Vardenafil for the treatment of erectile dysfunction

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Practice Points

- Oral therapy with phosphodiesterase-5 (PDE-5) inhibitors represents the first-line therapy for erectile dysfunction.
- Vardenafil is effective starting from 30 min after administration, and its efficacy extends up to at least 8 h after administration.
- Vardenafil's effectiveness is reduced by heavy, fatty meals.
- The recommended starting dose is 10 mg, which could be modified according to the patient's response and side effects.
- In patients with a mild liver impairment, the starting dose should be 5 mg.
- Vardenafil is effective in treating difficult patients (e.g., diabetic, hypertensive or radical prostatectomy patients).
- Daily chronic administration of vardenafil seems to be no better than on-demand administration.
- Orodispersible vardenafil formulation is as effective and safe as the film-coated tablet.

SUMMARY Vardenafil is a highly selective phosphodiesterase-5 (PDE-5) inhibitor approved for the treatment of erectile dysfunction. PDE-5 inhibition determines the increase in intracellular cGMP in the corpora cavernosa that, in response to sexual stimuli, results in enhanced erections. It has been found to be effective in a high percentage of patients and a broad spectrum of underlying conditions. In particular, a high percentage of men suffering from diabetes, hypertension, patients with cardiovascular risk factors and cardiovascular disease, as well as patients with spinal cord injury or depressive disorders, were found to respond to vardenafil treatment. An improvement in sexual function seems to contribute to quality of life and improve satisfaction in couples. The drug's overall tolerability and safety profile is acceptable, with headaches, flushing, rhinitis and dyspepsia being the major reported side

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effects. Of particular importance, its tolerability and safety in cardiovascular patients seems to be adequate with no significant increase in cardiovascular events that could be directly attributed to the pharmacologic agent.

Phosphodiesterase-5 (PDE-5) inhibitors are effective drugs for treatment of erectile dysfunction (ED) in most patients [1]. Current guidelines recommend the use of PDE-5 inhibitors (vardenafil, sildenafil and tadalafil) as a first-line therapy for ED stemming from varying etiologies and severities [2]. Vardenafil (Levitra, Bayer Healthcare) is a selective PDE-5 inhibitor that has been commercially available since March 2003, and is characterized by a rapid onset of action, increased duration of erection, high rates of first-dose success and reliable efficacy that can be maintained with continued use.

The aim of the present paper is to review clinical evidence supporting the use of vardenafil for treatment of ED with the intent of providing a practical guide for the daily management of patients suffering from erectile impairment.

Background to therapy

Isoform 5 of the PDE enzyme catalyzes the hydrolysis of cGMP and regulates its intracellular inactivation. cGMP is produced by the guanylate cyclase enzyme, which is localized in the smooth muscle cells and is activated by nitric oxide. Cytosolic cGMP acts as a second messenger to activate a pattern of protein kinases and ion channels. In smooth muscle cells, the decreased concentration of intracellular calcium causes relaxation and reduced muscular tone. In this way, the pharmacological inhibition of PDE-5 increases cGMP levels and induces smooth muscle relaxation. Isoform 5 of PDE is present in the corpora cavernosa of the penis within the vascular and trabecular smooth muscles and in the platelets [3,4]. The pharmacological inhibition of PDE-5 enhances penile erection and has a direct effect on pulmonary pressure. Recently, we have demonstrated that acute administration of vardenafil in healthy volunteers determined a twofold increase in platelet cGMP and that following chronic administration of a low dose of vardenafil in patients with ED, there is an enduring enhancement of platelet cGMP levels. A cGMP increase displayed a significant correlation with the RigiScan test after video sexual stimulation and was not sensitive to a placebo effect. Therefore, platelet cGMP can provide information on the activity and duration of PDE-5 inhibition and could be used as a useful tool in future ED clinical studies [5].

Vardenafil is highly selective for PDE-5. According to the review article by Gresser *et al.* a concentration of 0.14 nmol/l vardenafil is sufficient for 50% inhibition of PDE-5 activity [4]. In studies by Saenz de Tejada *et al.,* the IC_{50} of vardenafil was 0.7 nmol/l for PDE-5, 11 nmol/l for PDE-6 and 180 nmol/l for PDE-11 [6]. Vardenafil has a 40-fold higher affinity for PDE-5 over sildenafil, but this difference does not show a correlation in terms of clinical efficacy [7]. Upon oral administration, vardenafil is rapidly absorbed with maximum vardenafil plasma concentrations (C_{max}) achieved within 0.5–2 h. Measurable amounts of vardenafil were found as early as 8 min after oral intake in some cases and after 15 min in most of the patients, especially if taken at the 20 mg dose.

The half-life of vardenafil and its active metabolite is approximately 4.5 h (compared with the half-life of sildenafil, which is 4 h, and the tadalafil half-life, which is 17.5 h). Mild renal impairment did not alter the pharmacokinetics of vardenafil. The drug is metabolized predominantly by the hepatic reduction–oxidation enzyme cytochrome P450 (CYP) 3A4, and, to a lesser extent, the CYP3A5 and CYP2C9 isoforms. The major desethylated metabolite (M-1) has PDE-5 selectivity similar to that of vardenafil and accounts for approximately 7% of the total pharmacological activity of vardenafil. In patients with hepatic insufficiency, peak plasma concentration and bioavailability (AUC) may increase significantly. As a consequence, a lower starting dose (5 mg) is recommended in patients with moderate hepatic impairment [8].

