

Vardenafil

A Review of its Use in Erectile Dysfunction

Gillian M. Keating and Lesley J. Scott

Adis International Limited, Auckland, New Zealand

Various sections of the manuscript reviewed by:

K.-E. Andersson, Department of Clinical Pharmacology, Lund University Hospital, Lund, Sweden; *J.D. Corbin*, Department of Molecular Physiology and Biophysics, Vanderbilt University School of Medicine, Nashville, Tennessee, USA; *W.J.G. Hellstrom*, Department of Urology, Tulane University Medical Center, New Orleans, Louisiana, USA; *M.K. Li*, Department of Surgery, National University Hospital, Singapore; *C.G. McMahon*, Australian Centre for Sexual Health, St Luke's Hospital, Sydney, New South Wales, Australia; *J. Pryor*, Lister Hospital, London, UK; *D. Ralph*, Institute of Urology, London, UK; *E. Wespes*, Department of Urology, CHU de Charleroi, Belgium; *J.M. Young*, South Orange County Urological Medical Associates, Laguna Woods, California, USA.

Data Selection

Sources: Medical literature published in any language since 1980 on vardenafil, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'vardenafil'. EMBASE search terms were 'vardenafil'. AdisBase search terms were 'vardenafil'. Searches were last updated 3 November 2003.

Selection: Studies in men with erectile dysfunction who received vardenafil. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Vardenafil, erectile dysfunction, pharmacodynamics, pharmacokinetics, therapeutic use.

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Summary

Abstract

Vardenafil (Levitra®) is a potent and highly selective oral phosphodiesterase type 5 (PDE5) inhibitor.

Vardenafil improved erectile function in men with mild to severe erectile dysfunction (ED) of varying aetiology in two randomised, double-blind, multicentre, fixed-dose studies of 12 or 26 weeks' duration. Men receiving vardenafil 10 or 20mg had significantly greater improvements in International Index of Erectile Function (IIEF) questionnaire erectile function domain scores than placebo recipients. Moreover, improvements in penetration and maintenance of erection (assessed using IIEF or Sexual Encounter Profile [SEP] questions) were significantly greater with vardenafil 5–20mg than with placebo. Improvements in IIEF intercourse satisfaction and orgasmic function domain scores were significantly greater with vardenafil 10 or 20mg than with placebo and the proportion of patients with a positive response to a Global Assessment Question (GAQ) concerning improvement in erections after 12 or 26 weeks' therapy was significantly higher with vardenafil 5–20mg than with placebo.

Vardenafil improved erectile function in men with ED associated with diabetes mellitus or ED following unilateral or bilateral nerve-sparing radical retropubic prostatectomy in two randomised, double-blind, multicentre, fixed-dose, 3-month studies. In both studies, improvements from baseline in the erectile function domain score of the IIEF and in positive responses to SEP questions were significantly greater with vardenafil 10 or 20mg than with placebo. In addition, a significantly higher proportion of vardenafil 10 or 20mg recipients than placebo recipients had positive GAQ responses.

Vardenafil was generally well tolerated in men with ED; treatment-emergent adverse events were of mild to moderate intensity and transient in nature. The most commonly reported adverse events (typical of those seen with PDE5 inhibitors) in vardenafil 5–20mg recipients included headache, flushing, rhinitis, dyspepsia and sinusitis. There were no reports of abnormal colour vision in men with ED taking vardenafil at clinically recommended doses (5–20mg).

Conclusion: Vardenafil is a potent and highly selective oral PDE5 inhibitor. It is effective and generally well tolerated in men with mild to severe ED of varying aetiology, as well as in men with ED associated with diabetes mellitus or ED after radical prostatectomy. Vardenafil should be considered a first-line treatment

Pharmacodynamic Profile

option in men with ED who are suitable candidates for oral PDE5 inhibitor therapy.

Vardenafil is a potent and highly selective inhibitor of phosphodiesterase type 5 (PDE5). The vardenafil concentration required to inhibit 50% of the activity (IC_{50}) of PDE5 ranged from 0.11–0.7 nmol/L, depending on the assay used. Vardenafil, like sildenafil and tadalafil, showed highly selective inhibition of PDE5, with limited or no activity against other known PDE isoenzymes. Relative to PDE5, vardenafil (4- to 25-fold selectivity) and sildenafil (\approx 10-fold) demonstrated some selectivity for PDE6, whereas tadalafil (5-fold) had some activity against PDE11A.

Both vardenafil and sildenafil inhibited cyclic guanosine monophosphate (cGMP) hydrolysis in a competitive manner in human corpus cavernosum smooth muscle cell extracts; IC_{50} values were \approx 5-fold lower for vardenafil than for sildenafil. The accumulation of cGMP in human corpus cavernosum tissue induced by the nitric oxide donor sodium nitroprusside (SNP) was significantly augmented by vardenafil 3 nmol/L. This effect was also seen with sildenafil 30 nmol/L, but not with lower concentrations. Vardenafil significantly enhanced relaxation in human trabecular smooth muscle induced by SNP, acetylcholine or transmural electrical stimulation.

Oral vardenafil successfully induced penile erections in a conscious rabbit model; a dose-dependent erectile response was seen with oral vardenafil 1–10 mg/kg. It has been suggested that the duration of effect of vardenafil may be much longer than its measured elimination half-life ($t_{1/2}$). In a conscious rabbit model, a significant erectile response was obtained with SNP 7 hours after oral vardenafil administration (vardenafil $t_{1/2}$ of 1.2 hours in rabbits).

Single-dose oral vardenafil 10–40mg significantly increased penile rigidity and tumescence during visual sexual stimulation in men with erectile dysfunction (ED) in two double-blind, randomised, placebo-controlled crossover studies. The mean total duration of erections with $>60\%$ rigidity was significantly longer with vardenafil 10–40mg than with placebo, and the mean total duration of erections with $>80\%$ rigidity was significantly longer with vardenafil 20 or 40mg than with placebo. Rigidity activity units and tumescence activity units were significantly higher with vardenafil 10–40mg than with placebo. The mean time to onset of the first erection was 26.8, 26.2 and 34.9 minutes with vardenafil 20 or 40mg or placebo.

Administering oral vardenafil 10mg 1–24 hours before sublingual nitroglycerin (glyceryl trinitrate) 0.4mg in healthy men did not potentiate the blood pressure (BP)-lowering effect of the latter drug (the coadministration of vardenafil and nitrates in men with ED is contraindicated). Some healthy men who received concomitant administration of vardenafil 10 or 20mg and α -blockers experienced hypotension.

Oral vardenafil 10 or 20mg did not impair the ability of men with stable coronary artery disease to exercise to a level similar to or greater than that associated with sexual intercourse in two randomised, double-blind, placebo-controlled, crossover studies. In one study, the time to ST-segment depression of

≥ 1 mm was significantly longer with vardenafil 10mg than with placebo (381 vs 341 seconds). Coadministration of oral vardenafil 20mg in men with essential hypertension did not alter the antihypertensive effect of extended-release nifedipine 30 or 60 mg/day to a clinically significant extent. In men with ED, small decreases in mean BP occurred with oral vardenafil 5–20mg between 11 minutes and 5 hours after treatment (reduction in mean systolic and diastolic BP of -1.4 to -6.6 mm Hg and -2.0 to -4.8 mm Hg). Changes in systolic and diastolic BP were -0.4 to $+0.6$ mm Hg and -1.3 to $+1.5$ mm Hg with placebo.

Pharmacokinetic Profile

Plasma concentrations rose rapidly after oral administration of single-dose vardenafil 10–40mg in men with ED. The mean maximum plasma vardenafil concentration (C_{\max}) increased in an almost dose-proportional manner and the median time to C_{\max} (t_{\max}) was slightly longer with vardenafil 10mg (≈ 0.9 hours) than with vardenafil 20 or 40mg (≈ 0.7 hours). Vardenafil has a mean absolute bioavailability of 15% and a mean volume of distribution at steady state of 208L. Both vardenafil and its major circulating metabolite (M1) are highly protein bound. In healthy men, the median t_{\max} was prolonged by 1 hour after consumption of a high-fat meal, compared with the fasting state.

Vardenafil is predominantly metabolised by cytochrome P450 (CYP) 3A4 and to a lesser extent by CYP3A5 and CYP2C. The M1 metabolite is pharmacologically active with an estimated efficacy contribution of $\approx 7\%$. In men with ED, the mean $t_{1/2}$ of single-dose vardenafil 10–40mg ranged from 3.94 to 4.79 hours. Vardenafil has a total body clearance of 56 L/h and the mean renal clearance of vardenafil was 2.3 L/h. Approximately 91–95% of the administered vardenafil dose is excreted as metabolites in faeces and ≈ 2 –6% is excreted as metabolites in the urine.

Elderly volunteers (aged >65 years) had higher C_{\max} and area under the plasma concentration-time curve (AUC) values (by 34% and 52%) and reduced hepatic clearance compared with younger volunteers (aged 18–45 years) after receiving single-dose vardenafil 40mg; $t_{1/2}$ was slightly longer in elderly than in young volunteers (6.0 vs 4.8 hours). Renal clearance was $\approx 50\%$ lower in men with mild to severe renal impairment than in healthy volunteers. In addition, the C_{\max} was lower (18.4 vs 31.8 $\mu\text{g/L}$) and the t_{\max} (1.4 vs 0.8 hours) and $t_{1/2}$ (56.1 vs 4.7 hours) were prolonged in men with severe renal impairment compared with healthy volunteers. Vardenafil clearance was reduced in men with mild to moderate hepatic impairment in proportion to the degree of impairment.

