

SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Vivanza. For information on changes after approval please refer to module 8.

1. Introduction

Erectile dysfunction (ED) has been defined as the persistent inability to achieve and maintain an erection sufficient to permit satisfactory sexual performance.

Although erectile dysfunction is regarded as a benign disorder, it has a medical and social impact due to its high prevalence, costs and implications for quality of life for many men (and their partners). The exact incidence of ED is difficult to determine. A recent review has concluded that the prevalence of erectile dysfunction of all degrees is 52% in men 40 to 70 years old, with the incidence increasing along with age. Therefore, it is expected that as the population ages, the prevalence of ED will continue to increase with an estimated 328 million men world-wide affected by this condition by Year 2025.

Normal erectile function requires the coordination of psychological, hormonal, neurological, vascular and anatomic factors. Alteration of any of these factors is sufficient to cause this condition. Main causes of erectile dysfunction are chronic systemic illnesses (diabetes mellitus, heart disease, hypertension and peripheral vascular disease), neurological disorders (post-traumatic spinal-cord injuries, multiple sclerosis or post-surgical lesions as radical prostatectomy), hormonal disorders as hyperprolactinemia, local conditions as Peyronie's disease or congenital or traumatic deformities of the penis; drug induced erectile dysfunction (antidepressants, beta adrenergic blocking agents, thiazides, anabolic steroids, cimetidine, digoxin, or metoclopramide) and psychogenic factors are other causes of erectile dysfunction.

There are several approaches to the management of erectile dysfunction: psychosexual counselling, vacuum constriction devices, vascular surgery, penile prosthesis and pharmacological treatment (oral therapy, intraurethral therapy and intracavernous injection therapy).

Penile injection therapy was the commonest form of therapy of erectile dysfunction before the introduction of sildenafil. It is indicated when oral therapy is not suitable or fails. Alprostadil (an stable, synthetic form of prostaglandin E1) and papaverine (a non-specific phosphodiesterase inhibitor) were the most used agents by this route, although fentolamine has also been used in this way. They can be used alone or in combination. Regarding efficacy and safety, this method is effective in 80% of patients with organic erectile dysfunction and main side effects include fibrosis, penile pain and priapism.

Alprostadil is also approved in the EU for intraurethral administration. The advantages of this therapy include local application, minimal systemic effects, and the rarity of drug interactions, but its efficacy is limited.

Sublingual apomorphine (Uprima) was approved in year 2000 for the same indication. Apomorphine 3 mg showed a success rate of 40-50% of the attempts of intercourse compared to a success rate of 30% with placebo. Main adverse effects are nausea, dizziness, hypotension and vaso vagal syncopes.

Since the introduction in 1998 of sildenafil (Viagra), as the first oral treatment for the erectile dysfunction, the pharmacological treatment has acquired a more relevant role in the management of the disease and oral therapy should be considered as a first line treatment at this moment. Sildenafil has shown a success rate of 62-73% of the attempts of intercourse compared to a success rate of 22-25% with placebo. Although the product is generally well tolerated, adverse effects such as headache (12.8%), flushing (10.4%), and dyspepsia (4.6%) may occur. Also visual disturbances (1.9%), dizziness (1.2%), and nasal congestion (1.1%) may occur. Sildenafil produces mild and transitory decreases of blood pressure and it is contraindicated in patients taking nitrates for the treatment of the ischaemic heart disease. Sildenafil has been associated with an increase of the occurrence of cardiovascular adverse events although is still not clear if it is related to the product or if it is related to

the risk inherent to the sexual activity in patients with underlying diseases. A large variety of clinical studies have been undertaken to address this question, and of the studies reported to date, none has demonstrated a link between sildenafil and serious cardiovascular events. Approximately 35% of patients do not respond to sildenafil. This suggests that there is an additional need for further treatment options for ED.

The new directions of ED therapy are: The first is the improvement of current therapies (apomorphine and PDE inhibitors with increasing pharmacological selectivity). The second one is the combination of existing therapies (i.e., apomorphine and sildenafil, nitric oxide donation + α 1 antagonist adrenoreceptor), the third direction is new targets within the central nervous system (i.e., melanocortin receptor agonists, growth hormone-releasing peptide receptor) and finally, a new peripheral target.

Vardenafil has been shown to be a potent and selective inhibitor of PDE5, an enzyme responsible for the degradation of cGMP in the corpus cavernosum. When nitric oxide is released by nerve endings or endothelium, as is the case with sexual stimulation, the cGMP pathway is activated. PDE5 inactivates cGMP inside the cytoplasm. Inhibition of this enzyme causes increased concentrations of cGMP, which in turn enhance smooth muscle relaxation and hence the erectile response. Vardenafil seems to be more selective for PDE5 relative to PDE1, PDE6 and PDE11 compared to Sildenafil.

2. Chemical, pharmaceutical and biological aspects

Composition

This medicinal product has been developed as an immediate formulation and is presented in three different strengths, i.e. 5 mg, 10 mg, and 20 mg of vardenafil (as vardenafil hydrochloride trihydrate) and it is presented as film coated tablets. Crospovidone, magnesium stearate, cellulose microcrystalline, silica colloidal anhydrous have been selected as excipients of the tablets core and macrogol 400, hypromellose, titanium dioxide, ferric oxide yellow, ferric oxide red as excipients of the coating. The rationale for the selection of the individual excipients is given.

Film coated tablets are supplied in polypropylene/aluminium blisters.

Active substance

Vardenafil is a new active substance. IUPAC name: 2-[2-Ethoxy-5-(4-ethyl-piperazine-1-sulfonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one monohydrochloride trihydrate. Vardenafil HCl.3H₂O is an achiral compound, which its solubility is pH dependent and decreases significantly with rising pH. The trihydrate form is thermodynamically stable at ambient conditions. The synthesis process is carried out in 3 steps followed by crystallization and drying procedures. Despite its favorable solubility in aqueous solutions of low pH, vardenafil HCl 3H₂O is milled to achieve optimal homogeneity of drug product powder blends, especially for the lower dose strengths. Adequate in-process controls are applied during the synthesis of the active substance. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Active substance specification

The active substance specification reflects all relevant quality attributes of the active substance. The analytical methods used in the routine controls are suitability described. The validation studies are in accordance with the ICH Guidelines. Impurity limits in the specification are justified by toxicology studies.

The batch analysis data show that the active ingredient can be manufactured reproducibly.

Stability

18 month ICH stability studies have been performed. 6 months accelerated data are also presented. The stability under stress test conditions has been investigated: thermal stress up 60°C, oxidative and hydrolytic stress at various pH-values. Light sensitivity has also been studied. The data provided are sufficient to confirm the re-test period.

Other ingredients

Conventional pharmaceutical excipients crospovidone, magnesium stearate, cellulose microcrystalline, silica colloidal anhydrous, and macrogol 400, hypromellose, titanium dioxide are of Ph Eur quality, and ferric oxide yellow, ferric oxide red are of Ph. Franc. Certificates of analyses are provided and show compliance with respective monographs.

The magnesium stearate is of vegetable origin, and statements concerning the absence of risk for TSE transmission are provided.

The medicinal product is supplied in polypropylene/aluminium blister packs. Controls and specifications of primary packaging are presented and well described.