Since 2011, a new orodispersible tablet (ODT) formulation for vardenafil has been available on the market. Vardenafil 10 mg ODT is rapidly absorbed after oral administration without water. The pharmacokinetic profile is comparable to the vardenafil film-coated tablet, except that the ODT exhibited significantly greater bioavailability. This was demonstrated by 21–44% higher AUC values for the vardenafil ODT compared with the vardenafil film-coated tablet 10 mg

formulation. This difference in bioavailability is most likely related to drug absorption through the lingual and buccal mucosa. Drugs absorbed via the oral mucosa enter the systemic circulation directly and thereby avoid the first-pass metabolism that occurs when the tablet is swallowed. Food ingestion does not have any inhibitory effect on the pharmacokinetics of vardenafil ODT. Multiple-dose administration of vardenafil ODT demonstrated time-linear pharmacokinetics for vardenafil and no drug accumulation with daily use [9].

Clinical evidence

To date, clinical efficacy of vardenafil for the treatment of ED has been tested in many published clinical trials [2]. Its efficacy was first tested and documented on a conscious rabbit model that had similarly been used for investigations on sildenafil [10]. After initial dose-finding studies, the first study was conducted and vardenafil 5, 10 or 20 mg was administered to 601 men with mild-to-severe ED. Efficacy was evaluated using the International Index of Erectile Function (IIEF). Primary end points (vaginal penetration and maintenance of erection) were improved in all dosage groups compared with placebo. In the 20 mg group, 80% of the patients reported improved erections compared with 30% in the placebo group [11].

Since this first study, many trials have been conducted to confirm the efficacy and safety of vardenafil taken on demand for the treatment of ED. The main postmarketing vardenafil studies are summarized in **Table 1**.

In a double-blind, randomized study, Stief *et al.* demonstrated the long-term efficacy and tolerability of vardenafil. Five-hundred and fifty-six men with ED were treated with vardenafil 10 or 20 mg for 2 years. Improvement in their IIEF and Sexual Encounter Profile (SEP) scores was observed over the entire treatment period [12].

In a recent multicentric, prospective, double-blind study, 358 patients suffering from ED were randomized to receive vardenafil 10 mg or placebo for 12 weeks. Vardenafil significantly improved the IIEF and SEP scores when compared with placebo. Furthermore, positive Global Assesment Questionnaire (GAQ) responses were reported in 82.6% of patients treated with vardenafil versus 24.3% of placebo patients. The drug was generally well tolerated and its most common adverse effects were flushing and headache [13].

In 2009, the ENDURANCE study demonstrated that the PDE-5 inhibitor vardenafil, taken on demand at a 10 mg dose prolonged erection in men with ED, when compared with placebo treatment. Duration of erection, timed with a stopwatch, was defined as the time of erection perceived hard enough for penetration until its withdrawal from the partner's vagina. This was the first study where a stopwatch assessment tool was used to measure erection duration time leading to successful intercourse as a primary successful end point following PDE-5 inhibitor therapy [14].

Vardenafil treatment is also associated with significant patient satisfaction. In a randomized, double-blind, placebo-controlled study, Ralph *et al.* recruited 611 men with ED. Patients were randomized between vardenafil and placebo. After 18 weeks, the mean of improvement score in the IIEF-EF group compared with the baseline was 12.70 in the vardenafil group and 1.69 in the placebo group. This significant difference was observed starting from the fourth week of therapy. Significant improvements were also noted in Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) and Centre for Epidemiological Studies Short Depression Scale (CES-D) scores compared with placebo ($p < 0.001$). The researchers concluded that ED improvement with vardenafil treatment resulted in greater overall satisfaction amongst the patients and their partners [15]. More recently, a double-blind, placebo-controlled trial assessed the efficacy of vardenafil in men with ED and analyzed the effects of treatment on their female partner's sexual quality of life. Men were randomized to receive either vardenafil 10 mg or placebo, which could be modified to 20 or 5 mg after 4 weeks. Efficacy of treatment was measured by question 3 of the SEP questionnaire (SEP3) and the quality-of-life domain of the modified Sexual Life Quality Questionnaire. Vardenafil significantly improved both erection maintenance and the female partners' sexual quality of life after 12 weeks of treatment [16].

In 2008, Valiquette *et al.* demonstrated that most patients who respond initially to vardenafil 20 mg are likely to experience successful intercourse on their subsequent attempts at a probability similar to their first-dose success. Results of their multicenter, randomized, double-blind, parallel-group, placebo-controlled trial (RELY-II study) revealed that patients receiving a 20 mg vardenafil dose had successful penetration (SEP2)

Table 1. Summary of main vardenafil postmarketing studies.