Alterations in the pharmacokinetics of vardenafil were seen with concomitant administration of potent CYP3A4 inhibitors such as ritonavir, indinavir and ketoconazole, and the bioavailability of a single dose of vardenafil 20mg was increased by 12% when it was coadministered with cimetidine (a nonspecific inhibitor of CYP isoenzymes). Concomitant administration of vardenafil 5mg and the CYP3A4 inhibitor erythromycin increased the AUC of vardenafil 4-fold and the C_{\max} of vardenafil 3-fold.

Therapeutic Efficacy

Oral vardenafil improved erectile function in men with mild to severe ED of varying aetiology in two randomised, double-blind, multicentre, fixed-dose studies of 12 or 26 weeks' duration (n = 580–895 [intent-to-treat]). Men receiving vardenafil 10 or 20mg had significantly greater improvements in International Index of Erectile Function (IIEF) questionnaire erectile function domain scores than placebo recipients after 12 or 26 weeks' therapy. In addition, in the 26-week study, the proportion of patients responding 'yes' to two Sexual Encounter Profile (SEP) questions ('Were you able to insert your penis into your partner's vagina' [SEP-2] and 'Did your erection last long enough for you to have successful intercourse' [SEP-3]) was significantly greater with vardenafil 5–20mg than with placebo at both weeks 12 and 26. In the 12-week study, the improvement from baseline in IIEF question 3 ('When you attempted sexual intercourse how often were you able to penetrate your partner?') and IIEF question 4 ('During sexual intercourse how often were you able to maintain your erection after you had penetrated your partner?') was significantly greater with vardenafil 5–20mg than with placebo.

In both studies, improvements in IIEF intercourse satisfaction and orgasmic function domain scores were significantly greater with vardenafil 10 or 20mg than with placebo. Moreover, the proportion of patients with a positive response to the Global Assessment Question (GAQ) ['Has the treatment you have taken over the past 4 weeks improved your erections?'] was significantly higher with vardenafil 5–20mg than with placebo after 12 and 26 weeks' therapy (65–85% vs 28–39%). With regards to health-related quality of life (assessed using the Fugl-Meyer questionnaire), improvements from baseline in mean scores for the question relating to sex life satisfaction were significantly greater with vardenafil 5–20mg than with placebo. A dose-response was seen for improvement in IIEF domain scores and for GAQ.

In a randomised, double-blind, multicentre, fixed-dose, 52-week study in men with mild to severe ED of varying aetiology (n = 1000) who received vardenafil 10 or 20mg, the mean IIEF erectile function domain score increased from ≈13 at baseline to ≈23 after 52 weeks' therapy; at 104 weeks the erectile function domain score was ≈25. Improvements in positive responses to SEP-2 and SEP-3 were also seen at week 104.

Pooled analyses of randomised, double-blind studies in men with ED who received vardenafil 5–20mg or placebo revealed that compared with placebo, vardenafil significantly improved erectile function irrespective of age, aetiology, baseline ED severity, the presence of comorbidities or whether or not patients were receiving concomitant antihypertensive therapy.

In a 12-week flexible-dose study in men with moderate to severe ED who had not responded to prior sildenafil therapy, the improvement from baseline in the IIEF erectile function domain score and SEP-2 and SEP-3 response rates were significantly greater with vardenafil than with placebo.

Vardenafil improved erectile function in men with ED associated with diabetes mellitus in a randomised, double-blind, multicentre, fixed-dose study (452 randomised patients). The improvements from baseline in the erectile function

domain score of the IIEF and the proportion of positive SEP-2 and SEP-3 responses were significantly greater with vardenafil 10 or 20mg than with placebo. Significantly more vardenafil 10 or 20mg than placebo recipients had a positive GAQ response (57% and 72% vs 13%). Improvement with vardenafil occurred irrespective of glycaemic control at baseline. Following study completion, 340 men continued in a 3-month extension study in which placebo recipients switched to receive vardenafil 10 or 20mg. Erectile function domain scores improved in both men who had received vardenafil 10 or 20mg for the entire 6 months and in patients initially randomised to placebo who switched to vardenafil. Improvements were also seen in the percentage of patients able to maintain an erection during intercourse and the percentage of patients responding 'yes' to the GAQ

Vardenafil improved erectile function in men with ED following unilateral or bilateral nerve-sparing radical retropubic prostatectomy in a randomised, double-blind, multicentre, fixed-dose study (442 randomised patients). The improvements from baseline in the erectile function domain score of the IIEF and the proportion of positive SEP-2 and SEP-3 responses were significantly greater with vardenafil 10 or 20mg than with placebo. Positive GAQ response rates were significantly higher with vardenafil 10 or 20mg than with placebo (59% and 65% vs 13%).

Tolerability

Vardenafil was generally well tolerated in men with ED. Treatment-emergent adverse events were generally of mild to moderate intensity and transient in nature.

Across three large, well designed, placebo-controlled trials, the most commonly reported adverse events (typical of those seen with oral PDE5 inhibitors) in vardenafil 5–20mg recipients included headache (6.8–22%), flushing (5–13%) and rhinitis (2.8–17%). Dyspepsia (0.7–6.7%) and sinusitis (1–6%) were also reported. Serious adverse events occurred infrequently and were reported in 1–5% of vardenafil 5–20mg recipients and in 3–5% of placebo recipients. Adverse events resulting in treatment discontinuation occurred in 1–5% of vardenafil 5–20mg recipients and in 1% of placebo recipients.

Small decreases in mean BP occurred with vardenafil. In a pooled analysis of five randomised, double-blind trials, ECG abnormalities, oedema, syncope, angina pectoris, hypotension and myocardial ischaemia occurred with an incidence of 0% to <0.6% and were not dose related. Myocardial infarction occurred in one vardenafil and one placebo recipient. Another placebo recipient experienced a cerebrovascular accident and a third required cardiovascular surgery.

There were no reports of abnormal colour vision in men with ED taking vardenafil at clinically recommended doses (5–20mg). Transient vision changes such as mild haziness or an increase in the perceived brightness of light were reported infrequently (incidence of 1% in vardenafil and placebo recipients combined in one study).

Dosage and Administration

Vardenafil is approved in the US and the EU for the treatment of ED. The recommended dose of vardenafil in adult men is 10mg; however, the dose may be increased to the maximum recommended dose (20mg) or decreased to 5mg according to efficacy and tolerability. It is recommended that vardenafil not be taken more than once daily. Vardenafil should be taken orally prior to sexual intercourse. Vardenafil is not indicated for use in women or in individuals aged <18 years.

A starting dose of 5mg should be used in elderly men. EU prescribing information states that a starting dose of 5mg should also be considered in men with mild to moderate hepatic impairment and in men with severe renal impairment, and US prescribing information recommends a starting dose of 5mg in moderate hepatic impairment.

Vardenafil is contraindicated in the EU and not recommended in the US in men with severe hepatic impairment; end-stage renal failure needing dialysis; hypotension; a recent history of stroke or myocardial infarction; unstable angina pectoris; or known hereditary degenerative disorders of the retina (e.g. retinitis pigmentosa). US prescribing information also states that the use of vardenafil is not recommended in patients with uncontrolled hypertension, a recent history of life-threatening arrhythmia or severe heart failure; vardenafil use should also be avoided in men with QT prolongation. Vardenafil should generally not be prescribed to men with ED for whom sexual activity is inadvisable.

Concomitant administration of vardenafil and nitrates or nitric oxide donors is contraindicated. In the EU, coadministration of vardenafil and potent CYP3A4 inhibitors such as ritonavir, indinavir, oral ketoconazole or oral itraconazole is contraindicated in men aged >75 years and should be avoided in younger men. In the US, reduced doses of vardenafil are recommended when it is administered in combination with ritonavir, indinavir, ketoconazole or itraconazole. Coadministration of vardenafil and grapefruit juice should be avoided and the vardenafil dose should not exceed 5mg when it is coadministered with the CYP3A4 inhibitor erythromycin. Coadministration of vardenafil and α -blockers is not recommended in the EU and contraindicated in the US.

1. Introduction

Erectile dysfunction (ED) is defined as the consistent inability to achieve and/or maintain a penile erection sufficient for sexual performance.^[1] ED is a common condition associated with increasing age, certain diseases (e.g. diabetes mellitus, heart disease, depression, chronic renal failure, hypertension), pelvic surgery, spinal cord injuries and various modifiable risk factors (e.g. cigarette smoking, alcohol consumption, use of certain drugs).^[2-5] It is

projected that by 2025 there will be 322 million men worldwide with ED.^[5]

ED is traditionally classified as being of organic, psychogenic or mixed aetiology.^[5] Psychogenic ED may arise from depression, psychological stress, relationship problems or performance anxiety.^[6] Organic ED may be further classified as being of neurogenic, hormonal, vasculogenic or drug-induced origin.^[7] An underlying organic cause can be identified in $\approx 75\%$ of patients.^[8]

In recent times, oral phosphodiesterase type 5 (PDE5) inhibitors have become the focus of attention in the treatment of ED. Sildenafil was the first PDE5 inhibitor to be approved for use in ED and vardenafil (Levitra^{®1}) and tadalafil are the most recent PDE5 inhibitors to gain approval in this indication. This review focuses on the pharmacological properties of vardenafil and its therapeutic efficacy and tolerability in men with ED.

