 18.71%
	Week 12 (LOCF)	30.7% ± 33.33%	69.6% ± 35.27%
	Change from Baseline	15.2% ± 29.55%	53.2% ± 33.22%
≥ 65 years		n = 79	n = 84
(arithmetic mean ± SD)	Baseline	15.5% ± 22.29%	9.3% ± 18.50%
	Week 12 (LOCF)	24.3% ± 31.47%	48.1% ± 39.81%
	Change from Baseline	8.7% ± 29.15%	38.8% ± 38.32%
Total		n = 160	n = 168
(arithmetic mean ± SD)	Baseline	15.5% ± 20.94%	12.9% ± 18.89%
	Week 12 (LOCF)	27.5% ± 32.48%	58.8% ± 39.01%
	Change from Baseline	12.0% ± 29.44%	46.0% ± 36.47%

(LS-mean)	Baseline	15.18	12.52
	Week 12 (LOCF)	26.59	60.02

Comparison (LS-mean difference [95% CI]; p-values [ANCOVA])

Treatment: Placebo – Vardenafil	-33.43% [-40.44% to -26.43%]
Age group: < 65 years – ≥ 65 years	10.87% [3.83% to 17.90%]
Treatment	p < 0.0001
Age group	p = 0.0026

CI: confidence interval; IIEF: International Index of Erectile Function; LS: least squares; SD: standard deviation

Ancillary analyses

Not applicable.

Analysis performed across trials (pooled analyses and meta-analysis)

An integrated analysis was also submitted; data for both studies taken together showed that the treatment group differences and the differences between ages are consistent throughout the study from week 4 to week 12.

Clinical studies in special populations

Comparisons of results in subpopulations were done. Sufficiently sized subgroups were ED patients with and without diabetes/diabetic complications, dyslipidaemia or hypertension.

All analyses (for IIEF Erectile Function Score, SEP 2 and SEP 3) showed a nominally significant superiority (p<0.0001) of ODT treatment when compared with placebo within stratum and any disease subgroup. There were nominally significant differences between subgroups, always reflecting poorer success rates in the elderly or in the subgroup with the underlying disease compared to the younger or the subgroup without the disease, respectively. Nevertheless, there were no significant 'stratum/subgroup*treatment' interactions.

Efficacy of the ODT treatment was shown less pronounced in diabetic patients than in the other disease subgroups assessed.

Supportive study

Not applicable.

2.5.3. Discussion on clinical efficacy

Two Phase III studies of identical design have been performed to investigate the efficacy and safety of the ODT formulation compared to placebo in patients with erectile dysfunction.

In both studies, there was a 4-week run-in period without erectile dysfunction therapy (medication or devices). During the 12-week treatment period, visits were planned on Week 0, Week 4 and Week 12. Forty-eight hours after the last dose of study medication was administered, a follow-up telephone call (or personal visit) was performed to obtain information about the possible occurrence of serious adverse events (SAEs) or deaths.

The efficacy was assessed using the same efficacy parameters that those already used in studies investigating the film coated tablets, i.e. IIEF-EF Domain score, SEP 2 (success rates of penetration),

and SEP 3 (success rates of maintenance of erection). The clinical efficacy documentation showed that the ODT was significantly superior to placebo in the parameters assessed.

Major baseline demographic and clinical characteristic were similar for each group of treatment (placebo vs. vardenfil ODT) in both studies. The average age of all safety subjects was about 62 years (for both studies). This is due to the increased number of elderly subjects required in this study as maintained by the forced randomization technique. The average age in the younger patient stratum was about 53 years, while elderly subjects had an average age of approximately 70 years. The calculated age at entry in the study ranged from 21 to 84 years.

These results showed for the primary efficacy variables in both studies that vardenafil 10 mg ODT treatment was significantly superior to placebo with respect to change from baseline to Week 12/LOCF in the IIEF-EF domain and in the change from baseline to Week 12 overall in the diary item SEP 2 (penetration) success rate and the SEP 3 (maintenance of erection) success rate.

Subjects <65 year-of-age achieved slightly higher scores on the IIEF-EF and had better success rates in the SEP 2 and SEP 3 than subjects ≥65 years-of-age.