Study (year)	Patients (n)	Patient characteristics	Study methodology	Treatment	Main findings	Ref.
Stief *et al.* (2004)	755	Men with ED >6 months	Double-blind Randomized Placebo-controlled	Vardenafil 10 mg vs 20 mg vs placebo On demand for 12 months	In the vardenafil 10 mg group, IIEF score improved from 13.4 at baseline to 24.7, while in the vardenafil 20 mg group, the score improved from 13.8 to 25.7 In the vardenafil 10 mg group, positive responses to SEP2 improved from 47.7 to 92.0% and in vardenafil 20 mg group improved from 43.4 to 94.2% In the vardenafil 10 mg group, positive responses to SEP3 improved from 15.9 to 86.5% and in the vardenafil 20 mg group improved from 17.4 to 89.3%	[12]
Tan *et al.* (2008)	413	Men with ED >6 months	Double-blind Randomized Placebo-controlled	Vardenafil 10 mg vs placebo On demand for 12 weeks	IIEF-EF domain score in men receiving vardenafil was 22.40, significantly greater than the score of 14.30 observed in men receiving placebo ($p < 0.001$) SEP2 success rates were 82.2 and 43.6 for vardenafil and the placebo, respectively ($p < 0.001$) SEP3 success rates were 66.1 in the vardenafil group and 24.0 in the placebo group ($p < 0.001$)	[13]
Rosenberg *et al.* (2009)	201	Men with ED aged 18–64 years old and IIEF score >5, <26	Double-blind Randomized Placebo-controlled	Vardenafil 10 mg vs placebo On demand for 4 weeks	Duration of erection leading to successful intercourse was statistically superior in the vardenafil group vs the placebo group (12.81 ± 1.00 vs 5.45 ± 1.00 min)	[14]
Ralph *et al.* (2007)	611	Men with ED with IIEF-EF score ≤25	Double-blind Randomized Placebo-controlled	Vardenafil 10 mg (titration at preferred dose 5–10–20 mg after 4 weeks) vs placebo On demand for 18 weeks	Improvement in the IIEF-EF at 18 weeks vs baseline was 12.70 in the vardenafil and 1.69 in the placebo group ($p < 0.001$) Significant improvements with vardenafil vs placebo in all IIEF domains, EDITS and CES-D scores ($p < 0.001$)	[15]
Valiquette *et al.* (2008)	573	Men with ED with IIEF score >5, < 26	Double-blind Randomized Placebo-controlled	Vardenafil 20 mg vs placebo On demand for 12 weeks	81% of patients achieved first-time success for penetration (SEP2) and 70% reported successful erection maintenance (SEP3) Success rates in men with comorbidities were as follows: - Hypertension: 76% (SEP2) and 64% (SEP3) - Dyslipidemia: 75% (SEP2) and 63% (SEP3) - BPH: 76% (SEP2) and 66% (SEP3) - Diabetes mellitus: 72% (SEP2) and 60% (SEP3)	[17]
Valiquette *et al.* (2006)	600	Men with ED with IIEF score >5, < 26	Double-blind Randomized Placebo-controlled	Vardenafil 10 mg vs placebo On demand for 12 weeks	87% of patients achieved first-time success for penetration (SEP2) and 74% reported successful erection maintenance (SEP3) Success rates in men with comorbidities were as follows: - Hypertension: 84% (SEP2) and 66% (SEP3) - Dyslipidemia: 84% (SEP2) and 72% (SEP3) - Diabetes mellitus: 75% (SEP2) and 58% (SEP3)	[19]
Nehra *et al.* (2008)	440	Men with severe ED who underwent NS-RRP	Double-blind Randomized Placebo-controlled	Vardenafil 10 mg or vardenafil 20 mg vs placebo On demand for 12 weeks	Significant improvement in IIEF intercourse satisfaction domain score for vardenafil 10 mg (+2.2 vs placebo) and 20 mg (+2.1 vs placebo) Significant improvement in IIEF orgasmic function domain score for vardenafil 10 mg (+1.6 vs placebo) and 20 mg (+1.2 vs placebo) Significant improvement in overall IIEF score for vardenafil 10 mg (+1.8 vs placebo) and 20 mg (+1.6 vs placebo)	[20]

ED: Erectile dysfunction; EF: Erectile function; IIEF: International Index of Erectile Function; NS-RRP: Nerve-sparing radical retropubic prostatectomy; ODT: Orodispersible tablet; SEP: Sexual Encounter Profile Questionnaire.

Table 1. Summary of main vardenafil postmarketing studies (cont.).