2. Pharmacodynamic Properties

During sexual stimulation, nitric oxide (NO) is released from neurons and vascular endothelial cells in the corpus cavernosum of the penis and activates soluble guanylyl cyclase, resulting in cyclic guanosine monophosphate (cGMP) formation.^[7,9,10] This triggers a biochemical cascade which ultimately results in relaxation of smooth muscle in the penile arteries.^[9,11] The reduction in vascular tone leads to increased blood flow and enlargement of the corpus cavernosum tissue.^[9] This increased tumescence compresses veins between the corpus cavernosum and the tunica albuginea, decreasing the outflow of blood and increasing intracavernosal pressure, resulting in an erection.^[2,7,9]

PDE5 is the enzyme primarily responsible for degrading the second messenger cGMP in the corpus cavernosum of the penis.^[9,11,12] When NO is released during sexual stimulation, inhibition of PDE5 will increase cGMP levels in the penis, enhancing the endogenous effects of NO.^[9] Sexual stimulation is required for PDE5 inhibitors to be effective (NO and cGMP levels are low in the absence of sexual stimulation).^[7,9]

2.1 Receptor Selectivity and *In Vitro* Effects

Vardenafil (figure 1) is a potent and highly selective inhibitor of PDE5. The inhibitory effect of vardenafil on PDE5 isoenzymes has been examined in several *in vitro* studies;^[13-15] results vary between studies according to the assay used. For example,

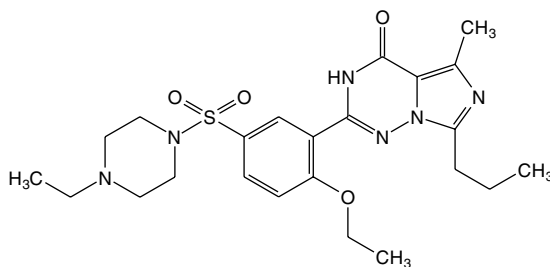


Fig. 1. Structural formula of vardenafil.

the vardenafil concentration required to inhibit 50% of the activity (IC₅₀) of PDE5 ranged from 0.11–0.7 nmol/L.^[13-15] Vardenafil had ≈10-fold greater potency than sildenafil with regards to the inhibition of PDE5 isolated from human platelets in an *in vitro* study (IC₅₀ values of 0.7 vs 6.6 nmol/L).^[13] In addition, the potency of vardenafil was ≈9-fold greater than that of tadalafil or sildenafil in an *in vitro* study, available as an abstract, using recombinant human PDE5 (IC₅₀ values of 0.11, 0.96 and 0.96 nmol/L for vardenafil, tadalafil and sildenafil, respectively).^[14] In a third study, also available as an abstract and using native human PDE5, the potency of vardenafil was ≈25-fold greater than that of sildenafil and ≈50-fold greater than that of tadalafil (table I).^[15]

Vardenafil, like sildenafil and tadalafil, showed highly selective inhibition of PDE5, with limited or no activity against other known PDE isoenzymes (table I).^[15] Relative to PDE5, vardenafil (4- to 25-fold selectivity) and sildenafil (≈10-fold) demonstrated some selectivity for PDE6, whereas tadalafil (5-fold) had some activity against PDE11A (table I).

Both vardenafil and sildenafil inhibited cGMP hydrolysis in a competitive manner in human corpus cavernosum smooth muscle cell extracts.^[17] However, the IC₅₀ values for vardenafil were ≈5-fold lower than for sildenafil (≈200 vs ≈1100 nmol/L at cGMP concentration of 10 μmol/L [values estimated from graph]).

Vardenafil 30 nmol/L significantly augmented the cGMP levels of human corpus cavernosum tis-

1 The use of tradenames is for product identification purposes only and does not imply endorsement.

Table 1. IC₅₀ values and selectivity ratios of vardenafil (VAR), sildenafil (SIL) and tadalafil (TAD) for PDE isoenzymes^[15]

PDE isoenzyme	IC ₅₀ value (nmol/L)			Selectivity ratio (vs PDE5)		
	VAR	SIL	TAD	VAR	SIL	TAD
PDE1 ^a	70	281 ^b	>30 000	500	80	>4450
PDE2 ^a	6200	>30 000 ^b	>100 000	44 290	>8570	>14 800
PDE3 ^a	>1000	16 200 ^b	>100 000	>7140	4630	>14 800
PDE4 ^a	6100	7680 ^b	>100 000	43 570	2190	>14 800
PDE5 ^a	0.14	3.5 ^b	6.74	1	1	1
Rod PDE6 ^a	3.5	37	1260	25	11	187
Cone PDE6 ^a	0.6	34	1300	4	10	193
PDE7A ^c	>30 000	21 300	>100 000	>214 000	6090	>14 800
PDE8A ^c	>30 000	29 800	>100 000	>214 000	8510	>14 800
PDE9A ^c	581	2610	>100 000	4150	750	>14 800
PDE10A ^c	3000	9800	>100 000	21 200	2800	>14 800
PDE11A ^c	162	2730	37	1160	780	5

a IC₅₀ values determined using native human enzyme.

b Previously published in Ballard et al.^[16]

c IC₅₀ values determined using recombinant human enzyme.

IC₅₀ = concentration required to inhibit 50% of the PDE activity; PDE = phosphodiesterase.

sue ($p < 0.05$ vs vehicle control).^[13] No such effect was seen with sildenafil 30 nmol/L.^[13] However, neither vardenafil nor sildenafil increased basal cGMP levels in a study using cultured human corpus cavernosum smooth muscle cells.^[17]

The accumulation of cGMP induced by the NO donor sodium nitroprusside (SNP) in human corpus cavernosum tissue was significantly augmented by vardenafil 3 nmol/L ($p < 0.05$ vs SNP alone). This effect was also seen with sildenafil 30 nmol/L ($p < 0.05$ vs SNP alone), but not with sildenafil 3 or 10 nmol/L.^[13] Similar results were seen in the study using cultured human corpus cavernosum smooth muscle cells.^[17] Significant augmentation of SNP-induced cGMP accumulation occurred with vardenafil 50 and 100 nmol/L and sildenafil 100 nmol/L ($p = 0.05$ vs vehicle control). However, a greater increase in cGMP accumulation was seen with vardenafil versus sildenafil (2.37- vs 1.60-fold increase at 100 nmol/L).

Vardenafil 3 nmol/L significantly enhanced SNP-induced relaxation in human trabecular smooth muscle ($p < 0.05$ vs vehicle control).^[13] Sildenafil significantly potentiated SNP-induced relaxation at a concentration of 10 nmol/L ($p < 0.05$ vs vehicle

control), but not at 3 nmol/L.^[13] Vardenafil also significantly enhanced the relaxation of human trabecular smooth muscle induced by acetylcholine or transmural electrical stimulation ($p < 0.005$ vs vehicle control for both).^[13]

2.2 In Animal Models

Vardenafil successfully induced penile erection in a conscious rabbit model.^[13,18,19] In rabbits administered oral vardenafil 1–30 mg/kg, a dose-dependent erectile response was seen between 1 and 10 mg/kg; an increase in dose to 30 mg/kg did not result in a further significant increase in response.^[18] The onset of action of vardenafil was ≈20 minutes after administration, with a maximum erectile response achieved ≈45–90 minutes after administration; the duration of effect was between 30 minutes and >4 hours (depending on dose).^[18] The efficacy of oral vardenafil was potentiated by intravenous SNP.^[13,18]

Similarly, intravenous vardenafil 0.1–1 mg/kg induced erection in a dose-dependent manner and its efficacy was potentiated by intravenous SNP in this same rabbit model.^[19] Intravenous sildenafil also had a dose-dependent effect; the time to onset and

duration of effect were similar with vardenafil and sildenafil.^[19] However, a 3 mg/kg intravenous dose of sildenafil was approximately equivalent to a 0.3 mg/kg intravenous dose of vardenafil.^[19]

It has been suggested that the duration of effect of vardenafil may be much longer than its measured elimination half-life ($t_{1/2}$) [section 3.2].^[20] In a conscious rabbit model, a significant ($p < 0.05$) erectile response was obtained with SNP 7 hours after oral vardenafil administration (vardenafil $t_{1/2}$ of 1.2 hours in rabbits).^[20] This study is available as an abstract.

Increases in intracavernosal pressure were of greater magnitude with vardenafil than with sildenafil in an anaesthetised rabbit model.^[21] Dose-dependent increases in intracavernosal pressure that were significant versus vehicle control ($p \leq 0.05$) occurred with intravenous vardenafil 3–30 $\mu\text{g}/\text{kg}$ and with intravenous sildenafil 10 or 30 $\mu\text{g}/\text{kg}$ (rabbits underwent submaximal electrical field stimulation of the pelvic nerve to induce erection). The duration of effect was significantly longer with vardenafil 10 $\mu\text{g}/\text{kg}$ than with sildenafil 10 $\mu\text{g}/\text{kg}$ (169 vs 137 seconds; $p \leq 0.05$) but similar with 30 $\mu\text{g}/\text{kg}$ doses. Intracavernosal vardenafil 1–10 $\mu\text{g}/\text{kg}$ (without pelvic nerve stimulation) induced significantly greater increases ($p \leq 0.05$) in intracavernosal pressure than intracavernosal sildenafil 1–10 $\mu\text{g}/\text{kg}$ at most timepoints following administration.^[21] The

duration of effect was significantly longer with vardenafil 1, 3 or 30 $\mu\text{g}/\text{kg}$ than with equivalent doses of sildenafil ($p \leq 0.05$).

2.3 In Men with Erectile Dysfunction

Single-dose oral vardenafil 10–40mg significantly increased penile rigidity and tumescence in men with ED in two randomised, double-blind, placebo-controlled crossover studies.^[22,23] In the studies, penile rigidity and tumescence was assessed from 0.5 hours before until 2.5 hours after vardenafil or placebo administration using the Rigiscan™ ambulatory monitoring device. The men (aged 22–59 years; 21 men in each study) watched erotic videos for three 20-minute periods; videos were viewed at 20-minute intervals starting 20 minutes after administration of vardenafil or placebo.