There was a treatment-independent statistically significant age effect. And nominally significant country-specific difference, due lower success rates in Australian centers.

All secondary efficacy measures showed significant differences in favour of vardenafil 10 mg ODT (diary success rates reported for SEP 1, SEP 4, SEP 5, SEP 6, Treatment Satisfaction Scale (TSS) domains, higher percentages of subjects taking vardenafil 10 mg ODT reported “back to normal erectile” function, higher percentage of subjects treated with vardenafil 10 mg ODT responded positively to the Global Assessment Question, subjects treated with vardenafil 10 mg ODT needed to initiate fewer sexual attempts until their first successful maintenance of erection.

2.5.4. Conclusions on the clinical efficacy

The efficacy results obtained for the primary efficacy variables in both studies showed that vardenafil 10 mg ODT treatment was significantly superior to placebo with respect to change from baseline to Week 12/LOCF in the IIEF-EF domain and in the change from baseline to Week 12 overall in the diary item SEP 2 (penetration) success rate, and the SEP 3 (maintenance of erection) success rate. Also all secondary efficacy measures demonstrated nominally significant differences in favour of vardenafil 10 mg ODT (diary success rates reported for SEP 1, SEP 4, SEP 5, SEP 6, Treatment Satisfaction Scale (TSS) domains, higher percentages of subjects taking vardenafil 10 mg ODT reported “back to normal erectile” function, higher percentage of subjects treated with vardenafil 10 mg ODT responded positively to the Global Assessment Question and subjects treated to initiate fewer sexual attempts until their first successful maintenance of erection).

The clinical efficacy documentation showed that the ODT was significantly superior to placebo in all parameters assessed. These clinical results support the claimed indication.

2.6. Clinical safety

The clinical program for Vivanza ODT is based on Phase I studies in healthy volunteers and subjects suffering from ED and on two pivotal Phase III studies in subjects suffering from ED.

Patient exposure

From the phase III studies (12903 and 12094) 695 patients made up the safety population, 343 received placebo and 358 received 10 mg ODT. A total of 357 of the 695 patients were ≥65 years of age (175 patients in the placebo group and 182 patients in the 10 mg ODT group). The inclusion and exclusion criteria for both phase III studies were very similar thereby justifying pooling of the safety data for integrated analyses.

The average exposure time per treatment group is 72 days (placebo; median: 78 days) and 76 days (vardenafil; median: 81 days). About 80% of all randomized subjects have been treated for up to 12 weeks (84 days), 20% have been treated for more than 12 weeks.

From the phase I studies, 52 patients made up the safety population.

Adverse events

The most frequently adverse events observed with ODT in the submitted clinical trials were headache, followed by flushing, nasal congestion, dyspepsia, and back pain. All of them are already covered in film coated tablets and were reported to be mild or moderate in intensity.

In clinical studies phase III, 355 patients were treated with 10 mg ODT, 135 (38.0%) reported a treatment emergent AE, but only 86 (24.2%) patients had Adverse Events considered to be study-drug-related.

Serious adverse event / deaths / other significant events

In clinical studies phase III, the incidence of serious adverse events was low, with 5 (1.4%) patients in the ODT group and 2 (0.6%) patients in the placebo group. None of these Serious Adverse Events were considered to be related to 10 mg ODT treatment.

In phase I studies there were two serious adverse events, none of them drug related according to the investigator (motorcycle accident and CK elevation after physical exercise).

Laboratory findings

There were no signs of drug associated changes in the Laboratory findings and vital signs did not show relevant differences between placebo and Vivanza ODT.

Safety in special populations

Subgroup analysis showed higher incidence only in patients with history of hypertension (patients without hypertension 13.6% versus patients with hypertension 18.4%). Specifically dizziness was seen more frequent in patients on ODT with hypertension (3.5%) as compared to patients without hypertension (1.4%). Adverse Events by age were similar for most body systems except for vascular disorders with more elderly patients reporting Adverse Events (3%) than younger patients (1%).

Safety related to drug-drug interactions and other interactions

An interaction study investigating the additional effect of a single dose of vardenafil 10 mg ODT on blood pressure and heart rate on the background of a vasodilator is ongoing as a post-marketing commitment in conjunction with the FDA approval of 10 mg ODT.