Product development and finished product

The product development has taken into account the physicochemical characteristics of the active drug substance; the compatibility of the active substance with excipients, content uniformity and chemical stability in the presence of excipients was also studied. Conventional pharmaceutical excipients have been selected and the function of each individual excipient is standard and well known.

Different dose strengths are differentiated by tablet size and embossing.

The process for the manufacturing of the finished product is a standard dry-granulation process, which follows conventional pharmaceutical practises.

The manufacturing process has adequately been described and is satisfactory. The in process controls are adequate for this preparation.

The batch analysis data of three full-scale production batches show that this medicinal product can be manufactured reproducibly according to the finished product specification, which is suitable for the use of this oral preparation.

Product Specification

The product specifications include tests by validated methods for appearance, tablet marking, identification, assay, impurities / degradation products, uniformity of contents, water content dissolution and microbial purity.

Degradation products are controlled and their limits are justified by reference to stability studies and toxicology studies.

Stability of the Product

The stability samples for stability testing were packaged in a polypropylene/aluminium blister.

The results indicate satisfactory stability and support the shelf life stated in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The quality of the medicinal product is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorization. There are no major deviations from EU and ICH requirements.

The finished product intended for marketing are well suited; the manufacturing process is under control and ensures both batch to batch reproducibility and compliance with standard procedures and specifications; the analytical methods have been validated and seem to be suitable to ensure consistent quality of the active substance and the finished product, the synthetic pathway is presented and the structure and impurity profile are well characterised and in line with current ICH guidelines. The stability data on the active substance supports the proposed re-testing period;

Based on stability data of the finished product in the proposed primary package, the proposed shelf life stated in the SPC is acceptable.

3. Toxicopharmacological aspects

Vivanza contains the active substance vardenafil hydrochloride trihydrate, a new reversible inhibitor of the cyclic guanosine monophosphate (cGMP) phosphodiesterase, PDE type 5, intended for the treatment of male erectile dysfunction.

Human penile erection requires the relaxation of both penile resistance arteries and the trabecular smooth muscle of the corpus cavernosum. Nitric oxide (NO) released from non-adrenergic, non-cholinergic neurones and endothelial cells upon sexual stimulation appears to mediate this process. Upon release, NO diffuses into smooth muscle cells and activates the cytosolic form of the enzyme guanylyl cyclase, thereby increasing levels of cyclic GMP. Cyclic GMP in turn activates protein kinase G, triggering phosphorylation events that result in decreased cytosolic calcium levels and relaxation. The actions of cyclic GMP are terminated by phosphodiesterases, including PDE5, which catalyse its hydrolysis to 5'-GMP.

PDEs are known to be expressed in a variety of tissues and have been classified according to their regulatory characteristics, substrate specificity and pharmacological profile. The determination of the selectivity of vardenafil for the PDE5 subtype and its functional effects on several organ systems and cells were further investigated in several studies described below supporting the efficacy of the compound for use in erectile dysfunction.

Pharmacodynamics

The pharmacodynamic effects of vardenafil and its main circulating metabolites M1, M4 and M5 were determined during a series of in vitro and in vivo experiments in animals. Results of these studies conducted indicate that vardenafil exerts PDE5 inhibiting activity. This causes smooth muscle relaxation, inducing a rise in intracavernosal pressure and consequently penile erection.

Some of these studies used sildenafil and tadalafil as comparators. In these studies an IC₅₀ (PDE5 inhibition)= 0.89 nM (human recombinant enzyme) was observed for vardenafil compared to an IC₅₀=8.5 nM and IC₅₀=9.4 nM for sildenafil and tadalafil, respectively. The metabolites M1, M4, and M5 showed a potency of 3.6, 18, and 20 fold less than the parent compound in inhibiting human recombinant PDE5, respectively.

No study has been conducted to assess possible effects of vardenafil on other potential therapeutic indications.

- *In vitro* studies

Studies in isolated human and rabbit corpus cavernosum slices demonstrated that vardenafil dose dependently increased the concentration of cGMP, both in unstimulated and in stimulated slices. Rabbit tissue was found to be less sensitive to vardenafil than human tissue.

Electrophysiological studies were also conducted in a human cell line (HEK293) transfected with human hERG gene to address the direct influence of vardenafil on the repolarizing I_{Kr} current. Sildenafil was used as a comparator. Block of the hERG channel was shown at IC₅₀=84 μM for vardenafil and IC₅₀=111 μM for sildenafil (not statistically significantly different). If the threshold concentrations are considered, the hERG-blockade becomes apparent at 3 μM, a concentration about 88-fold above the peak plasma level in man at the highest clinically recommended dose of 20 mg. Taking into account these results, the potential for QT prolongation in humans can be considered low. Regarding vardenafil's main metabolites, the risk for QT prolongation has been studied *in vivo* in preclinical studies at multiples of the maximum therapeutic dose. In terms of C_{max}, M1 and M4 were assessed at 21 and 14 times the maximum therapeutic dose. ECG analysis did not reveal any potential for QT prolongation.

- *In vivo* studies

A new animal model using conscious adult male rabbits was developed to evaluate the efficacy of vardenafil *in vivo*. This new animal model has been validated and sildenafil was tested as a standard and found to be active in the model. In this rabbit model the maximal erection achievable with sildenafil was half of that achieved with vardenafil, and for sildenafil 3-5 times higher doses were needed to achieve comparable effects.

- Pharmacodynamic drug interactions

As for other PDE5 inhibitors, coadministration of nitrates or nitric oxide donors is contraindicated in the SPC.

In *in vitro* and *in vivo* studies it has been shown that sodium nitroprusside, a NO-donor, clearly enhances the action of vardenafil. Studies on vardenafil's binding to e.g. alpha- or beta-adrenoceptors, cholinergic, histaminergic and serotonergic receptors etc, demonstrated vardenafil's selectivity for PDE receptors. There is no concern about clinically relevant receptor interactions.

- General and safety pharmacology programme

The effects of vardenafil on the cardiovascular system were assessed in anaesthetised and conscious dogs. Vardenafil has been shown to have vasodilating cardiovascular activity in dogs, resulting in decreased mainly systolic blood pressure, and increased heart rate. The total peripheral resistance dropped by a maximum of 19% after the administration of 0.3 mg/kg, a dose yielding a C_{max} slightly higher than seen in man following the proposed maximum recommended dose of 20 mg. This is not an unexpected effect for vardenafil due to the mechanism of action and vardenafil use is not recommended in hypotensive patients as stated in the SPC.

There was no evidence for a direct effect on electrical conductance in the heart. In the anaesthetised dog, the QT-interval decreased dose-dependently and after the Bazett's correction, there was no substantial change in QTc. In the conscious dog after Bazett's correction there was no substantial change in QTc.

Up to 10 mg/kg, the highest dose tested, vardenafil displayed no adverse effect on blood pharmacological parameters, the CNS, psychomotor activity, respiration, blood glucose, gastrointestinal function, renal function or coagulation.

- Summary of salient findings

General pharmacodynamic studies were carried out on experimental models generally used to assess the safety of this type of medicinal products.

As summarised above several adverse events can be associated with the use of vardenafil. However, it should be noted that almost all of the possible adverse effects only occur at doses or (plasma) concentrations at least 30 times higher than that needed for the therapeutic effect of vardenafil. At therapeutic doses slight effects on haemodynamics can not be excluded but are explainable on basis of vardenafil's pharmacological profile and are reported in the SPC.