The mean total duration of erections with >60% rigidity (primary endpoint in both studies) was significantly longer with vardenafil 10–40mg than with placebo (table II).^[22,23] In addition, administration of vardenafil 20 or 40mg, but not 10mg, resulted in a significantly longer mean total duration of erections with >80% rigidity than administration of placebo (table II).^[22,23] Rigidity activity units and tumescence activity units were significantly higher with vardenafil 10–40mg than with placebo (table II).^[22,23] There were no significant differences be-

Table II. Effect of oral vardenafil (VAR) on penile rigidity and tumescence. Results of two single-dose, randomised, double-blind, crossover studies, each conducted in 21 men with erectile dysfunction^[22,23]

Reference	Treatment (mg)	Base of the penis (mean values)				Tip of the penis (mean values)			
		time with rigidity (min)		rigidity activity	tumescence	time with rigidity (min)		rigidity activity	tumescence
		60–100%	80–100%	units ^a	activity units ^b	60–100%	80–100%	units ^a	activity units ^b
Klotz et al. ^[22]	VAR 10	54.1**	25.2	47.9**	25.0*	39.2**	9.4	33.1**	17.9*
	VAR 20	66.9***	31.6*	59.5***	35.5***†	44.6***	21.5*	43.0***	19.1**
	PL	30.6	15.7	27.4	14.2	17.1	6.9	16.6	8.1
Stark et al. ^[23]	VAR 20	58.1***	29.8***	51.0***	28.3***	48.7***	18.5*	43.1***	25.9***
	VAR 40	64.5***	39.1***	56.0***	30.2***	48.7***	22.6**	46.1***	24.7***
	PL	13.6	6.0	16.6	10.2	12.8	5.2	13.9	7.9

a Calculated as the product of the degree of rigidity multiplied by the time.

b Calculated as the product of the degree of tumescence multiplied by the time.

PL = placebo; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs PL; † $p < 0.05$ vs VAR 10mg.

tween vardenafil doses (vardenafil 10 vs 20mg and vardenafil 20 vs 40mg), except for tumescence activity units which were significantly higher at the base of the penis with vardenafil 20mg than with vardenafil 10mg (table II).^[22]

The mean time to onset of the first erection was 26.8 minutes with vardenafil 20mg, 26.2 minutes with vardenafil 40mg and 34.9 minutes with placebo.^[23]

Vardenafil 20mg was shown to be significantly more effective than placebo as early as 16 minutes after ingestion in an at-home study, available as an abstract, in men with mild to severe ED (n = 471).^[24] At 16 minutes, 34% of vardenafil recipients versus 24% of placebo recipients (p = 0.013) perceived that they had an erection sufficient for penetration and intercourse; this perception was confirmed by intercourse completion. At 25 minutes, corresponding response rates were 48% and 30% (p < 0.0001).

2.4 Cardiovascular Effects

2.4.1 In Healthy Volunteers

Administering oral vardenafil 10mg 1–24 hours before sublingual nitroglycerin (glyceryl trinitrate) 0.4mg in healthy men aged 40–65 years (n = 18) did not potentiate the blood pressure (BP)-lowering effect of the latter drug, according to the results of a randomised, placebo-controlled, crossover study (available as an abstract).^[25] However, the possibility of outliers should be borne in mind,^[26] as well as the fact that there are no data concerning the coadministration of vardenafil and nitrates in patients with ED; thus, their concomitant use is contraindicated (section 6).^[27]

Coadministration of vardenafil 10 or 20mg and α -blockers such as terazosin and tamsulosin to healthy volunteers resulted in some subjects experiencing hypotension (section 6).^[28] Simultaneous administration of terazosin 10mg and vardenafil 10 or 20mg resulted in a standing systolic BP of <85mm Hg in six of eight and two of nine patients, respectively. With an interval of 6 hours between

administration of vardenafil 20mg and terazosin 10mg, 7 of 28 volunteers experienced a standing systolic BP of <85mm Hg. Administration of vardenafil 10mg and tamsulosin 0.4mg simultaneously, or administration of vardenafil 20mg and tamsulosin 0.4mg 6 hours apart, resulted in a standing systolic BP of <85mm Hg in 1 of 24 and 2 of 16 volunteers, respectively.

One hour after administration of a single dose of vardenafil 10 or 80mg to 59 healthy men aged 45–60 years, the individual corrected QT interval had increased by 4 and 6 msec, respectively, in a double-blind, randomised, crossover study; the individual corrected QT interval increased by 7 msec with moxifloxacin 400mg (active control).^[28] Corresponding increases in the Fridericia corrected QT interval were 8, 10 and 8 msec.

2.4.2 In Men with Cardiovascular Disease

Vardenafil did not impair the ability of men with stable coronary artery disease to exercise to a level similar to or greater than that associated with sexual intercourse.^[29,30] Two randomised, double-blind, crossover studies included men (n = 41^[29] and 39^[30]) of mean age 62^[29] and 64^[30] years who had stable, reproducible, exertional angina.^[29,30] In one study, 17% of patients had ED;^[29] the proportion of patients with ED in the other study was not stated (study available as an abstract).^[30] The men were randomised to receive a single dose of oral vardenafil 10^[29] or 20mg^[30] or placebo, and then underwent exercise testing.

The mean total exercise time (433 vs 427 seconds^[29] and 414 vs 411 seconds^[30]) and the time to first being aware of angina pectoris (291 vs 292 seconds^[29] and 354 vs 347 seconds^[30]) did not significantly differ between vardenafil 10 or 20mg and placebo administration. Similarly, there was no significant difference between vardenafil 20mg and placebo recipients in the time to ST-segment depression of ≥ 1 mm (364 vs 366 seconds);^[30] however, the time to ST-segment depression of ≥ 1 mm was significantly longer with vardenafil 10mg than with placebo (381 vs 341 seconds; p = 0.0004).^[29]

The exertional level was ≈ 5 –10 metabolic equivalents; this level of exertion is similar to or greater than the amount of energy expended in completing sexual intercourse.^[29] Changes in BP and heart rate during exercise did not significantly differ between vardenafil 10mg and placebo when corrected for baseline (resting) values.^[29]

Coadministration of oral vardenafil 20mg in men with essential hypertension ($n = 22$) did not alter the antihypertensive effect of extended-release nifedipine 30 or 60 mg/day to a clinically significant extent in a single-dose, randomised, double-blind, placebo-controlled, crossover study, available as an abstract.^[31] The difference between vardenafil and placebo administration was -5.9 mm Hg for the maximal change from baseline in supine systolic BP and -5.2 mm Hg for the maximal change from baseline in supine diastolic BP. The 90% confidence intervals lay within predefined limits, indicating that vardenafil and nifedipine did not have a synergistic effect on BP.

2.4.3 In Men with Erectile Dysfunction

In men with ED, small decreases in mean BP occurred with oral vardenafil between 11 minutes and 5 hours after treatment (reduction in mean systolic BP of -1.4 to -6.6 mm Hg and in mean diastolic BP of -2.0 to -4.8 mm Hg with vardenafil 5–20mg); these data were obtained from two randomised, double-blind, placebo-controlled studies^[32,33] (see section 4 for further study details) and a pooled analysis of five randomised, double-blind trials available as an abstract.^[34] Changes in systolic and

diastolic BP were -0.4 to $+0.6$ mm Hg and -1.3 to $+1.5$ mm Hg in placebo recipients.^[32,33]

2.5 Other Effects

A single dose of oral vardenafil 20mg had no effect on sperm parameters (e.g. concentration, total count, motility, vitality or morphology) in healthy men.^[35] Sixteen healthy men aged 24–43 years were enrolled in this randomised, double-blind, crossover, placebo-controlled study, available as an abstract.

3. Pharmacokinetic Properties

This section provides an overview of the pharmacokinetic properties of vardenafil. Some of the data in this section were obtained from the prescribing information^[27] and several of the studies discussed in this section are available as abstracts.^[31,36–41]

3.1 Absorption and Distribution

Plasma vardenafil concentrations rose rapidly after oral administration of single-dose vardenafil 10–40mg to men (aged 22–59 years) with ED.^[22,23] Mean maximum plasma vardenafil concentration (C_{max}) increased in an almost dose-proportional manner (table III). The median time to C_{max} (t_{max}) was slightly longer with vardenafil 10mg (≈ 0.9 hours) than with vardenafil 20 or 40mg (≈ 0.7 hours) [table III].^[22,23] Vardenafil has a mean absolute bioavailability of 15%.^[27]

The mean volume of distribution of vardenafil at steady state is 208L.^[27] Vardenafil is highly protein

Table III. Pharmacokinetic parameters of single-dose, oral vardenafil (VAR) 10–40mg in men (aged 22–59 years) with erectile dysfunction^[22,23]

Parameter (mean unless stated otherwise)	VAR 10mg ^[22]	VAR 20mg ^[22]	VAR 20mg ^[23]	VAR 40mg ^[23]
C_{max} ($\mu\text{g/L}$)	9.05	20.9	19.3	50.8
AUC ($\mu\text{g} \cdot \text{h/L}$)	32.6	74.5	69.8	164
t_{max}^a (h)	0.917	0.660	0.660	0.677
$t_{1/2}$ (h)	4.18	3.94	4.44	4.79

a Median.

AUC = area under the plasma concentration-time curve; **C_{max}** = maximum plasma concentration; **t_{max}** = time to C_{max} ; **$t_{1/2}$** = elimination half-life.

bound, as is its major circulating metabolite (M1) [protein binding of $\approx 95\%$ for vardenafil or M1].^[27] The proportion of the administered vardenafil dose appearing in the semen of healthy men was $\leq 0.00012\%$ (assessed 90 minutes after drug administration).^[27]

No significant alteration in vardenafil pharmacokinetics occurred when the drug was administered immediately after consumption of a meal with a moderate fat content ($\approx 30\%$ fat), compared with the fasting state.^[42] Mean C_{\max} was modestly reduced by 18% and median t_{\max} was prolonged by 1 hour after consumption of a high-fat meal ($\approx 57\%$ fat), compared with the fasting state. Twenty-five healthy men received vardenafil 20mg in the fasting state or after a moderate- or high-fat meal in this nonblind, randomised, crossover study.