The study (BAY 38-9456 / 15345) is performed in a placebo-controlled, 2-fold crossover design in elderly patients with erectile dysfunction and hypertension receiving chronic nifedipine treatment. The statistical analysis of this study is currently ongoing while the clinical part is completed.

Discontinuation due to adverse events

Ten adverse events in 5 subjects lead to discontinuation of vardenafil compared to 2 AE in 2 subjects leading to discontinuation of placebo. Each AE has been reported only once, except dizziness, which is reported twice with vardenafil. The other AE leading to discontinuation are: chest pain, acute coronary syndrome, vision blurred, ALT increased, muscle spasm, flushing, dysphagia and headache with vardenafil, anxiety and deafness neurosensory with placebo.

Of these discontinuations, particular attention has been provided to subject 14013-0009, who is a 39 year old man with no relevant past medical history that discontinued the study prematurely due to drug related adverse events (chest pain and blurry vision). However, the day in which these adverse events occurred, the subject took two doses of study treatment, which could reasonably explain the AEs.

Post marketing experience

Post-marketing data with the 10 mg ODT is available as a product containing the same active substance and the same new formulation is available in currently about 22 countries under the trade names Levitra 10 mg orodispersible tablets and Staxyn.

Since market authorization in 2010 Levitra 10 mg ODT was introduced country by country with the first overall sales presented in the most recent PSUR no. 15 covering the reporting period 05 MAR 2011 – 04 MAR 2012. During this period 8.515.877 tablets of Levitra ODT and Staxyn were sold. Thus, based on the recommended maximum dosing frequency of one (1) tablet per day, approximately 0.023 Mio patient years of vardenafil ODT exposure can be estimated.

The safety data from this product are in line with the known safety profile of Vivanza film-coated tablet.

Ongoing Clinical Pharmacology Studies

An interaction study investigating the additional effect of a single dose of vardenafil 10 mg ODT on blood pressure and heart rate on the background of a vasodilator is ongoing as a post-marketing commitment in conjunction with the FDA approval of Levitra 10 mg ODT. The study (BAY 38-9456 / 15345) is performed in a placebo-controlled, 2-fold crossover design in elderly patients with erectile dysfunction and hypertension receiving chronic nifedipine treatment. The statistical analysis of this study is currently ongoing while the clinical part is completed.

2.6.1. Discussion on clinical safety

The most frequently adverse events observed with the ODT in the submitted clinical trials were headache, followed by flushing, nasal congestion, dyspepsia, and back pain. All of them are already covered in the film coated tablets and were reported to be mild or moderate in intensity.

In clinical studies phase III, 355 patients were treated with 10 mg ODT, 135 (38.0%) reported a treatment emergent AE, but only 86 (24.2%) patients had Adverse Events considered to be study-drug-related.

Subgroup analysis showed higher incidence only in patients with history of hypertension (patients without hypertension 13.6% versus patients with hypertension 18.4%). Specifically dizziness was

seen more frequent in patients on the ODT with hypertension (3.5%) as compared to patients without hypertension (1.4%). Adverse Events by age were similar for most body systems except for vascular disorders with more elderly patients reporting Adverse Events (3%) than younger patients (1%).

In clinical studies phase III, the incidence of serious adverse events was low, with 5 (1.4%) patients in the ODT group and 2 (0.6%) patients in the placebo group. None of these Serious Adverse Events were considered to be related to 10 mg ODT treatment.

In phase I studies there were two serious adverse events, none of them drug related according to the investigator (motorcycle accident and CK elevation after physical exercise).

There were no signs of drug associated changes in the Laboratory findings and vital signs did not show relevant differences between placebo and ODT.

2.6.2. Conclusions on the clinical safety

Overall, the available safety data from clinical studies with the 10 mg ODT formulation confirmed the safety profile of vardenafil. No new or previously unreported side effects with respect to Vivanza film-coated tablets have been reported. The post-marketing safety data from the already commercialised 10 mg ODT is also reassuring.

2.7. Pharmacovigilance

The CHMP considered that the Pharmacovigilance system as described by the MAH fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

The RMP submitted along with this procedure (Line Extension Application for Vivanza 10 mg orodispersable tablets) is the RMP version 2.0 dated 15th January 2010 which is the RMP submitted to support the Line Extension Application of Levitra 10 mg orodispersable tablets which was approved in September 2010.