Study	Patients (n)	Patient characteristics	Study methodology	Treatment	Main findings	Ref.
Demir *et al.* (2006)	39	Men with ED and functioning renal grafts (creatinine <2 mg/dl)	Double-blind Randomized Placebo-controlled	Vardenafil 10 or 20 mg vs placebo On demand for 4 weeks	After vardenafil treatment, 82% of patients presented an IIEF score >26	[23]
Van Ahlen *et al.* (2010)	73,946	Men with ED in a real-life setting	Open-label Prospective Noncomparative Noninterventional study	Vardenafil at the preferred dose	High percentages of patients reported improvements in EF, irrespective of baseline ED severity (mild, 97.0%; moderate, 96.2%; severe, 85.5%), BMI (<25, 94.1%; ≥25 and <30, 94.6%; ≥30, 92.9%), presence of hypertension (93.6%), diabetes (92.6%), lipid metabolism disorder (94.7%) or CVD (93.3%)	[24]
Sperling *et al.* (2010)	402	Men with ED >6 months	Double-blind Randomized Placebo-controlled	Vardenafil 10 mg ODT vs placebo On demand for 12 weeks	Mean IIEF-EF domain score was statistically significantly greater following vardenafil ODT treatment compared with placebo (21.5 vs 14.4; $p < 0.0001$) Mean overall SEP2 success was statistically significantly improved following vardenafil ODT treatment compared with placebo (73.7 vs 46.7%; $p < 0.0001$) Mean overall SEP3 success rate following vardenafil ODT therapy was statistically significantly improved compared with placebo (64.9 vs 26.7%; $p < 0.0001$)	[26]
Gittelman *et al.* (2010)	473	Men with ED >6 months	Double-blind Randomized Placebo-controlled	Vardenafil 10 mg ODT vs placebo On demand for 12 weeks	Mean IIEF-EF domain score was statistically significantly higher in the vardenafil ODT group than the placebo group (20.8 vs. 13.9, respectively; $p < 0.0001$) Mean overall SEP2 success rate was statistically significantly greater following vardenafil ODT treatment compared with placebo (69.0 vs placebo, 43.0%; $p < 0.0001$) Mean overall SEP3 success rate was statistically significantly higher among subjects receiving vardenafil ODT treatment compared with those receiving placebo (60.0 vs 26.6%; $p < 0.0001$) Subjects aged <65 years had higher IIEF-EF scores and higher overall SEP2 and SEP3 success rates compared with those aged >65 years	[27]
Ishii *et al.* (2006)	778	Men aged 24–64 years old with ED and diabetes >3 years or HbA1c >6.5%, <12%	Double-blind Randomized Placebo-controlled	Vardenafil 10 mg vs vardenafil 20 mg or placebo	Vardenafil 10 and 20 mg both significantly improved EF domain score from 13.6 and 13.9 at baseline to 21.8 and 22.9, respectively, compared with placebo (13.7 at baseline to 16.3; $p < 0.0001$) Vardenafil 20 mg demonstrated superior efficacy to 10 mg ($p < 0.05$) The difference between 10 and 20 mg was more evident in severe ED patients	[29]
Zumbé *et al.* (2008)	236	Men with mild-to-moderate ED	Double-blind Randomized Placebo-controlled	Vardenafil 10 mg on demand vs vardenafil 10 mg once daily For 24 weeks	No statistically significant between-group differences in IIEF-EF scores changes from baseline (+2.29 from baseline for once-daily vardenafil, +2.63 from baseline for on-demand vardenafil)	[30]

ED: Erectile dysfunction; EF: Erectile function; IIEF: International Index of Erectile Function; NS-RRP: Nerve-sparing radical retropubic prostatectomy; ODT: Orodispersible tablet; SEP: Sexual Encounter Profile Questionnaire.

and successful erection maintenance compared with placebo over the 12-week study period [17].

In recent years, several investigations were conducted on the efficacy of vardenafil on special patient populations.

ED is highly prevalent in patients suffering from diabetes mellitus. A multicenter randomized study on 452 patients with diabetes mellitus demonstrated improved rates of successful penetration and intercourse at all baseline levels of ED severity, and at each level of plasma HbA1c in both Type 1 and Type 2 diabetes mellitus [18].

Recent investigations have emphasized that vardenafil is highly effective in patients with multiple cardiovascular risk factors, such as diabetes mellitus, hyperlipidemia and hypertension, across all efficacy measures evaluated, regardless of race, age, weight or ED etiology [19].

Vardenafil was also tested in patients who underwent nerve-sparing radical prostatectomy. In a randomized, double-blind, placebo-controlled trial conducted in 58 centers in the USA and Canada; 444 men who had recently undergone nerve-sparing radical retropubic prostatectomy were randomized to receive either placebo (145), 10 mg vardenafil (146) or 20 mg vardenafil (149) on demand. Results for both the 10 and 20 mg vardenafil recipients in improved IIEF domain for intercourse satisfaction, orgasmic function and overall satisfaction with sexual experience were significantly superior to the placebo group ($p < 0.001$). Patients treated with vardenafil showed significant improvement of erection hardness compared with patients treated with placebo ($p < 0.0001$). Headache, vasodilatation and rhinitis were the more frequent side effects, but in general treatment was fairly well tolerated [20]. The REINVENT study investigated the possible daily administration of vardenafil for penile rehabilitation after nerve-sparing radical prostatectomy. This randomized, double-blind, double-dummy, multicenter, parallel group study involved 87 centers all over the world. A total of 628 men, aged 18–64 years, were randomized to receive either 9 months of treatment with 10 mg nightly of vardenafil (which could be decreased to 5 mg if required) plus on-demand placebo, 9 months of treatment with flexible-dose (starting at 10 mg with the option to titrate to 5 or 20 mg), on-demand vardenafil plus nightly placebo, or 9 months of treatment with nightly placebo plus on-demand placebo. After a 2-month washout period, an open label extension for 2 months with vardenafil on demand was carried out. Results of this study showed that on-demand use of vardenafil determined a significant improvement in IIEF-EF scores compared with placebo. In addition, the IIEF-EF scores and SEP3 success rates were higher for the vardenafil on-demand group compared with the nightly group. This data clearly shows that nightly dosing with vardenafil did not produce any benefits over the on-demand therapy [21].