3.2 Metabolism and Elimination

Vardenafil is predominantly metabolised by cytochrome P450 (CYP) 3A4; CYP3A5 and CYP2C also contribute to the metabolism of the drug.^[27] Desethylation of vardenafil results in M1 (the major circulating metabolite). M1 is pharmacologically active with an estimated efficacy contribution of $\approx 7\%$.^[27]

The mean $t_{1/2}$ of vardenafil 10–40mg ranged from 3.94–4.79 hours in men (aged 22–59 years) with ED (table III).^[22,23] Vardenafil has a total body clearance of 56 L/h.^[27] The mean renal clearance of vardenafil was 2.3 L/h in healthy volunteers (aged 30–60 years) who received a single dose of vardenafil 20mg.^[36] Approximately 91–95% of the administered vardenafil dose is excreted as metabolites in faeces and ≈ 2 –6% is excreted as metabolites in the urine.^[27]

3.3 Special Patient Populations

Nine healthy elderly men (aged >65 years) had greater total exposure to a single oral dose of vardenafil 40mg than nine healthy younger men (aged 18–45 years); the elderly volunteers had higher C_{\max} and area under the plasma concentra-

tion-time curve (AUC) values (by 34% and 52%) and reduced hepatic clearance compared with younger volunteers.^[27,37] The t_{\max} value was similar in younger and elderly volunteers (0.6 and 0.5 hours), although the $t_{1/2}$ was slightly longer in elderly than in younger volunteers (6.0 vs 4.8 hours). A reduced starting dose (5mg) should be used in the elderly (section 6).^[27]

Renal clearance of vardenafil was $\approx 50\%$ lower in men with renal impairment (0.8–1.3 L/h) than in healthy volunteers (2.3 L/h) after a single 20mg dose.^[36] In addition, the C_{\max} was lower (18.4 vs 31.8 $\mu\text{g/L}$) and the t_{\max} (1.4 vs 0.8 hours) and $t_{1/2}$ (56.1 vs 4.7 hours) were prolonged in men with severe renal impairment compared with healthy volunteers. Single-dose vardenafil 20mg was administered to 32 men with normal renal function or mild (creatinine clearance [CLCR] 3–4.8 L/h [50–80 mL/min]), moderate (CLCR 1.8–3 L/h [30–50 mL/min]) or severe (CLCR <1.8 L/h [<30 mL/min]) renal impairment.^[36] No dose adjustment is recommended in men with mild to moderate renal impairment;^[27,28] in the EU it is recommended that a reduced starting dose be considered in men with severe renal impairment (section 6).^[27] The pharmacokinetics of vardenafil have not yet been examined in men with severe renal impairment who require dialysis.^[27]

Vardenafil clearance was reduced in men with mild to moderate hepatic impairment in proportion to the degree of impairment, resulting in increased exposure to the drug.^[27] Compared with healthy controls, the C_{\max} and AUC of vardenafil increased by 22% and 17% in men with mild hepatic impairment (Child-Pugh A) and by 133% and 160% in men with moderate hepatic impairment (Child-Pugh B).^[27] A reduced starting dose is recommended in men with moderate hepatic impairment;^[27,28] in the EU it is also recommended that a reduced starting dose be considered in men with mild hepatic impairment (section 6).^[27] The pharmacokinetics of vardenafil have not yet been examined in patients with severe hepatic impairment.^[27,28]

3.4 Potential Drug Interactions

Alterations in the pharmacokinetics of vardenafil were seen with concomitant administration of potent CYP3A4 inhibitors such as ritonavir, indinavir and ketoconazole; concomitant use of these agents is not recommended in the EU^[27] and dosage adjustment is recommended in the US^[28] (section 6). Administration of vardenafil 5mg in addition to ritonavir 600mg twice daily resulted in 49- and 13-fold increases in the vardenafil AUC and C_{max} .^[28] Co-administration of vardenafil 10mg and indinavir 800mg three times daily resulted in 16- and 7-fold increases in the AUC and C_{max} of vardenafil.^[27] In addition, 10- and 4-fold increases in vardenafil AUC and C_{max} values occurred with coadministration of vardenafil 5mg and ketoconazole 200mg.^[27]

Concomitant administration of vardenafil 5mg and the CYP3A4 inhibitor erythromycin 500mg three times daily increased the AUC of vardenafil 4-fold and the vardenafil C_{max} 3-fold.^[27] Adjustment of the vardenafil dose is recommended in men receiving concomitant erythromycin (section 6).^[27]

The bioavailability of a single dose of vardenafil 20mg was increased by 12% when it was coadministered with cimetidine.^[39] Twelve healthy men (aged 24–44 years) received 3 days' treatment with cimetidine 400mg twice daily or ranitidine 150mg twice daily, followed by coadministration with vardenafil on day 4. T_{max} and $t_{1/2}$ values were similar regardless of whether vardenafil was administered alone or in combination with cimetidine or ranitidine. It has been suggested that the bioavailability of vardenafil is increased with cimetidine coadministration because, unlike ranitidine, cimetidine non-specifically inhibits CYP isoenzymes.

The pharmacokinetics of vardenafil 20mg were not significantly altered by coadministration of the antacid aluminium hydroxide/magnesium hydroxide (single dose),^[38] warfarin,^[27] glibenclamide (glyburide)^[27] or alcohol (ethanol).^[41] Moreover, coadministration of vardenafil 20mg did not significantly alter the steady-state plasma trough concentration or AUC of digoxin 0.375 mg/day^[40] or the

pharmacokinetics of extended-release nifedipine 30 or 60mg (see section 2.4 for pharmacodynamic effects).^[31]

Population pharmacokinetic analyses indicate that concomitant administration of aspirin (acetylsalicylic acid), ACE inhibitors, β -blockers, weak inhibitors of CYP3A4, diuretics or antihyperglycaemics (e.g. sulphonylureas or metformin) has no apparent effect on the pharmacokinetics of vardenafil, although specific drug interaction studies have not been conducted.^[27]

4. Therapeutic Efficacy

A number of studies have examined the use of oral vardenafil in men with mild to severe ED of varying aetiology (section 4.1),^[32,43–48] or in men with ED associated with diabetes mellitus (section 4.2)^[33] or after nerve-sparing radical prostatectomy (section 4.3).^[49] Most studies were of randomised, double-blind, multicentre, fixed-dose design ($n = 440–1020$),^[32,33,43,44,49] although two randomised studies evaluated a flexible-dose regimen of vardenafil ($n = 323$ ^[47] and 463^[48]) [section 4.1.2]. Studies were of 12,^[33,43,46–49] 26^[32,45] or 52^[44] weeks' duration.

Patients received vardenafil 5–20mg and were instructed to take the drug on an as-needed basis but not more than once daily;^[32,33,43,45,49] vardenafil was to be taken ≈ 1 hour prior to intercourse.^[32,33,43]

Inclusion criteria included age >18 ^[32,33] or 21–70^[43] years and ED of >6 months duration;^[32,33,43,46] ED was defined as the inability to achieve or maintain penile erection sufficient for satisfactory sexual performance.^[32,43] Most studies included a 4-week run-in phase;^[32,33,43] patients had to attempt intercourse on ≥ 4 separate days and be unsuccessful in $\geq 50\%$ of these attempts.^[32,33]

Full exclusion criteria details are not available for all trials. In addition to the exclusion of patients for whom the use of vardenafil is contraindicated/not recommended (section 6), exclusion criteria included ED as the result of radical prostatectomy,^[32,33,43,46] hypoactive sexual desire^[32,33] or spinal

cord injury;^[32,33,43] hypertension;^[32,33] a history of hepatitis B or C;^[32,43] chronic haematological disease;^[32,33] diabetes mellitus^[43,46,49] (poorly controlled^[32]); hyperthyroidism or hypothyroidism^[33] (inadequately treated^[32]); malignancy in the previous 5 years;^[32] low serum testosterone levels;^[32,43,49] and serum creatinine values >2.5 mg/dL.^[32] In the study enrolling patients with diabetes mellitus, exclusion criteria also included recent severe uncontrolled migraines, proliferative diabetic retinopathy that had progressed in the previous 6 months and autonomic neuropathy associated with clinically significant gastroparesis.^[33] Treatment with nitrates was contraindicated.^[32,33,43] Prior treatment with sildenafil was allowed but in most studies, patients who did not respond to sildenafil^[32,43,49] or who discontinued sildenafil because of a lack of response or adverse effects^[33,49] were excluded. However, one study was conducted in patients who had not responded to sildenafil (including nonresponse to a sildenafil dose of 100mg) [section 4.1.2].^[48]

Efficacy was assessed using the intent-to-treat population.^[32,33,43,44,47-49] Primary endpoints included the week 12 erectile function domain score of the International Index of Erectile Function (IIEF) questionnaire (last observation carried forward [LOCF] analysis);^[32,33,47-49] two IIEF questions: 'When you attempted sexual intercourse how often were you able to penetrate your partner?' (question 3 [Q3]) and 'During sexual intercourse how often were you able to maintain your erection after you had penetrated your partner?' (Q4) [both LOCF analysis];^[43] and two Sexual Encounter Profile (SEP) questions: 'Were you able to insert your penis into your partner's vagina' (SEP-2) and 'Did your erection last long enough for you to have successful intercourse' (SEP-3).^[32,33,48,49]

Additional endpoints included other IIEF domain scores (intercourse satisfaction, orgasmic function, sexual desire and overall satisfaction);^[43,50,51] other diary questions (e.g. satisfaction with erection hardness^[50,51] or sexual experience^[51]); the Global Assessment Question (GAQ): 'Has the treatment you

have taken over the past 4 weeks improved your erections?';^[32,33,43,47,49] and the Fugl-Meyer Quality of Life Questionnaire: 'How satisfactory are these different aspects of your life?'.^[43]