Overall, from the results of general pharmacodynamics studies, there is no doubt that, within the therapeutic dose-range, vardenafil is a safe drug for the proposed indication.

Pharmacokinetics

Preclinical pharmacokinetics of vardenafil and its pharmacologically active metabolite M1 were investigated in several species. Studies were performed in rats, mice and dogs on absorption, bioavailability, protein binding, distribution, biotransformation and excretion following single intravenous, oral and intraduodenal administration of [¹⁴C]-labelled vardenafil hydrochloride or non-labelled vardenafil hydrochloride.

No evident pharmacokinetic interaction was reported after sufficient studies for that purpose had been performed.

Absorption

Vardenafil is rapidly absorbed from the gastrointestinal tract. The mean oral bioavailability is between 7 and 33% for rat and dog and approximately 15% for man. The elimination of vardenafil occurs almost exclusively by biotransformation as indicated by only small fractions (0.7 - 3 % of the dose) being excreted unchanged.

Distribution

The binding of vardenafil to plasma proteins is high and species-dependent and independent on concentration and gender. Vardenafil distributes rapidly to organs and tissues and highest maximum radioactivity concentrations are measured in the liver, adrenal glands and kidneys. Total radioactivity penetrates the blood/brain barrier to a moderate extent and the placental barrier of rats to a low extent. The terminal half-life for the body excluding gastrointestinal tract (representing the sum of all organs and tissues) is 37 h. At 168 h postdosing, vardenafil related material, was detectable in liver and kidney. Small amounts were also still detectable in the testes at 168 h postdosing. However, on the basis of the results of toxicity studies, the presence of vardenafil related material in the testes does not seem to have consequences.

Vardenafil shows affinity to melanin-bearing tissues. Such an affinity to melanin-containing structures, also described for other PDE5 inhibitors, does not appear to be related to any possible adverse effects on the retina. The results of a 12-month dog toxicity study are of especial relevance to exclude any risk resulting from the presence of vardenafil in the eye due to its binding to melanin (the retina of dogs contains melanin).

Biotransformation

The biotransformation of vardenafil has been studied in mice, rats and dogs and revealed an extensive and qualitatively comparable metabolism in these species. Metabolic profiling of plasma of rat, mouse, dog and man revealed the unchanged drug and M-1, formed by N-deethylation, to be the major component. No significant human-specific metabolites have been identified.

Excretion

Vardenafil and the metabolites were rapidly and completely excreted, predominantly via the hepatobiliary system and to a small extent in the urine (approximately 5 % in all species). In lactating rats, 3.3% of the administered dose was excreted into the milk.

Single-dose/repeated dose studies

The plasma concentrations of the unchanged compound were almost dose-proportional in man in the therapeutic dose range (5 to 20 mg per subject), dose-proportional in dogs after single oral administration of 0.3 to 3 mg/kg, while an over-proportional increase of the plasma concentrations was observed in rats in the same dose range.

The pharmacokinetics of vardenafil in the rat was sex dependent. In dogs and in a phase I study in man, no sex-dependence of the pharmacokinetics was found.

Taking the free fractions and the *in vitro* PDE5 inhibitory activity into account, only the M-1 metabolite is expected to have some contribution to the pharmacological effect (but clearly less than vardenafil, about 7% relative to it), whereas M-4 is not relevant for the pharmacological effect due to its low exposure compared to vardenafil and M-1 (0.06% relative to vardenafil). The plasma clearance of the major active metabolite M-1 was 6.0 and 2.4 l/h.kg in rat and dog, respectively, and the volume of distribution at steadystate was higher than that of vardenafil approximately 9 l/kg.

Toxicology

A battery of toxicity studies has been conducted in order to assess possible toxic effects.

Since the toxicological programme was designed to support a once daily (o.d.) tablet formulation, the same dosing scheme (o.d.) was applied in the majority of toxicological studies.

Single dose toxicity

Used by the oral route, vardenafil showed effects in rats and mice compatible with effects on the cardio-vascular system.

Repeated dose toxicity

Repeated dose studies were carried out in mice, rats and dogs. In mice, little toxicity was found up to high doses. In both rats and dogs, effects were found consistent with the haemodynamic effect of vardenafil. Other toxicological findings in the pancreas, liver, kidney, exocrine glands and the thyroid in repeated dose studies were observed in the rat (the two other species, dog and mouse, were not susceptible) and are expected in the rat by the pharmacology of a phosphodiesterase inhibitor as well. The lowest no observed effect level was 3 mg/kg in dogs and male rats.

In rats as well as dogs special attention was given to effects on the testes and eyes. No adverse effects on these organs were found.

Oral reproduction toxicity

Studies were performed in rats and rabbits. The clinical indication of vardenafil does not include treatment of women and thus, the results of the embryo-foetal and prenatal/postnatal studies are not immediately relevant for the human risk assessment in the human male.

Testing for reproductive toxicity did not reveal impairment of male or female fertility. No specific primary teratogenic potential was shown.

Genotoxicity

Representative batches of vardenafil were tested for *in vitro* mutagenic and clastogenic potential in a bacterial reverse mutation test, a mammalian cell gene mutation test and a chromosome aberration test and in the *in vivo* mouse micronucleus test. Overall, no indication for a genotoxic hazard was observed.

Carcinogenicity

Two long-term carcinogenicity studies were conducted in rats and mice. The systemic exposure (AUC) achieved at the top dose in the 2-year studies was about 120-350 times (rat) and 25 times (mice) the exposure in human at the proposed maximum recommended therapeutic dose.

Neither a 2-year study in rats nor a 2-year study in mice revealed a carcinogenic potential of vardenafil up to and including the highest dose tested.

Other studies

There are no adverse environmental effects anticipated as a consequence of the use of vardenafil. The environmental risks have not been evaluated.

Vardenafil is presented as a tablet to be taken orally. No local tolerance studies were submitted

Discussion on toxico-pharmacological aspects

The preclinical pharmacodynamic programme has demonstrated that vardenafil has a high potency and selectivity for PDE5 and induces a rise in intracavernosal pressure during sexual stimulation.

From the pharmacokinetic point of view, rats, mice and dogs were the most relevant species for preclinical efficacy and safety studies. The main toxicity findings are well understood and do not raise concern for human safety. This information has been included in the SPC.

4. Clinical aspects

Clinical pharmacology

The clinico-pharmacological characteristics of vardenafil were investigated in 35 studies involving 712 subjects treated with vardenafil. Studies were conducted in Europe, South Africa, USA and Japan.

Pharmacodynamics

- **Mechanism of action**

The efficacy of PDE5 inhibition with respect to treatment of erectile dysfunction has been established with sildenafil in the past. Vardenafil has been shown to be a potent and selective inhibitor of PDE5. Pre-clinical tests demonstrated that it is at least 5 times more potent than sildenafil in inhibiting PDE5. In principle, lower doses can be given in order to attain or maintain erections in patients with ED. Vardenafil is also more selective for PDE5 relative to PDE1, PDE6 and PDE11 compared to sildenafil potentially resulting in an improved risk/benefit ratio.