Since the last adopted RMP for vardenafil no regulatory actions have been taken for safety reasons leading to additional risk minimisation measures or pharmacovigilance activities not covered in the submitted RMP. Nevertheless, an update to the RMP is considered warranted.

Therefore, the Applicant should submit an updated RMP together with the next PSUR submission (DLP 03/03/2013): The updated RMP should:

- be submitted in the new format according to the Guideline on good pharmacovigilance practices, Module V – Risk management systems
- at least, include information gathered with the already marketed orodispersible formulation,
- take into account the actions taken for safety reasons on vardenafil containing products since last RMP version.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Summary of safety concerns	
Important identified risks	Hypersensitivity Decrease in blood pressure Effects on QT-interval and cardiac rhythm Prolonged erection, priapism Counterfit 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 Sudden Deafness
Important missing information	None

The CHMP endorsed this advice without changes.

2.9. User consultation

Vivanza 10 mg orodispersable tablets is a duplicate of Levitra 10 mg orodispersable tablets, and since no major changes have been made to the package leaflet for Levitra, no additional user consultation was required.

3. Benefit-Risk Balance

Benefits

Vardenafil is a potent and selective phosphodiesterase type-5 (PDE5) inhibitor, an extensive preclinical and clinical development program demonstrated the safety and efficacy of Vivanza film-coated tablets for the indication of erectile dysfunction. The orodispersible tablet (ODT) disintegrates rapidly in the mouth in the presence of saliva and permits a convenient mode of intake without water. It could benefit patients that have difficulty swallowing tablets or that would prefer a more discreet mode of administration.

Risks

The most common treatment emergent AEs were headache (14.4%), flushing (7.6%), nasal congestion (3.1%), dyspepsia (2.3%), dizziness (2.3%), and back pain (2.0%). Most of the treatment-related AEs reported were of mild severity. The rate of drug discontinuations due to AEs was low (placebo 0.6%, Vivanza 10 mg ODT 1.4%). For this new formulation there are no new unfavourable effects added to the already known for Vivanza film coated tablets. Importantly, the available post-

marketing data from the same ODT formulation that has been approved in September 2010 under a different invented name does confirm the known safety profile.

PK studies show that vardenafil ODT is suprabioavailable when compared to vardenafil film coated tablets, so both formulations are not bioequivalent. The submitted documentation showed that verdanafil PK levels are inside the therapeutic window considered safe for the film coated tablets. This information is clearly reflected in the SPC to allow prescribers knowing that ODT 10 mg and film coated tablet are not bioequivalent. Furthermore,

PK studies showed a 10% increase in Cmax if the orodispersible tablet is taken with water. The SmPC indicates that Vivanza 10 mg ODT tablet must not be taken with water and that the maximum dose to be administered is one 10 mg orodispersible tablet, which is considered appropriate..

Benefit-risk balance

The available data shows that this new formulation achieves the characteristic flat dose response curved linked to this active substance. Furthermore, it shows that its pharmacokinetic profile is inside the safety/efficacy window already studied for vardenafil film coated tablet. This was confirmed with Phase III studies were vardenafil 10 mg ODT was significantly superior to placebo in all parameters assessed and safety data indicate that the safety profile is in line with that already known for Vivanza film coated tablets formulation and the information is already included in the current SPC.

The applicant should also submit the results when available of the interaction study investigating the additional effect of a single dose of vardenafil 10 mg ODT on blood pressure and heart rate on the background of a vasodilator. Study BAY 38-9456 / 15345 placebo-controlled, 2-fold crossover design, in elderly patients with erectile dysfunction and hypertension receiving chronic nifedipine treatment.

The overall benefit-risk balance of Vivanza 10 mg orodispersable tablets is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the benefit-risk balance of Vivanza 10 mg orodispersible tablet in the following indication:

“Treatment of erectile dysfunction in adult men. Erectile dysfunction is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance. In order for Vivanza to be effective, sexual stimulation is required”

is favourable and therefore recommends the granting of the extension of the marketing authorisation subject to the following conditions:

Furthermore, the Product Information is being brought in line with the latest QRD template version.

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreeed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.