The IIEF erectile function domain score and responses to SEP-2, SEP-3 and GAQ were secondary endpoints in the 52-week study (the primary aim of the study was to assess the long-term tolerability of vardenafil).^[44]

The 15-item IIEF questionnaire scored responses from 1–5, with 1 being almost never/never and 5 being almost always/always; a score of 0 was assigned if intercourse was not attempted.^[52] The Fugl-Meyer Quality of Life Questionnaire graded responses from 1 (very dissatisfying) to 6 (very satisfying).^[53] The diary questions and GAQ calculated success rates (i.e. percentage of patients responding 'yes'). GAQ was assessed in patients who completed 12^[32,33,43,49] or 26^[32] weeks' therapy using logistic regression analysis; two studies also reported the GAQ response according to LOCF analysis.^[32,33]

The severity of ED was assessed using IIEF erectile function domain scores. Normal erectile function was defined as a score of ≥ 26 and mild, mild to moderate, moderate and severe ED were defined as scores of 22–25, 17–21, 11–16 and <11, respectively.^[32,54]

Some studies/analyses are only available as abstracts and/or posters.^[44-46,48-51,54-65]

4.1 In Mild to Severe Erectile Dysfunction of Varying Aetiology

Vardenafil improved erectile function in men with mild to severe ED of varying aetiology in terms of primary efficacy endpoints. Men receiving vardenafil 10 or 20mg had significantly greater improvements in IIEF erectile function domain scores than placebo recipients after 12^[32,43] or 26^[32] weeks' therapy; vardenafil 5mg was associated with a significantly greater improvement in erectile function domain scores than placebo at 12,^[32,43] but not 26,^[32] weeks (table IV). The proportion of patients re-

Table IV. Efficacy of vardenafil (VAR) in men with mild to severe erectile dysfunction (ED). Results of randomised, double-blind, fixed-dose, multicentre studies^a

Reference	ED aetiology (organic/ psychogenic/ mixed; %)	Treatment (mg)	No. of patients (ITT population) ^g	Mean IIEF EF domain score (LOCF analysis)			Mean Q3 score ^b (LOCF analysis)		Mean Q4 score ^c (LOCF analysis)		SEP-2 success rate ^d (% of patients)			SEP-3 success rate ^e (% of patients)			GAQ (% of patients) ^f	
				score (LOCF analysis)			score (LOCF analysis)		score (LOCF analysis)		score (LOCF analysis)			score (LOCF analysis)			score (LOCF analysis)	
				BL	wk12 ^h	wk26	BL	wk12 ⁱ	BL	wk12 ^j	BL	wk12 ^j	wk26	BL	wk12 ^j	wk26	BL	wk12 ^j
Hellstrom et al. ^[32]	61/7/33	VAR 5	190	12.5	18.4**	17.8					42.8	65.5**	65.9**	14.0	50.6**	51.7**	64.5*	64.9* (55.9**k)
	59/7/34	VAR 10	196	13.4	20.6**	21.2**					45.4	75.5**	75.6**	14.6	64.5**	64.7**	72.9*	79.8* (76.5**k)
	60/7/33	VAR 20	186	12.8	21.4**	21.8**					40.9	80.5**	81.1**	14.7	64.5**	66.7**	80.9*	85.2* (80.7**k)
	54/9/37	PL	177	13.6	15.0	14.8					46.0	51.7	51.9	14.9	32.2	32.7	38.6	27.6 (22.9 ^k)
Porst et al. ^[43]	32/28/40	VAR 5	146	14.2	20.9*		2.5	3.7*	2.1	3.5*							66*	
	30/25/45	VAR 10	140	14.1	22.1*		2.6	3.9*	2.1	3.6*							76*	
	27/25/48	VAR 20	147	13.8	22.8*		2.5	4.0*	2.1	3.8*							80*	
	34/30/36	PL	147	14.0	15.6		2.5	2.7	2.0	2.5							30	

a The studies were of 12^[43] or 26^[32] weeks' duration.

b Q3: 'When you attempted sexual intercourse how often were you able to penetrate your partner?' Graded from 1 (almost never/never) to 5 (almost always/always).

c Q4: 'During sexual intercourse how often were you able to maintain your erection after you have penetrated your partner?' Graded from 1 (almost never/never) to 5 (almost always/always).

d Percentage of patients responding 'yes' to the question 'Were you able to insert your penis into your partner's vagina?' Endpoint value is the mean for all attempts over 12 or 24wk.

e Percentage of patients responding 'yes' to the question 'Did your erection last long enough for you to have successful intercourse?' Endpoint value is the mean for all attempts over 12 or 24wk.

f Percentage of patients responding 'yes' to the question 'Has the treatment you have been taking over the past 4wk improved your erections?'. Assessed using logistic regression analysis. Among VAR 5mg, VAR 10mg, VAR 20mg and PL recipients, 155, 169, 153 and 111 patients were evaluable at wk12 and 128, 148, 140 and 91 were evaluable at wk24 in Hellstrom et al.^[32] and 140, 129, 138 and 134 were evaluable at wk12 in Porst et al.^[43] (completers analysis).

g The no. of evaluable patients varied for each endpoint.

h Primary endpoint in Hellstrom et al.^[32] secondary endpoint in Porst et al.^[43]

i Primary endpoint in Porst et al.^[43]

j Primary endpoint in Hellstrom et al.^[32]

k LOCF analysis.

BL = baseline; **EF** = erectile function; **GAQ** = Global Assessment Question; **IIEF** = International Index of Erectile Function; **ITT** = intent-to-treat; **LOCF** = last observation carried forward; **PL** = placebo; **SEP** = Sexual Encounter Profile; * p < 0.001, ** p < 0.0001 vs PL.

sponding 'yes' to questions SEP-2 and SEP-3 was significantly greater with vardenafil 5–20mg than with placebo (table IV).^[32] The improvement from baseline in both Q3 and Q4 was significantly greater with vardenafil 5–20mg than with placebo (table IV).^[43]

In addition to the erectile function domain (table IV), improvements in scores for other IIEF domains were significantly greater with vardenafil 5–20mg than with placebo in the 12-week study (figure 2).^[43] In the 26-week study, significantly greater improvement in the IIEF intercourse satisfaction domain score occurred with vardenafil 5–20mg (from 6.8 at baseline to 8.9–10.3 at 26 weeks) than with placebo (from 6.7 to 7.7) [$p < 0.01$].^[51] The improvement in the IIEF orgasmic function domain score was significantly greater with vardenafil 10 or 20mg (from 5.0 at baseline to 7.1 and 6.9 at 26 weeks) than with placebo (from 4.8 to 5.3) [$p < 0.01$].^[51]

Improvements in satisfaction with erection hardness, satisfaction with the sexual experience and the ability to ejaculate were also significantly greater with vardenafil 5–20mg than with placebo in the 26-week study (figure 3).^[51]

The proportion of patients with a positive response to GAQ was significantly higher with vardenafil 5–20mg than with placebo after 12^[32,43] and 26^[32] weeks' therapy (table IV). With regards to health-related quality of life (assessed using the Fugl-Meyer questionnaire), improvements from baseline in mean scores for the question relating to sex life satisfaction were significantly greater with vardenafil 5, 10 and 20mg than with placebo (+1.1, +1.5 and +1.7 vs +0.5 points; $p < 0.001$).^[43]

A dose-response was seen for improvement in the erectile function domain score. Scores improved by a significantly greater extent with vardenafil 10mg ($p < 0.01$)^[32] or 20mg ($p < 0.05$)^[32,43] versus vardenafil 5mg at week 12. This superiority was maintained at week 26 ($p < 0.0001$).^[32] A dose-response also occurred for other IIEF domains besides erectile function^[43] and for GAQ.^[32,43]

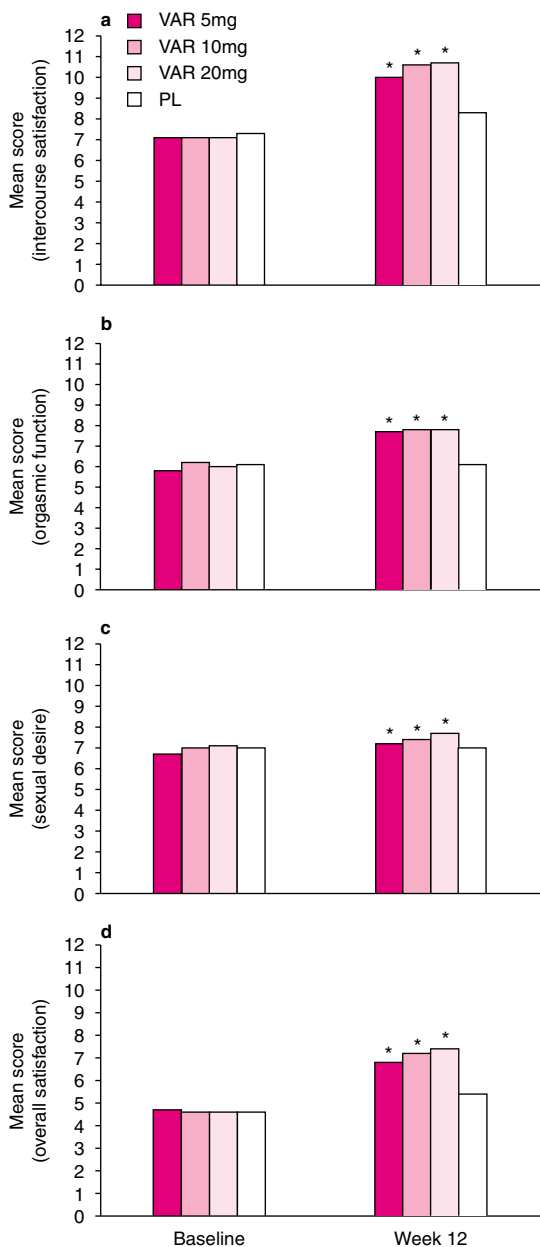


Fig. 2. Efficacy of vardenafil (VAR) in men with erectile dysfunction. Baseline and 12wk IIEF mean domain scores for (a) intercourse satisfaction, (b) orgasmic function, (c) sexual desire and (d) overall satisfaction (erectile function domain scores are reported in table IV). Patients were randomised to receive VAR 5, 10 or 20mg or placebo (PL) to be taken on an as-needed basis (not more than once daily) for 12 weeks.^[43] There were 140–147 patients in each treatment group (intent-to-treat population). IIEF = International Index of Erectile Function; * $p < 0.001$ vs PL.