Primary pharmacology

Primary pharmacodynamics of vardenafil was evaluated in three randomised, double blind, placebo-controlled, 3-fold crossover studies in patients with erectile dysfunction, using Rigiscan device, which is a valid method to evaluate pharmacodynamic effect on penile erection. This system allows measuring the duration, frequency and degree of rigidity and tumescence of the penis. Rigidity is defined as the degree of hardness of the penis and is measured by the software as a percentage, using a proprietary algorithm derived from the changes in tumescence from baseline.

Vardenafil (10 mg, 20 mg and 40 mg) has been found to be effective and significantly different in comparison to placebo with respect to time of rigidity >60%, which is considered the minimal rigidity necessary for sexual intercourse.

One study evaluated the time to onset of penile rigidity =60% at the base. Although the time to onset of the effect could not be elucidated in this study, the applicant has provided data justifying the recommendation given in the SPC of taking the drug between 25 minutes and 1 hour before intended sexual intercourse.

Secondary pharmacology:

Vardenafil, as other drugs belonging to the same pharmacological group, has an effect on visual function, probably due to the fact that PDE6, which is involved in the phototransduction of the retina (transformation of light into electrical signals), is also inhibited, at least to a certain degree. Data after 40 mg single dose indicate a mild and transient impairment of colour discrimination in the blue/green range and the purple range. Electroretinogram (ERG) measurements showed no clinically relevant changes. The absence of a positive control in this study (i.e. sildenafil) indeed precludes a firm conclusion in this regard. The effect on visual function with vardenafil might be longer than the effect observed with sildenafil, but again, the lack of comparative data do not allow to draw definite conclusions on this issue.

Effect on sperm motility was studied in healthy volunteers, in a placebo controlled study using a, single oral dose of 20 mg of vardenafil. Vardenafil did not produce any acute effect on spermiogram parameters. In addition, vardenafil did not cause any alteration in serum levels of FSH (Follicle Stimulating Hormone), LH (Luteinising Hormone), testosterone, DHEAS (Dehydroepiandrosteron Sulfate), and S-HBG (Sex-Hormone Binding Globuline).

Vardenafil has been shown to have no effect on the ability of patients with stable ischaemic coronary artery disease to complete an exercise treadmill test. There were no differences between vardenafil and placebo either in the total exercise treadmill time (ETT) and or in total time to angina. Also, for patients with 1 mm or greater ST-segment depression on the ETT, vardenafil improved by 15% the patient's time to the appearance of 1 mm or greater ST-segment depression.

Vardenafil, as described for other PDE5 inhibitors, decreased supine systolic and diastolic blood pressure. After dosing with 20 mg and 40 mg of vardenafil the maximal decreases for systolic blood pressure were – 6.9 mmHg under 20 mg and – 4.3 mmHg under 40 mg of vardenafil, when compared to placebo; the corresponding values for diastolic blood pressure were – 7.1 mmHg under 20 mg and – 5.2 mmHg under 40 mg of vardenafil. The decrease of blood pressure was typically followed by a compensatory increase of heart rate.

Vardenafil and alcohol decrease systolic blood pressure in the same magnitude and no clear additive or synergistic effects could be detected.

There is some experimental evidence in healthy volunteers suggesting that vardenafil does not potentiate the hypotensive effect of nitrates, when nitrates are given 1 hour or later after vardenafil administration. Nevertheless, since the study performed has some limitations, as a safety precaution, the contraindication of co administration vardenafil with nitrates or nitric oxide donors in any form according to other PDE5 inhibitors is proposed.

Vardenafil combined with aspirin did cause neither clinically relevant nor statistically significant increases in bleeding time.

In a formal drug interaction study between vardenafil and nifedipine there was an additive hypotensive effect of vardenafil when administered concomitantly with nifedipine (slow release formulation). The decrease attributed to vardenafil is around 5-6 mmHg in systolic blood pressure and 3-5 mmHg in diastolic blood pressure.

Pharmacokinetics

- General:

Vardenafil is rapidly and almost completely absorbed from the gastrointestinal tract reaching maximum plasma concentrations 30–120 minutes (median 60 minutes) after oral administration in the fasted state. Vardenafil AUC and C_{max} increase almost dose-proportionally over the recommended dose range from 5–20 mg.

No accumulation occurs after multiple administration once daily. Vardenafil is highly bound to plasma proteins (93.3–95.3%), mainly to serum albumin (approx. 79%). The large volume of distribution at steady state of 208 L (= 2.5 L/kg) indicates distribution of vardenafil into the tissues. With a clearance of 56 L/h vardenafil can be regarded as a high clearance drug with elimination determined by liver blood flow. The plasma elimination half-life is 4 to 5 hours. After dosing radioactive labelled vardenafil 4.89% of the total radioactivity was excreted in the urine and 92.5% in the faeces. Vardenafil is eliminated via biotransformation. Vardenafil is metabolised predominantly by hepatic enzymes via cytochrome P450 (CYP) isoform 3A4, with some contribution from CYP3A5 and CYP2C isoforms.

The plasma pharmacokinetics of the major metabolites M1 and M4 are quite similar to the pharmacokinetic characteristics of the parent drug with comparable times to maximum concentration and terminal elimination half-lives. The metabolites M1 and M4 were found to be inhibitors of PDE5 with 28% and 5.6% potency (IC₅₀-values) of the parent drug in vitro. Based on their exposure in man, only M1 may contribute to any meaningful extent (7%) to overall effect of vardenafil. The absolute bioavailability of vardenafil is approximately 14.5%. The inter and intra individual variability in vardenafil pharmacokinetics is high (AUC 37-51%, C_{max} 38-59% and AUC 20%, C_{max} 31%, respectively)

In a placebo controlled trial, elderly subjects had higher AUC and C_{max} values than younger subjects. On average, elderly males had a 52 % higher AUC and 34 % higher C_{max} than young males with no

statistical significance. Nevertheless, as it cannot be ruled out that these differences are of clinical relevance, the SPC recommends elderly patients to start with the lowest dose (5 mg) and increase it, if necessary, based on efficacy and tolerability.

Population pharmacokinetic investigations of Phase III data revealed no significant effect of age on the pharmacokinetics of vardenafil. Vardenafil pharmacokinetics after multiple doses were also assessed but changes were not found.

The pharmacokinetics of vardenafil has been assessed in patients with different degrees of renal impairment (including patients with a Cr Cl below 30ml/min although not in dialysis). Although a significant correlation between creatinine clearance, as a measure for deterioration in renal function and AUC and C_{max} was not observed, a dose recommendation has been addressed in the SPC, since the number of subjects with severe renal impairment investigated was low.

As expected, the clearance of vardenafil is strongly influenced by the hepatic function status. The exposure to vardenafil in patients with hepatic insufficiency grade B is significantly increased, in a magnitude that is double compared to the one observed in healthy volunteers. The recommendation in the SPC is as follows: a starting dose of 5 mg should be considered in patients with mild and moderate hepatic impairment (Child-Pugh A-B), which based on tolerability and efficacy may be increased to 10 mg and then 20 mg. In addition, the use of vardenafil in patients with severe hepatic impairment should be contraindicated.