Renal transplantation can represent a risk factor for developing ED [22]. Therapy with vardenafil seems to be able to restore erectile function in renal transplant recipients. A Turkish study demonstrated that treatment with vardenafil for 4 weeks can improve IIEF scores without impairing renal-function tests and without affecting the dosage of immunosuppressive drugs. The most common side effects observed were flushing, palpitation, headache and dyspepsia [23].

The Real-Life Safety and Efficacy of vardenafil (REALISE) study conducted on a wide population of men with ED and published in 2010 confirmed the above findings. In this international, open-label, prospective, noncomparative and noninterventional study 73,946 patients with ED aged 18 years or older were enrolled in order to determine vardenafil's efficacy and safety in a real-life setting. Many patients in this group presented comorbidities, such as hypertension, diabetes, lipid metabolism disorder or cardiovascular disorders. Improvements in erectile function were observed in a high percentage of patients regardless of either baseline ED severity (mild, 97.0%; moderate, 96.2%; severe, 85.5%) or the presence of hypertension (93.6%), diabetes (92.6%), lipid metabolism disorder (94.7%) or cardiovascular disorders (93.3%). Most of the patients in the study (>90%) reported a high satisfaction level with vardenafil efficacy and expressed their willingness to continue vardenafil use after the end of the study period. The incidence of adverse events was low and 97.0% of patients were satisfied with vardenafil's tolerability [24]. More recently, Eardley *et al.* reviewed data on 4326 patients suffering from ED treated with vardenafil. Their findings

confirmed that vardenafil is effective and safe in patients with ED and underlying conditions, such as diabetes, hypertension, dyslipidemia or metabolic syndrome, irrespective of level of glycemic control or use of concomitant medications [25].

First data on the efficacy and safety of the new orodispersible vardenafil formulation is now available.

The POTENT I study was conducted on 409 men suffering from ED who were enrolled in 40 centers across Europe and South Africa and demonstrated that on-demand vardenafil 10 mg ODT was better than placebo in improving SEP2, SEP3, GAQ question and IIEF after a 12-week treatment period. The study proved that the adverse effects were the same with the film-coated tablet formulation [26].

Findings from the multicentric POTENT II study confirmed the results of POTENT I. In this double-blind, placebo-controlled, multicenter study, 473 men were enrolled in 35 different centers in Australia, Canada, Mexico and the USA. Primary and secondary efficacy was measured by IIEF, SEP2 and SEP3, and vardenafil 10 mg ODT was shown to be superior to placebo for all primary and secondary efficacy variables. The vardenafil ODT was generally well tolerated [27].

Place in therapy

Oral therapy with PDE-5 inhibitors is the first-line therapy for ED. Vardenafil is effective starting from 30 min after administration and is available in 5, 10 and 20 mg doses. The effectiveness of the drug is reduced by heavy, fatty meals. According to EAU guidelines, the recommended starting dose is 10 mg and should be modified in accordance with the patient's response and side effects [2].

It has been widely demonstrated that vardenafil is effective in improving erections in difficult-to-treat subgroups [28].

A total of 72% of the diabetic patients ina study by Goldstein *et al.* reported improved erections (i.e., improved GAQ) compared with 13% of patients taking placebo and the final IIEF-EF score was 19 compared with 12.6 for the placebo group [18]. A recently reported Japanese study proved that vardenafil 20 mg seemed to be more efficacious in men with diabetes over 10 mg in a comparable safety profile of both dosages [29]. Based upon our experience in patients with severe ED and organic etiology or in the presence of comorbidity, vardenafil should be administered on demand at a starting dose of 20 mg. Conversely, Reffelmann *et al.* recommend that in patients with moderate hepatic impairment and those who are elderly (>65 years old) the starting dose should be 5 mg [8].

To date no data have shown the superior effects of chronic daily administration of vardenafil compared with administration on demand. The RESTORE study compared once-daily vardenafil 10 mg plus on-demand placebo for 12 or 24 weeks and once-daily placebo plus on-demand vardenafil 10 mg for 24 weeks. The study findings showed that once-daily vardenafil did not produce greater sustained effects on erectile function than on-demand therapy [30].

The prescribing information for vardenafil recommends that a dose be taken approximately 1 h before sexual intercourse [31]. Montorsi *et al.* suggested that patients using vardenafil for the first time should be advised to engage in sexual activity approximately 1 h after ingestion of the pill, but vardenafil responders can shorten the time of initiation of sexual activity after taking the drug if they have the desire to do so [32]. Data from a randomized, double-blind, placebo-controlled study demonstrated that vardenafil, when taken by men with ED 8 h before intercourse, showed statistically significant improvements in SEP3 and SEP2, GAQ, IIEF-EF domain score, GCQ and EQS, compared with placebo. The findings of this study showed that the efficacy of vardenafil extends up to at least 8 h after dose administration, which allows couples to engage in sexual activities within this extended time frame [33].

Market research revealed the demand for a more convenient method of using vardenafil, and in general, ODT formulations offer improved convenience. Patient preference studies of ODT versus film-coated tablet formulations have shown that the orodispersible formulation is preferred by the majority of subjects [34]. The new ODT formulation can guarantee efficacy and ease of administration, convenience and overall compatibility with a 'natural' sexual experience, which are important considerations that govern whether a particular therapy is suitable for a patient and his partner [35]. The ODT vardenafil provides an

attractive option for long-term ED therapy for most patients suffering from ED irrespective of their age and underlying conditions.