An additional analysis^[66] of the 26-week study^[32] showed significantly ($p < 0.05$) greater improvements in the erectile function domain score and in response rates for questions SEP-2 and SEP-3 in vardenafil 5–20mg recipients versus placebo recipients as early as 4 weeks after the start of the study. Moreover, two post-hoc analyses of study data showed numerically higher response rates with vardenafil than with placebo for both first and subsequent attempts at sexual intercourse (statistical analysis not reported).^[60,64] Both analyses evaluated SEP-2 and SEP-3 success rates and overall satisfaction with the sexual experience for the first and subsequent attempts at intercourse up to week 12.

Subgroup analysis of the 12-week study^[43] revealed that vardenafil was effective regardless of the aetiology of ED or the baseline severity of ED.^[67] Final IIEF erectile function domain scores were significantly ($p < 0.01$) higher in vardenafil than in placebo recipients regardless of whether patients had organic, psychogenic or mixed ED and regardless of whether they had mild, moderate or severe ED at baseline.^[67] Among men with mild ED at baseline in the 26-week study, normal erectile function was achieved in 63.6–88.9% of vardenafil 5–20mg recipients and 21.4% of placebo recipients.^[32] Corresponding results were 44–54.9% and 16.7% in men with mild to moderate ED at baseline, 36.6–50.8% and 17.2% in men with moderate ED at baseline and 14.3–39.5% and 4% in men with severe ED at baseline (statistical analysis not reported).

In a 52-week study,^[44] patients ($n = 1000$) had a mean IIEF erectile function domain score of 13.0 at baseline and, after 52 weeks' therapy, 22.6 in vardenafil 10mg recipients and 23.9 in vardenafil 20mg recipients (statistical analysis not reported).^[44] 566 men subsequently continued treatment for another 52 weeks.^[63] At week 104, the erectile function domain score was 24.7 in vardenafil 10mg recipients and 25.7 in vardenafil 20mg recipients (statistical analysis not reported). In the corresponding treatment groups, positive responses to SEP-2 occurred in 92.0% and 94.2% (47.7% and 43.4% at

baseline), positive responses to SEP-3 occurred in 86.5% and 89.3% (15.9% and 17.4% at baseline) and positive responses to GAQ occurred in 90% and 92%.^[63]

The beneficial effects of vardenafil in men with ED were also observed in two noncomparative studies ($n = 160$ ^[46] and 494^[45]). With vardenafil 20mg, erectile function domain scores improved from 14.8^[46] and 13.5^[45] points at baseline to 24.0 points at 1 month,^[45] 25.5^[46] or 25.1^[45] points at 3 months and 25.5 points at 6 months.^[45] Moreover, the success rate with regards to the ability of patients to maintain an erection sufficient to complete intercourse was 17.3%^[46] and 15.4%^[45] at baseline and improved to 74.9%^[45] after 1 month's treatment, 80.5%^[46] or 80.7%^[45] after 3 months' treatment, and 83.8%^[45] after 6 months' treatment. These improvements were significant ($p < 0.001$ vs baseline) in the study that reported statistical analysis.^[46] Ninety-three percent of men reported improved erections (assessed by the GAQ) at 3 months.^[46]

4.1.1 Pooled Analyses

Pooled analyses of randomised, double-blind studies in men with ED who received vardenafil 5–20mg or placebo revealed that compared with placebo, vardenafil significantly improved erectile function irrespective of whether or not patients were receiving concomitant antihypertensive therapy ($p < 0.001$),^[59] irrespective of age ($p < 0.001$),^[56] ED aetiology ($p < 0.001$)^[55] or baseline severity of ED ($p < 0.05$)^[55] and irrespective of comorbidities such as hyperlipidaemia ($p < 0.01$) and diabetes mellitus ($p < 0.01$).^[57]

Another pooled analysis demonstrated that when analysed according to the baseline severity of ED, significantly more vardenafil 5–20mg than placebo recipients achieved normal erectile function (all $p < 0.05$), regardless of severity.^[54] Among recipients of vardenafil 5–20mg, normal erectile function was achieved in 61.9–70.6% of patients with mild ED at baseline, 39.3–50.6% of patients with mild to moderate ED at baseline, 37.8–46.7% of patients with moderate ED at baseline and 15.8–39.1% of patients

with severe ED at baseline. Normal erectile function was achieved in 24.0%, 13.9%, 14.7% and 2.5% of placebo recipients in the corresponding patient groups.

4.1.2 Flexible-Dose Studies

In two 12-week flexible-dose studies, patients were initially randomised to receive vardenafil 10mg or placebo on an as-needed basis; at 4 and 8 weeks, the vardenafil dose could be adjusted up to 20mg or down to 5mg.^[47,48] One of these studies was conducted in patients with moderate to severe ED who had not responded to prior sildenafil therapy.^[48]

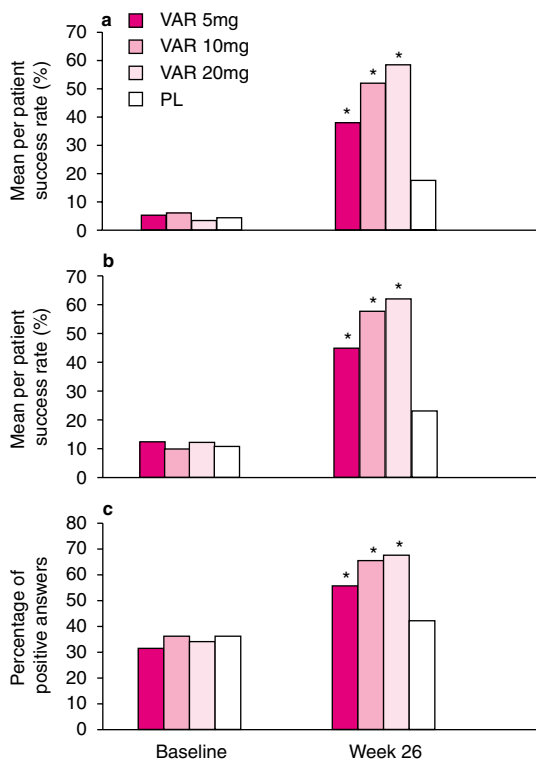


Fig. 3. Efficacy of vardenafil (VAR) in men with erectile dysfunction. Improvement in (a) patient satisfaction with erection hardness, (b) patient satisfaction with sexual experience and (c) the ability to ejaculate after 26 weeks' treatment. Patients in this double-blind study were randomised to receive VAR 5, 10 or 20mg or placebo (PL) to be taken on an as-needed basis (not more than once daily).^[51] There were 170–195 patients in each treatment group (intent-to-treat population). * $p < 0.01$ vs PL.

At week 12, the improvement from baseline in the IIEF erectile function domain score was significantly ($p < 0.01$) greater with vardenafil (all doses; from 12.6 at baseline to 22.9^[47] and from 9.3 to 17.6^[48]) than with placebo (from 13.1 to 14.4^[47] and from 9.7 to 10.5^[48]) in both studies (LOCF analysis). Vardenafil compared with placebo recipients had significantly ($p < 0.001$) greater improvements in response rates to SEP-2 (from 28.5% at baseline to 62.3% vs from 31.7% to 29.9%) and SEP-3 (from 10.1% to 46.1% vs from 11.6% to 16.1%) and significantly ($p < 0.001$) greater GAQ responses (61.8% vs 14.7%).^[48]

Patients who increased their vardenafil dose from 10 to 20mg had an increase in the GAQ response rate (figure 4).^[47] A GAQ response occurred in 92–100% of patients who received vardenafil 10mg throughout the study (figure 4). The final vardenafil dose was 5, 10 and 20mg in 3%, 28% and 68% of patients randomised to this treatment arm.

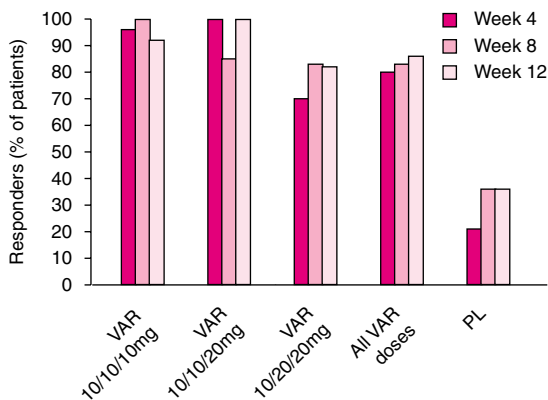


Fig. 4. Results of a flexible-dose study in men with erectile dysfunction. Percentage of patients with a positive response to the Global Assessment Question: 'Has the treatment you have taken over the past 4 weeks improved your erections?' Patients were randomised to receive vardenafil (VAR) 10mg or placebo (PL) for 12 weeks.^[47] At weeks 4 and 8, the VAR dose could be increased to 20mg or decreased to 5mg. Results of patients receiving VAR 10mg throughout (VAR 10/10/10mg; $n = 26$ at the start of the study), VAR 10mg at weeks 4 and 8 and 20mg at week 12 (VAR 10/10/20mg; $n = 19$) and VAR 10mg at week 4 and 20mg at weeks 8 and 12 (VAR 10/20/20mg; $n = 81$) are shown, as well as results pertaining to patients receiving VAR (any dose; $n = 150$) or PL ($n = 148$).