No changes in AUC are observed when vardenafil is taken after a standard meal or a high-fat meal in comparison to a fasting administration. However, after a high fat meal, there is a delay in t_{max} (from 1 hour to two hours) with a 20% decrease of C_{max}. This may have consequences in the onset of action and this information is reflected in the SPC. After a meal containing 30% fat (a standard meal), the rate and extent of absorption of vardenafil (t_{max}, C_{max} and AUC) are unchanged compared to administration under fasting conditions.

The population pharmacokinetic investigations did not show significant effects of acetylsalicylic acid, ACE inhibitors, beta-blockers, weak CYP 3A inhibitors, diuretics and medications for the treatment of diabetes (sulfonylureas and metformin) on the pharmacokinetics of vardenafil. Furthermore, population pharmacokinetic covariates in the target population of patients with ED, including diabetics, showed no difference compared to pharmacokinetic covariates in healthy subjects.

- Interaction studies:

Concomitant use of potent P450 CYP3A4 inhibitors produced marked increases of plasma levels of vardenafil (erythromycin: AUC 4.0-fold increase and C_{max} 3.1-fold increase, ketoconazole: AUC and C_{max} increase 10-fold and 4.1-fold and indinavir: AUC and C_{max} 16-fold and 7-fold, respectively). The decrease in M1, M4 and M5 concentrations in ketoconazole and indinavir studies, is also consistent with inhibition of this metabolic pathway. In the erythromycin study, vardenafil concentration increase with concomitant use which is explained by the inhibition of its metabolism.

As a consequence of the above mentioned results, the SPC clearly states that the concomitant use of vardenafil with potent CYP 3A4 inhibitors should be avoided. With the less potent CYP 3A4 inhibitor, erythromycin, the dose of vardenafil should not exceed 5 mg. This is clearly stated in the SPC.

Concomitant use of vardenafil and antacids does not appear to influence systemic exposure to vardenafil. There is a small decrease in vardenafil C_{max}, which is probably not clinically relevant. A slight but clinically irrelevant increase in bioavailability of vardenafil has been observed when co-administered with cimetidine, which is likely to be due to the inhibition of CYP3A4 by cimetidine.

Only M1 showed any potential for inhibitory activity towards CYP 3A4. This was further investigated in an in vivo interaction study with nifedipine as standard CYP 3A4 substrate. Concomitant use showed a marginal decrease of bioavailability of nifedipine.

The possible influence on one of the minor metabolic pathways (P450CYP 2C9) by the CYP2C9 substrate warfarin was also studied. No effect either on pharmacokinetics or pharmacodynamics of warfarin was found. Nevertheless warfarin appears to slightly reduce AUC and C_{max} of vardenafil.

According to the preliminary results from interaction studies with alpha-blockers, the concomitant use of vardenafil with alpha-blockers may lead to symptomatic hypotension in some patients. Therefore, until further information is available, their concomitant use is not recommended.

No pharmacokinetic or pharmacodynamic interactions are shown with the co-administration of vardenafil and glibenclamide, which is also substrate for CYP 3A4 and is a high plasma protein-binding drug.

- Bioequivalence studies:

Since the Phase III development program was performed with the Phase III tablet formulation (which is identical in composition to the tablet intended to be marketed) no bioequivalence studies between the different formulations used in clinical development are mandatory.

Clinical efficacy

The clinical program was developed to assess the efficacy and safety of vardenafil in male patients with ED. One Phase IIb study and seven Phase III studies were conducted.. An overall total of 5033 patients have been randomised to all these studies, among which 3876 have been randomised to vardenafil. There were 3780 vardenafil-treated patients valid for the safety evaluation and 3728 for the intent-to-treat analysis (ITT).

All clinical studies were performed according to Good Clinical Practice (GCP).

The six placebo-controlled studies are of parallel-arm design and evaluated the at-home use of vardenafil. Two of them will be considered in the dose finding studies. The remaining four studies form the basis for the proof of efficacy of vardenafil.

The two non placebo controlled studies are long term extensions that will be considered as supportive studies.

Dose response studies

Doses higher than 20 mg (40 mg) were badly tolerated in clinical pharmacology studies and were not finally included in dose finding studies in spite it was initially planned.

A placebo-controlled, parallel-group, dose-finding study, investigated the efficacy and safety of 5 mg, 10 mg or 20 mg of vardenafil versus placebo in the treatment of patients with erectile dysfunction. In this study the three vardenafil doses appear better than placebo.

Another study investigated the 2.5 mg dose in order to define the lowest dose with clinical efficacy. The differences from placebo of this dose were statistically significant, nevertheless, the 2.5 mg dose failed to reach the predefined level of clinical relevance. Therefore, the 5 mg dose was considered as the minimum efficacious dose.

Doses of 5 mg, 10 mg and 20 mg were included in those confirmatory trials versus placebo that are the basis for the efficacy demonstration and therefore, the best posology regimen is based on results from these studies.

In relation with the posology regimen, data justify the recommendation of taking the product between 25 minutes and one hour before starting sexual activity.

Main clinical studies

As commented before, four studies form the basis for efficacy of vardenafil. All four used the same three primary efficacy endpoints, two of these are performed in the general population with ED while two were performed in specific populations: diabetics in Study 100250 and patients after nerve sparing prostatectomy in Study 100285.

1. *Description of the study*

All of these studies followed a randomised, placebo-controlled, multi-centre, fixed-dose, parallel-group design. In all studies, there was a 4-week baseline period without ED therapy (including devices). During the double-blinded treatment period, visits were planned on a monthly basis. After the last dose of study medication, at day 7 and day 30 post-treatment there was a follow-up telephone call to collect data on the occurrence of SAEs and deaths. Design of pivotal studies is considered appropriate.

Different doses of Vardenafil or placebo were to be taken on demand, approximately one hour before sexual activity, at a maximum dose of once a day.

2. *Primary endpoints*

Three co-Primary efficacy parameters were used:

- The erectile function (EF) domain score of the International Index of Erectile Function (IIEF), calculated as the sum of scores from questions 1 to 5 and 15 at Week 12, using the last-observation-carried-forward (LOCF) method to account for missing data.
- Success in penetration, using question 2 of the Sexual Encounter Profile: "Were you able to insert your penis into your partner's vagina?". Answers were to be recorded in the patient diary after every attempt at intercourse from randomisation to Week 12 and the per-patient overall success rate was used.
- Success in maintaining erection during intercourse, using question 3 of the Sexual Encounter Profile: "Did your erection last long enough for you to have successful intercourse?". Answers were to be recorded in the patient diary after every attempt at intercourse from randomisation to Week 12 and the per-patient overall success rate was used.

The use of these three related measures of erectile function as three co-primary variables is considered adequate. IIEF is a validated scale to measure erectile dysfunction severity as well as to measure a treatment effect based on the retrospective evaluation by the patient of his erectile function in the four weeks before the interview.

Secondary parameters were the global assessment question (GAQ): "Has the treatment you have been taking over the past 4 weeks improved your erections?" The GAQ was self-administered and answered by "yes" or "no". Patients answering "yes" to the GAQ were considered to be responders to treatment. Other secondary efficacy parameters included individual IIEF questions. Responses on patient's diary concerning success of intercourse attempts and overall satisfaction with sexual experience were also used. Fugl-Meyer Quality of Life Questionnaire, Centre for Epidemiological Studies Depression Scale (CES-D) Questionnaire and, in addition, the Duke Health Profile questionnaire was used to assess general health.