In recent years, other possible clinical indications for vardenafil have been proposed and some preliminary studies have been conducted. Stief *et al.* tested the efficacy and safety of vardenafil 10 mg twice daily versus placebo in men with lower urinary tracts symptoms (LUTS) secondary to benign prostatic hyperplasia aged 46–64 years old [36]. Only patients with an International Prostate Symptom Score (IPSS) of at least 12 were enrolled in this randomized, double-blind trial. After 8 weeks of treatment there was a significant improvement in the IPSS total score (-5.9 and -3.6, respectively) and in both the irritative and obstructive subscores in the vardenafil group compared with placebo. No significant changes were observed in Q_{max} and postvoidal residual urine. Vardenafil was generally well tolerated in men with LUTS, and the adverse events profile was consistent with those previously reported for other PDE-5 inhibitors [36].

Vardenafil has also been investigated for its capacity to delay ejaculation. Aversa *et al.* have demonstrated that vardenafil 10 mg, taken on demand, increased intravaginal ejaculatory latency time and reduced postejaculatory refractory time in men suffering with lifelong premature ejaculation. In addition, patients reported improvements in confidence, perception of ejaculatory control and overall sexual satisfaction after drug intake [37]. Mathers *et al.* showed that the increased intravaginal ejaculatory latency time due to vardenafil is comparable to that observed for sertraline [38].

Furthermore, Al-Aown *et al.* have demonstrated on an experimental *in vitro* porcine model that vardenafil is able to determine ureteral relaxation resulting in a reduction of both rate and tension of the ureteral contraction [39]. Nevertheless, the observed effect was not concentration-dependent and internal controls were not used. Therefore, results of this study should be taken with caution.

Further studies are needed to evaluate if vardenafil and other PDE-5 inhibitors could be proposed for treatment of LUTS, premature ejaculation and urolithiasis.

Regarding the safety of vardenafil formulation, most clinical investigations using vardenafil emphasized the good tolerability and safety profile of vardenafil. The primary evaluation of the safety of vardenafil was derived from seven placebo-controlled trials. A total of 4374 patients were evaluated and of these 2660 patients received vardenafil. In these studies, 50.4% of patients reported adverse events (AEs). The incidence rates of treatment-emergent AEs in the vardenafil treatment group were greater than in the placebo group. AEs that occurred at least twice as often on vardenafil than on placebo were headache, flushing, rhinitis–sinusitis and dyspepsia. Data from fixed-dose trials indicated that all AEs were more frequent at higher doses [40].

Almost all side effects of vardenafil are related to its vasodilation activity. The main AEs reported (>2%) in randomized trials with vardenafil were headaches (15%), flushing (11%), rhinitis (9%), dyspepsia (4%), sinusitis (3%), flu symptoms (3%), dizziness (2%), increase in serum creatine kinase (2%) and nausea (2%). Back pain was reported in 2% of the patients taking vardenafil versus 1.7% of the placebo patients [29]. With regard to cardiovascular safety, in a retrospective analysis of five randomized trials there was no increase in the risk of a cardiovascular event under the influence of vardenafil [41].

Conclusion

Vardenafil has proven to be an effective and safe drug for the treatment of ED at a dose of both 10 and 20 mg, regardless of ED etiology and severity. Dose selection and the time between drug administration and the start of sexual activity should be customized for each patient. In addition, many studies have confirmed the effectiveness of vardenafil in treating special patient populations, such as diabetics, renal transplantation recipients, patients with multiple cardiovascular risk factors and patients who had undergone radical prostatectomy. In such subgroups, on-demand administration of 20 mg vardenafil seems to be the first therapeutic choice. No differences have been detected between on-demand and chronic administration of vardenafil, giving the clinician the possibility to choose the preferred administration schedule. The introduction of a new orodispersible formulation can provide efficacy and ease of administration ensuring the couple a more natural sexual experience. The new vardenafil ODT could represent an extremely

valuable alternative for long-term ED therapy for patients suffering from ED irrespective of their age and underlying conditions.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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References

Papers of special note have been highlighted as:

- ▪ of interest
- ▪▪ of considerable interest

1 Levine LA. Diagnosis and treatment of erectile dysfunction. *Am. J. Med.* 109, 3S–12S (2000).

2 Hatzimouratidis K, Amar E, Eardley I *et al.* European Association of Urology. Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. *Eur. Urol.* 57(5), 804–814 (2010).

▪▪ **European Association of Urology guidelines contain extremely useful information about the correct diagnostic and therapeutic management of patients with erectile dysfunction (ED).**

3 Wallis RM, Corbin JD, Francis SH, Ellis P. Tissue distribution of phosphodiesterase families and the effect of sildenafil on tissue cyclic nucleotides, platelet function, and the contractile responses of trabeculae carneae and aortic rings *in vitro*. *Am. J. Cardiol.* 83, 3C–12C (1999).

4 Gresser U, Gleiter CH. Erectile dysfunction: comparison of efficacy and side effects of the PDE-5 inhibitor sildenafil, vardenafil and tadalafil: review of the literature. *Eur. J. Med. Res.* 7, 435–446 (2002).

5 Mirone V, d'Emmanuele di Villa Bianca R, Mitidieri E *et al.* Platelet cyclic guanosine monophosphate as a biomarker of phosphodiesterase type 5 inhibitor efficacy in the treatment of erectile dysfunction: a randomized placebo-controlled study. *Eur. Urol.* 56(6), 1067–1073 (2009).

▪ **Presents important scenarios for the identification of objective markers of ED.**

6 Saenz de Tejada I, Angulo J *et al.* The phosphodiesterase inhibitory selectivity and the *in vitro* and *in vivo* potency of the new PDE5 inhibitor vardenafil. *Int. J. Impot. Res.* 13(5), 282–290 (2001).

7 Blount MA, Beasley A, Zoraghi R *et al.* Binding of tritiated sildenafil, tadalafil, or vardenafil to the phosphodiesterase-5 catalytic site displays potency, specificity, heterogeneity, and cGMP stimulation. *Mol. Pharmacol.* 66, 144–152 (2004).

8 Reffelmann T, Kloner RA. Vardenafil: a selective inhibitor of phosphodiesterase-5 for the treatment of erectile dysfunction. *Expert Opin. Pharmacother.* 8(7), 965–974 (2007).

9 Heinig R, Weimann B, Dietrich H, Böttcher MF. Pharmacokinetics of a new orodispersible tablet formulation of vardenafil: results of three clinical trials. *Clinic Drug Investig.* 31(1), 27–41 (2011).

10 Bischoff E, Niewoehner U, Haning H *et al.* The oral efficacy of vardenafil for inducing penile erection in a conscious rabbit model. *J. Urol.* 165, 1316–1318 (2001).

11 Porst H, Rosen R, Padma-Nathan H *et al.* The efficacy and tolerability of vardenafil, a new oral, selective phosphodiesterase type 5 inhibitor, in patients with erectile dysfunction: the first at-home clinical trial. *Int. J. Impot. Res.* 13, 192–199 (2001).

12 Stief C, Porst H, Sáenz De Tejada I, Ulbrich E, Beneke M. Vardenafil Study Group. Sustained efficacy and tolerability with vardenafil over 2 years of treatment in men with erectile dysfunction *Int. J. Clin. Pract.* 58(3), 230–239 (2004).

13 Tan HM, Chin CM, Chua CB *et al.* Efficacy and tolerability of vardenafil in Asian men with erectile dysfunction. *Asian J. Androl.* 10(3), 495–502 (2008).

14 Rosenberg MT, Adams PL, McBride TA, Roberts JN, McCallum SW. Improvement in duration of erection following phosphodiesterase type 5 inhibitor therapy with vardenafil in men with erectile dysfunction: the ENDURANCE study *Int. J. Clin. Pract.* 63(1), 27–34 (2009).

15 Ralph D, Eardley I, Kell P *et al.* Improvement in erectile function on vardenafil treatment correlates with treatment satisfaction in both patients and their partners. *BJU Int.* 100, 130–136 (2007).

▪ **Investigates the effect of vardenafil therapy in both patients and their partners, testifying to the efficacy of the drug in improving female partner's sexual quality of life.**

16 Martín-Morales A, Graziottin A, Jaoudé GB *et al.* Improvement in sexual quality of life of the female partner following vardenafil treatment of men with erectile dysfunction: a randomized, double-blind, placebo-controlled study. *J. Sex Med.* 8(10), 2831–2840 (2011).

17 Valiquette L, Montorsi F, Auerbach S. Vardenafil demonstrates first-dose success and reliability of penetration and maintenance of erection in men with erectile dysfunction – RELY-II. *CUAJ.* 2(3), 187–195 (2008).

18 Goldstein I, Young JM, Fischer J, Bangerter K, Segerson T, Taylor T. Vardenafil, a new phosphodiesterase type 5 inhibitor, in the treatment of erectile dysfunction in men with diabetes: a multicenter double-blind placebo-controlled fixed-dose study. *Diabetes Care* 26, 777–783 (2003).

19 Valiquette L, Montorsi F, Auerbach S; Vardenafil Study Group. First-dose success with vardenafil in men with erectile dysfunction and associated comorbidities: RELY-I. *Int. J. Clin. Pract.* 60, 1378–1385 (2006).

20 Nehra A, Grantmyre J, Nadel A, Thibonnier M, Brock G. Vardenafil improved patient satisfaction with erectile hardness, orgasmic function and sexual experience in men with erectile dysfunction following nerve sparing radical prostatectomy. *J. Urol.* 173, 2067–2071 (2005).

21 Montorsi F, Brock G, Lee J, Shapiro J, Van Poppel H, Graefen M, Stief C. Effect of nightly versus on-demand vardenafil on recovery of erectile function in men following bilateral nerve-sparing radical prostatectomy. *Eur. Urol.* 54(4), 924–931 (2008).

▪ **Investigates the efficacy of daily vardenafil for penile rehabilitation after nerve-sparing radical prostatectomy, demonstrating that nightly dosing did not produce any benefits over the on-demand therapy.**

22 Mirone V, Longo N, Fusco F, Verze P, Creta M, Parazzini F, Imbimbo C. Renal

transplantation does not improve erectile function in hemodialysed patients. *Eur. Urol.* 56(6), 1047–1053 (2009).