3. *Statistical analysis*

The primary time point for all efficacy variables was 12 weeks after randomisation. Primary efficacy analyses were based on the intent-to-treat (ITT) population. A secondary per protocol analyses of the primary efficacy parameters (VFE) was performed. Efficacy variables from the IIEF were analysed by analysis of covariance (ANCOVA) with baseline response as covariate and terms for centre and treatment. Least squares (LS) means at baseline and postrandomisation, together with the standard error (SE) for the LS means, were used. *P* values for each main effect in the model were presented together with *P* values obtained from the comparison of each active dose group to placebo. LS mean differences between each active dose and placebo and the associated nominal 95% confidence interval (CI) and the nominal Bonferroni 98.3% CI were also determined.

Diary questions (including the primary variables of penetration and maintenance of erection) were analysed by ANCOVA on the per-patient success rate, with terms for centre and treatment and including baseline as a covariate. The per-patient success rate was calculated from the whole duration of the trial

Clinically relevant differences between each of the vardenafil doses and placebo were predefined for power calculations as 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. No clinical definition of responders has been done and consequently no analysis on a responder basis is available.

RESULTS

4 Study populations/accountability of patients

All studies enrolled men, 18 years or older, with an stable heterosexual relationship of more than 6 months and 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). All patients who had taken at least one dose of study medication and for whom pre-and post-baseline efficacy data were available were included in the ITT analyses. Patients 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 unsuccessful attempts (according to the following questions from the patient diary (at least one question was to be answered 'no'): "were you able to achieve at least a partial erection?" "were you able to insert your penis into the partner's vagina?" and "did your erection last long enough for you to have successful intercourse?"). Because the response to treatments for ED in patients with diabetics or prostatectomy may differ from that in the general ED population, the diabetics and the post-prostatectomy population was studied separately (Studies 100250 and 100285).

Patients with cardiovascular illnesses within the preceding 6 months such as unstable angina, history of myocardial infarction, stroke, ECG ischaemic changes were excluded as well as those with uncontrolled tachyarrhythmia, as well as patients with retinitis pigmentosa, ED after spinal cord injury, penile anatomic abnormalities, resting hypotension, symptomatic postural hypotension, poorly controlled diabetes (HbA1c >12%), concomitant use of nitrates or other nitric oxide donors, use of the potent, CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir and indinavir were excluded from concomitant use with vardenafil 20 mg by protocol amendment, patients with severe chronic liver disease, liver function test abnormalities (AST, ALT >3 times the upper limit of normal), or renal failure (serum creatinine >2.5 mg/dl) were excluded.

Unresponsiveness to sildenafil therapy was an exclusion criterion in three of the major efficacy studies. Patients with history of radical prostatectomy were excluded for all protocols except 100285.

5 Efficacy results

Study 100249 was a randomised, double blind, placebo-controlled, multi-centre, fixed-dose, parallel-group, 6-month comparison study to investigate the efficacy and safety of 5 mg, 10 mg and 20 mg of vardenafil. At 12 weeks (primary analysis) for each of the primary endpoints there was a statistically significant difference from placebo for all three active groups.

Patients at baseline were in a moderate degree of ED based on the EF domain score. At week 12, patients in placebo group stayed in the same category while patients in vardenafil groups showed mean values of about 18.4, 20.6 (mild to moderate degrees) for vardenafil 5 mg and 10 mg and 21.4 for vardenafil 20 mg.

An analysis was performed to relate the response to the time between dosing and the start of sexual activity based on the patient's diary responses. From 30 min to 3 hours after taking the study drug, all vardenafil doses had higher success rates than the placebo group.

Study 10128, the second pivotal clinical trial, is a randomised, double blind, placebo controlled (Sildenafil), multi-centre, fixed-dose, parallel-group study. Primary analysis was the comparison of vardenafil to placebo.

The results of the study demonstrated that 5 mg, 10 mg and 20 mg of vardenafil and active control showed a statistically and clinically significant improvement relative to placebo in terms of all primary parameters, and was seen in both the ITT and the VFE population. An increased response was seen across the entire dose range with the greatest efficacy at the 20mg dose. Differences between 5 mg, 10 mg and 20 mg vardenafil treatment effects suggested a non-linear dose relationship for efficacy. The trial was also designed for testing the non inferiority of vardenafil 10 mg as compared to sildenafil 50 mg. Some problems in the study design did not allow the conclusions to be considered as reliable.

Clinical studies in special populations

Study 100250, a randomised, double-blind, placebo-controlled, multi-centre, fixed-dose, parallel-group, 3-month comparison study to investigate the efficacy and safety of vardenafil in males with erectile dysfunction and diabetes mellitus. Type 1 and 2 diabetes were balanced in all treatment groups. The response of diabetic patients to treatments for ED has been reported to be lower than in the general population.

For all treatment groups there was an increase at Week 12, compared with baseline, in all three endpoints. For the ITT population and all three primary efficacy variables, the LS mean differences between all vardenafil doses and placebo showed that there was a highly and statistically significant improvement for patients on vardenafil 10 mg and 20 mg. The improvements over placebo increased numerically with dose for all three endpoints. The results of the per protocol analysis are similar to that of the ITT population.

The results of the study demonstrate that 10 mg and 20 mg of vardenafil are effective in the treatment of ED in diabetic patients.

Study 100285, a randomised, double-blind, placebo-controlled, multi-centre, fixed-dose, parallel-group, 3-month comparison study to investigate the efficacy and safety of vardenafil in males with erectile dysfunction following nerve-sparing radical retropubic prostatectomy who have more severe ED than the previous population studied. Studied doses (10 mg and 20 mg) were more effective than placebo with statistically significant and clinically relevant differences for each of the primary endpoints, but there were no differences between the two doses. The results of the VEF population confirm the results of the ITT population.

Exploratory analysis performed across trials (pooled analyses and meta-analysis).

Two efficacy pools were defined. Efficacy pool 1 comprised all placebo-controlled studies in the general population with the 5 mg, 10 mg and 20 mg vardenafil dose groups, i.e. the pivotal studies 100249 and 10128. Efficacy pool 2 comprised all placebo-controlled studies with the 10 mg and 20 mg dose arms in both normal and special populations (10128, 100249, 100250 [diabetics] and 100285 [prostatectomy]).

There is a consistent superiority of all vardenafil doses over placebo in all trials and in all three co-primary variables.

Some subgroup analysis according to demographic and disease conditions have been performed. Efficacy is shown in all age groups, aetiology of the ED (organic, psychogenic or mixed), severity and duration of the disease, with a trend to higher efficacy as compared to placebo in those patients with the most severe disease and for longer duration of the disease. Diabetics and prostatectomised patients had, as expected, lower rates of efficacy than the general population.

Selection of the dose

The applicant proposes a starting dose of 10 mg, with further increase to 20 mg or decrease to 5 depending on response and tolerability.

There is a clear superiority of 10 mg and 20 mg over 5 mg, with statistically significant differences across studies, while differences between 10 mg and 20 mg are minimal

The benefit achieved with vardenafil 20 mg compared to that achieved with 10 mg in the broad-spectrum of ED population was not statistically significant. The magnitude of this benefit in diabetic patients, in patients with longer duration of erectile dysfunction (>3 years) and more severe disease (EF domain <11) was clinically relevant. These populations represent 30%, 66% and 50%, respectively, of the population studied.

In addition, data from flexible dose studies presented by the applicant show that for a relevant proportion of the ED population studied in similar conditions to that of clinical practice there is a need for titration to the 20 mg dose of vardenafil to achieve the optimal response. Therefore, from the data provided by the applicant it can be concluded that the efficacy and safety profile of the 20 mg dose of vardenafil is acceptable and their use is justified for the broad ED population who need it to achieve the optimal response.

Clinical relevance of the Effect

In efficacy pool 1, the mean magnitude of effect in IIEF-EF ranged from an improvement over baseline of 5.9 with vardenafil 5 mg to 8.3 with vardenafil 20 mg, as compared to 1.1 with placebo. In efficacy pool 2, improvements in IIEF-EF are of 0.8% with placebo and 6.8 and 7.7 with 10 and 20 mg.

Improvements in success in penetration ranged from 24% with vardenafil 5 mg to 35.8% with vardenafil 20 mg, compared to 4.6% with placebo. Similar results are showed in pool 2

Improvement in success of maintenance of erection for successful completion of intercourse ranged from 37.9% with 5 mg to 49.7% with 20 mg, as compared to 14.2% with placebo. Again, pool 2 show similar results.

Supportive studies

One dose ranging phase IIb study (100199), was performed in a selected population without serious medical conditions. There was one extension study with 3 months (100312) and two long-term studies with 1 year (10125) and 6 months (10152), respectively, conducted to assess safety, in which efficacy parameters were analysed by descriptive statistics only.

Discussion on clinical efficacy

Based on the pharmacodynamic, safety and tolerability results, it was decided to study doses of 5, 10 and 20 mg. Vardenafil, at these doses has consistently showed to have superior efficacy to placebo in the treatment of patients with erectile dysfunction. This effect has also been demonstrated in diabetic and prostatectomised patients with erectile dysfunction at doses of 10 and 20 mg. The magnitude of the effect, especially for the 10 and 20 mg doses are clinically. Other populations that might benefit from PDE5 inhibitor treatment have not been assessed (e.g. spinal cord injury or other CNS diseases). There are data suggesting that the effect of vardenafil in the studied population can be maintained on a long-term basis.

Clinical safety

Patient exposure

A total of 5317 patients were evaluable for safety in Phase I, II and III studies of vardenafil. In these studies, 4413 patients received vardenafil, 3783 of whom were from Phase II and III studies. The primary evaluation of the safety of vardenafil was derived from 6 adequate and well-controlled Phase IIb and III and 3 non-controlled Phase III trials involving 3780 patients with erectile dysfunction, many of whom had multiple other medical conditions. Over 1630 patients were treated with vardenafil for at least 6 months, of who over 730 were treated for at least 12 months.

A pooled safety analysis comprising the whole clinical Phase III study programme was performed. No formal weighting methods were used when the data were pooled. The 8 Phase III studies included were pooled as follows:

- Safety Pool 1: placebo-controlled studies using all three vardenafil doses (5, 10, 20 mg; 100249, 10128) in the general population. This pool was designed to describe dose-dependent differences and interactions in AEs and other safety parameters (pivotal studies in general populations).
- Safety Pool 2: placebo-controlled studies using vardenafil 10 and 20 mg (100249, 10128, 100250, 100285). This pool was designed to provide support for the benefit/risk assessment of vardenafil 10 mg and 20 mg in a pool of ED patients including diabetics and patients with ED following radical prostatectomy. These latter populations are generally less responsive to treatment, and co-morbid conditions tend to be more common (all pivotal studies).
- Safety Pool 3: placebo-controlled studies using vardenafil 5, 10, or 20 mg (100249, 10128, 100250, 100285, 10232). This pool was the largest placebo-controlled pool and comprised the primary safety analysis population from which rates for the various AEs were derived and a majority of the drug-drug and drug-disease interactions were evaluated.

Adverse events and serious adverse event/deaths

The analysis of the safety and tolerability pool from clinical pharmacological studies shows that vardenafil has a safety profile which is the expected for its pharmacological class, headache and vasodilatation (flushing) being the most frequently reported adverse events.

This adverse event profile was confirmed in the Phase III study programme.

There was a dose-dependent increase in the incidence of treatment-emergent AEs from placebo to 5 mg (48.3%), 10 mg (58.7%) and 20 mg (65%) vardenafil for most of the reported adverse events. AEs that demonstrated a possible dose-response relationship included headache, abdominal pain, vasodilatation (flushing, warm sensation), dyspepsia, nausea, dizziness, and rhinitis (safety pool 1). For safety pool 2, these percentages were very similar (40.2% for placebo, 57.4% for vardenafil 10 mg, 64.3% for vardenafil 20 mg and 60.8% for vardenafil total). The Applicant also reviewed the safety of the 20 mg dose of vardenafil in these same fixed dose studies (in general and also in special ED populations). The results in the general ED population showed a dose-related increase in the rates of AEs and drug-related AE (an increment about 7% in the incidence of AE from vardenafil 10 mg to 20 mg and 11% in the incidence of drug-related AE). Nevertheless, most of the AE in the 20mg dose were of mild intensity (>50%) and the incidence of AEs leading to discontinuation and SAEs were similar to that seen in the 10 mg dose. In conclusion, safety of the 20 mg dose in the general ED population has been adequately demonstrated. Therefore, the benefit/risk profile of the 20 mg dose of vardenafil seems acceptable.

Vardenafil may decrease blood pressure. Clinical relevance of such decreases was scarce. However, taken into account that the target population is likely to present risk factor, a relative warning has been included in the SPC, for section 4.8, on syncope. Simultaneous administration of vardenafil to patients taking non-selective alpha-blockers may lead to clinically relevant hypotension.

Vardenafil treatment was associated with a low incidence of AEs related to vision and eye complaints and most of these were of mild intensity. Most patients who experienced these side effects continued on treatment, and serious visual AEs related to treatment were not observed.

Although apparently rare for vardenafil, the colour vision abnormalities are mentioned in section 4.8. In addition the clinical relevance of such events are discussed (e.g. a warning on the ability to drive).

Although not in the clinical Phase IIb and III programme, two cases of priapism were reported in the Clinical Pharmacology Programme in subjects taking 40 mg vardenafil.

Patients who may be particularly at risk of priapism include those with sickle cell anaemia, multiple myeloma, or leukaemia. In addition, pharmacologic treatment of ED should generally be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease).

Overall, there were 7 deaths in the clinical Phase IIb/III study programme on vardenafil completed as yet: 4 patients in the placebo-controlled trials and 3 patients in non-controlled extension and safety studies. Moreover, one death has occurred in an ongoing trial.

In total, there were 5 deaths during vardenafil treatment in patients valid for safety. None of the cases was attributed to vardenafil.

Although myocardial infarction was the most common condition associated with death, the proximity of time of death to the last dose of vardenafil makes a causal relationship implausible.

The death rates for vardenafil and placebo were in the same range.