23 Demir E, Balal M, Paydas S, Sertdemir Y, Erken U. Efficacy and safety of vardenafil in renal transplant recipients with erectile dysfunction. *Transplant Proc.* 38(5), 1379–1381 (2006).

24 Van Ahlen H, Zumbé J, Stauch K, Hanisch JU. The Real-Life Safety and Efficacy of vardenafil (REALISE) study: results in men from Europe and overseas with erectile dysfunction and cardiovascular or metabolic conditions. *J. Sex Med.* 7(9), 3161–3169 (2010).

25 Eardley I, Lee JC, Shabsigh R, Dean J, Maggi M, Neuser D, Norenberg C. Vardenafil improves erectile function in men with erectile dysfunction and associated underlying conditions, irrespective of the use of concomitant medications. *J. Sex Med.* 7(1 Pt 1), 244–255 (2010).

■■ **The most updated review on vardenafil in patients with ED and underlying conditions.**

26 Sperling H, Debruyne F, Boermans A, Beneke M, Ulbrich E, Ewald S. The POTENT 1 randomized trial: efficacy and safety of an orodispersible vardenafil formulation for treatment of erectile dysfunction. *J. Sex Med.* 7(4 Pt 1), 1497–1507 (2010).

27 Gittelman M, McMahon CG, Rodríguez-Rivera JA, Beneke M, Ulbrich E, Ewald S. The POTENT 2 randomised trial: efficacy and safety of an orodispersible vardenafil formulation for the treatment of erectile dysfunction. *Int. J. Clin.* 64(5), 594–603 (2010).

■ **Demonstrates the first data (efficacy and safety) on vardenafil orodispersible tablet formulation.**

28 Martin Morales A, Mirone V, Dean J, Costa P. Vardenafil for the treatment of erectile dysfunction: an overview of the clinical evidence. *Clin. Interv. Aging* 4, 463–472 (2009).

■■ **One of the best reviews on vardenafil.**

29 Ishii H, Nagao K, Fujikawa K, Tachibana T, Iwamoto Y, Kamidono S: Vardenafil 20-mg demonstrated superior efficacy to 10-mg in Japanese men with diabetes mellitus suffering from erectile dysfunction. *Int. J. Urol.* 13, 1066–1072 (2006).

30 Zumbé J, Porst H, Sommer F, Grohmann W, Beneke M, Ulbrich E. Comparable efficacy of once-daily versus on-demand vardenafil in men with mild-to-moderate erectile dysfunction: findings of the RESTORE study. *Eur. Urol.* 54(1), 204–210 (2008).

31 Levitra®, prescribing information. Bayer Pharmaceuticals Corp., West Haven, CT, USA (2005).

32 Montorsi F, Salonia A, Briganti A *et al.* Vardenafil for the treatment of erectile dysfunction: a critical review of the literature based on personal clinical experience. *Eur. Urol.* 47(5), 612–621 (2005).

33 Porst H, Sharlip ID, Hatzichristou D; Vardenafil Study Group *et al.* Extended duration of efficacy of vardenafil when taken 8 hours before intercourse: a randomized, double-blind, placebo-controlled study *Eur. Urol.* 50, 1086–1095 (2006).

■ **Demonstrates that efficacy of vardenafil extends up to at least 8 h after administration.**

34 Dowson AJ, Almqvist P. Part III: the convenience of, and patient preference for, zolmitriptan orally disintegrating tablet. *Curr. Med. Res. Opin.* 21(Suppl. 3), S13–S17 (2005).

35 Hackett GI. Patient preferences in treatment of erectile dysfunction: the continuing importance of patient education. *Clin. Cornerstone* 7, 57–65 (2005).

36 Stief CG, Porst H, Neuser D, Beneke M, Ulbrich E. A randomised, placebo-controlled study to assess the efficacy of twice-daily vardenafil in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. *Eur. Urol.* 53(6), 1236–1244 (2008).

■ **Investigates the possible role of vardenafil in treating male lower urinary tract symptoms, suggesting a possible new indication for the drug.**

37 Aversa A, Pili M, Francomano D *et al.* Effects of vardenafil administration on intravaginal ejaculatory latency time in men with lifelong premature ejaculation. *Int. J. Impot. Res.* 21(4), 221–227 (2009).

38 Mathers MJ, Klotz T, Roth S, Lümmen G, Sommer F. Safety and efficacy of vardenafil versus sertraline in the treatment of premature ejaculation: a randomised, prospective and crossover study. *Andrologia* 41(3), 169–175 (2009).

39 Al-Aown A, Kyriazis I, Kallidonis P *et al.* Vardenafil effect on ureteric smooth muscle: *in vitro* study in porcine model. *J. Endourol.* 25(3), 505–509 (2011).

40 Markou S, Perimenis P, Gyftopoulos K, Athanasopoulos A, Barbalias G. Vardenafil (Levitra) for erectile dysfunction: a systematic review and meta-analysis of clinical trial reports. *Int. J. Impot. Res.* 16, 470–478 (2004).

41 Kloner RA, Mohan P, Segerson T *et al.* Cardiovascular safety of vardenafil in patients receiving antihypertensive medications: a post-hoc analysis of five placebo controlled trials. *J. Am. Coll. Cardiol.* 41(Suppl. A), 276A–277A (2003).

■ **Underlines the cardiovascular safety of vardenafil.**