Discontinuation rate

In all placebo-controlled Phase III trials (Safety Pool 3), a larger proportion of patients who received placebo discontinued prematurely compared with patients who received vardenafil. There were a higher proportion of patients on placebo who withdrew consent, had insufficient therapeutic effect or were lost to follow-up. A higher proportion of patients in the vardenafil group (3.7%) withdrew due to AEs compared to the placebo group (1.4%).

Regarding discontinuations in relation to dosage, there was an increase in the rate of discontinuation due to AEs with increasing doses of vardenafil (placebo: 2%, vardenafil 5 mg: 3%, vardenafil 10 mg: 3%, vardenafil 20 mg: 7%).

Among the vardenafil dose groups, the rate of discontinuation from insufficient therapeutic effect and withdrawal of consent was highest for vardenafil 5 mg.

Experience on long-term treatment from the 12-month safety trial 10125 the 6-month safety trial 10152 reveals no indication of a deviating safety and tolerability profile of vardenafil when used as proposed for long-term management of ED.

The safety and tolerability of vardenafil 5 mg, 10 mg and 20 mg were assessed in relation to both placebo and sildenafil 50 mg over a period of 75-80 days. Vardenafil 10 mg seems to be similar to sildenafil 50 mg.

Overdosage

Vardenafil has been administered at doses of up to 4 times the highest dose recommended for clinical use. The experience in healthy volunteers at dose levels above 20 mg describes dose-limiting symptoms. If overdose occurs, these symptoms may be severe, but are not anticipated to be associated with evidence of organ toxicity and are expected to be self-limiting.

Laboratory findings and other parameters

Evaluation of clinical laboratory data included haematology, clinical chemistry and urinalysis. There were no clinically significant changes in laboratory parameters during the studies.

Regarding the effect of vardenafil on QTc interval, it can be concluded that vardenafil does not affect the QT interval in a clinically significant way.

Vardenafil 10 mg increased the heart rate by 2 beats/min and Vardenafil 20 mg by 3 beats/min compared to placebo. These increases may be considered as of no clinical relevance. Regarding blood pressure, changes were comparable to placebo, and even vardenafil 20 mg reduced sitting systolic blood pressure to a lesser extent than placebo.

Retinal function was explored and a mild and transient impairment of colour discrimination in the blue-green range (tritane axis) and in the purple range (tetertane axis) using the Farnsworth-Munsell 100 test was detected with vardenafil 40 mg.

Effects on sperm function have been assessed, and no abnormalities were found.

Safety in special populations

Subgroup analyses raised no concerns regarding an interaction between the incidence of adverse events with age, race, body mass index, alcohol consumption, smoking, cardiovascular disease, pulmonary disease, hyperlipidemia, diabetes mellitus, hypertension, concomitant antihypertensive medications, weak to moderate CYP3A4 inhibitors or aspirin.

Safety in flexible dose studies

Study 10194 was a Phase III extension of study 10125 with a flexible-dose design. The adverse event rates were determined based on the “preferred” dose. This analysis, rather describes the overall safety experience of the subset of patients, who arrive non-randomly at a specific dose of vardenafil (“preferred dose”) at the last titration visit.

There is no evidence for greater rates of adverse events in patients who elect treatment with 20 mg.

Study 10769 was a 12-week, randomised, double blind parallel group, placebo-controlled Phase III study with a flexible-dose design. The tolerability of vardenafil-treated patients overall in this study was favorable compared to those treated with placebo. There was no apparent difference in the occurrence of adverse events, for either the vardenafil (10 or 20 mg dose) or the placebo treatment group.

There were no patients who titrated up to 20 mg who withdrew from the study for an adverse event. There were a total of 11 patients who reduced their dose for a drug-related adverse event, of whom 5 were on vardenafil 20 mg at the time of their adverse event. None of the events that led to down-titration and were attributed to study drug was considered serious, and all but two were mild or moderate in intensity.

Discussion on clinical safety

The number of exposed patients was appropriate for safety evaluation purposes. The most frequently reported adverse events associated with vardenafil were headache, vasodilatation (flushing, warm sensation), rhinitis, and gastrointestinal related disorders. The type of AEs are expected from the pharmacological class; headache, vasodilatation, dyspepsia, rhinitis/sinusitis, abnormal vision, and back pain. The AEs typical for a PDE5 inhibitor appear to be dose-dependent. The overall incidence of SAEs and the nature of individual AEs do not suggest a specific risk pattern during vardenafil treatment.

On the basis of the data provided, the overall safety profile of vardenafil is considered acceptable. The safety concerns with the use of vardenafil have been addressed in the SPC with the inclusion of appropriate warnings, precautions and contraindications.

5. Overall conclusions and benefit/risk assessment

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. At the time of the CPMP opinion there were some outstanding minor quality issues which had no impact on the benefit/risk profile. The applicant committed to provide the necessary information as follow up measures within an agreed timeframe, and to submit variations if required following the evaluation of this additional information.

Preclinical pharmacology and toxicology

Overall, the primary pharmacodynamic studies provided adequate evidence that vardenafil exerts PDE5 inhibitor activity. This causes smooth muscle relaxation, inducing a rise in intracavernosal pressure and consequently penile erection. A new animal model using conscious adult male rabbits was developed to evaluate the efficacy of vardenafil *in vivo*. From the pharmacokinetic point of view,

rats, mice and dogs were the most relevant species for preclinical efficacy and safety studies. The main toxicity findings are well understood and do not raise concern for human safety. This information has been included in the SPC

Efficacy

Vardenafil, at the doses of 5, 10 and 20 mg, has consistently showed superior efficacy to placebo in the treatment of patients with erectile dysfunction from a broad spectrum of etiology (including diabetes and prostatectomised patients). In order for vardenafil to be effective, sexual stimulation is required. The magnitude of the effect, especially for the 10 and 20 mg doses are clinically relevant and might be of about the same magnitude as for the other available PDE5 inhibitor. There are data suggesting that the effect of vardenafil in the studied population can be maintained on a long-term basis.

The proposed starting dose is 10 mg. Based on efficacy and tolerability the dose may be increased to 20 mg or decreased to 5 mg. For elderly people, the proposed starting dose is 5 mg, and it also should be considered for those with severe renal impairment, hepatic impairment and those taking concomitant CYP3A4 inhibitors, since vardenafil clearance is reduced in these populations.

Safety

Several special patient groups, those excluded from the clinical studies (severe hepatic impairment, hypotension, recent history of stroke or myocardial infarction and known hereditary degenerative retinal disorders such as retinitis pigmentosa) and those for who sexual activity is inadvisable (e.g. patients with severe cardiovascular disorders such as unstable angina or severe cardiac failure) have been contra-indicated. Since other PDE5 inhibitors have been shown to potentiate the hypotensive effects of nitrates, co-administration with nitric oxide donors or nitrates in any form is contra-indicated. The SPC includes appropriate warnings, precautions and contra-indications.

Benefit/risk assessment

In the light of the above mentioned considerations, the overall benefit/risk assessment for vardenafil was considered to be positive for the indication "treatment of erectile dysfunction".

Recommendation

Based on the CPMP review of data on quality, safety and efficacy, as well as the commitments to be undertaken by the applicant, the CPMP considered by consensus that the benefit/risk profile of this medicinal product in the treatment of erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance was favourable and therefore recommended the granting of the marketing authorisation.