4.2 In Erectile Dysfunction Associated with Diabetes Mellitus

ED is a common complication of diabetes mellitus;^[33] the prevalence of ED is >3-fold higher in men with diabetes mellitus than in men without diabetes mellitus.^[68] Men with ED who also have diabetes mellitus are generally regarded as difficult to treat.^[33]

Vardenafil improved erectile function in men with ED associated with diabetes mellitus. The improvement from baseline in the erectile function domain score of the IIEF and the proportion of patients responding 'yes' to SEP-2 and SEP-3 questions (primary endpoints) was significantly greater with vardenafil 10 or 20mg than with placebo (table V).^[33] Similarly, a significantly greater proportion of vardenafil 10 or 20mg recipients than placebo recipients responded 'yes' to the GAQ (secondary endpoint; completers analysis) [table V]. According to LOCF analysis, GAQ responses occurred in 54%, 70% and 13% of vardenafil 10 or 20mg or placebo recipients.^[33] A significant dose-response relationship was observed for the improvement in erectile function domain scores ($p = 0.03$) and the GAQ response ($p \leq 0.02$), but not for the improvement in SEP-2 or -3 success rates [table V].

Compared with placebo, vardenafil 10 or 20mg was also associated with significantly ($p < 0.001$) greater improvements from baseline in the IIEF domain scores for intercourse satisfaction (endpoint scores: 6.6 vs 8.4 and 9.2) and orgasmic function (endpoint scores: 5.3 vs 6.4 and 6.9) [baseline values not reported].^[62] Moreover, significantly ($p < 0.001$) more vardenafil 10 or 20mg than placebo recipients reported satisfaction with erection hardness (34.9% and 44.9% vs 12.0%) or sexual experience (41.8% and 54.0% vs 18.8%) and the ability to ejaculate (55.9% and 63.5% vs 36.3%) [baseline values not reported].

Further analysis revealed that vardenafil improved patient satisfaction with erection hardness and the sexual experience, irrespective of glycaemic control at baseline.^[65] For example, in patients with

a glycosylated haemoglobin level of >8% at baseline, a significantly ($p < 0.0001$) greater proportion of vardenafil 10 and 20mg recipients than placebo recipients reported satisfaction with erection hardness (30.8% and 42.6% vs 9.5%).

Following completion of this study, 340 men continued in a 3-month extension study in which placebo recipients switched to receive vardenafil 10 or 20mg.^[61] 328 men were evaluable for efficacy (results available as an abstract). Erectile function domain scores improved by 6.8 and 8.3 points in men who had received vardenafil 10 or 20mg for the entire 6 months. In patients initially randomised to placebo who switched to vardenafil 10 or 20mg, erectile function domain scores improved by 6.8 and 8.0 points after 3 months' therapy. Improvements were also seen in the percentage of patients able to maintain an erection during intercourse and the percentage of patients responding 'yes' to the GAQ (statistical analysis not reported) [figure 5].^[61]

4.3 In Erectile Dysfunction After Radical Prostatectomy

ED is a common occurrence following nerve-sparing radical prostatectomy.

Vardenafil improved erectile function in men with ED following unilateral or bilateral nerve-sparing radical retropubic prostatectomy.^[49] The improvement from baseline in the erectile function domain score of the IIEF and the proportion of patients responding 'yes' to SEP-2 and SEP-3 questions (primary endpoints) was significantly greater with vardenafil 10 or 20mg than with placebo (table VI).^[49] Similarly, a significantly greater proportion of vardenafil 10 or 20mg recipients than placebo recipients responded 'yes' to the GAQ (secondary endpoint) [table VI].

In addition, significantly greater improvements from baseline in scores for three other IIEF domains (intercourse satisfaction, orgasmic function and overall satisfaction) occurred with vardenafil 10 or 20mg than with placebo (figure 6).^[50]

After 12 weeks' therapy, the improvement from baseline in the proportion of patients satisfied with erection hardness was significantly greater (both $p \leq 0.002$) with vardenafil 10mg (from 1.0% to 27.9%) or 20mg (from 1.4% to 23.9%) than with placebo (from 0.1% to 7.6%).^[50]

5. Tolerability

Vardenafil was generally well tolerated in men with ED. Data in this section were obtained from four large, well designed trials of 12,^[33,43] 26^[32] or 104^[63] weeks' duration (439–762 men with ED evaluable for safety; see section 4 for further study details), a pooled analysis of five randomised, double-blind trials (2605 men with ED evaluable for safety) available as an abstract^[34] and the prescribing information for vardenafil.^[27]

Treatment-emergent adverse events were generally of mild to moderate intensity and transient in nature.^[33] Across three trials of 12 or 26 weeks' duration, the most commonly reported adverse events (typical of those seen with oral PDE5 inhibitors) in vardenafil 5, 10 and 20mg and placebo recipients included headache (6.8–10%, 8.5–22%, 15.3–21% and 3.9–7%), flushing (5–10.2%,

9–11.3%, 10–13% and <1%) and rhinitis (4.8–9%, 2.8–14%, 7.3–17% and 3.3–5%).^[32,33,43] These were also the most commonly reported adverse events among vardenafil 10 and 20mg recipients in a 104-week study (headache in 19% and 21%, flushing in 14% and 21% and rhinitis in 18% and 21%).^[63]

Dyspepsia and sinusitis were also reported; the incidence of dyspepsia was 0.7–6.7% in vardenafil 5–20mg recipients and <1% in placebo recipients^[32,43] and the incidence of sinusitis was 1–6% in vardenafil 5–20mg recipients and $\leq 1\%$ in placebo recipients.^[32,33] Statistical analyses were not reported in these studies.^[32,33,43]

Serious adverse events occurred infrequently and were reported in 1–5% of vardenafil 5–20mg recipients and in 3–5% of placebo recipients.^[32,33,43] In the 104 week trial, serious adverse events occurred in 11% of vardenafil 10mg recipients and in 13% of vardenafil 20mg recipients; only one of these (blurred vision) was considered to be drug related. Adverse events resulting in treatment discontinuation occurred in 1–5% of vardenafil 5–20mg recipients and in 1% of placebo recipients.^[33,43] Treatment discontinuation due to adverse events occurred in

Table V. Efficacy of vardenafil (VAR) in men with erectile dysfunction associated with diabetes mellitus. Results of a randomised, double-blind, fixed-dose, multicentre, 3mo study^[33]

Treatment (mg)	No. of patients (ITT population) ^e	Mean IIEF EF domain score (LOCF analysis) ^a		SEP-2 success rate ^{a,b} (% of patients)		SEP-3 success rate ^{a,c} (% of patients)		GAQ (% of patients) ^d
		baseline	endpoint	baseline	endpoint	baseline	endpoint	
VAR 10	149	11.2	17.1*	30 ^f	61*	10 ^f	49*	57*
VAR 20	141	12.2	19.0*†	39 ^f	64*	15 ^f	54*	72*†
PL	140	11.2	12.6	32 ^f	36	12 ^f	23	13

a Primary endpoint.

b Percentage of patients responding 'yes' to the question 'Were you able to insert your penis into your partner's vagina?' Endpoint value is the mean for all attempts over the 12wk treatment period.

c Percentage of patients responding 'yes' to the question 'Did your erection last long enough for you to have successful intercourse?' Endpoint value is the mean for all attempts over the 12wk treatment period.

d Percentage of patients responding 'yes' to the question 'Has the treatment you have been taking over the past 4wk improved your erections?' GAQ was assessed in patients completing 12wk treatment using logistic regression analysis (137, 131 and 133 recipients of VAR 10mg, VAR 20mg and PL completed treatment, respectively). Secondary endpoint.

e The no. of evaluable patients varied for each endpoint.

f Estimated from graph.

EF = erectile function; **GAQ** = Global Assessment Question; **IIEF** = International Index of Erectile Function; **LOCF** = last observation carried forward; **PL** = placebo; **SEP** = Sexual Encounter Profile; * $p < 0.0001$ vs PL; † $p < 0.03$ vs VAR 10mg.

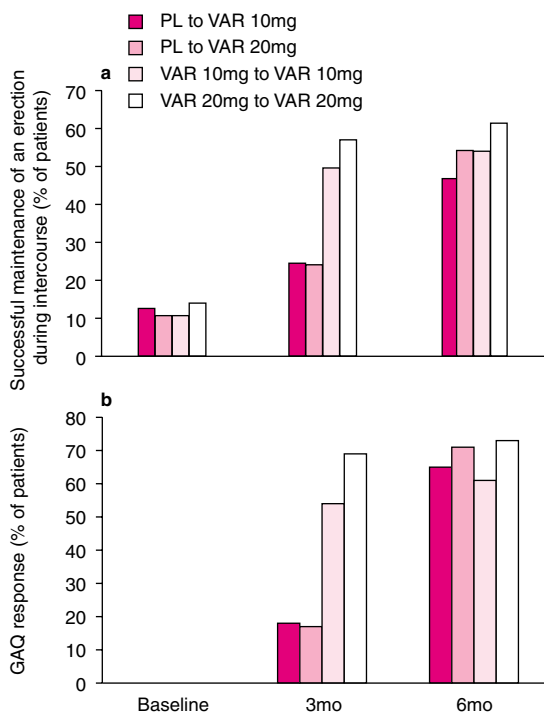


Fig. 5. Efficacy of vardenafil (VAR) in men with erectile dysfunction associated with diabetes mellitus. The (a) mean rate of successful maintenance of an erection during intercourse and the (b) percentage of patients responding 'yes' to the GAQ ('Has the treatment you have taken over the past 4wk improved your erections?'). Results of a 3mo extension study^[61] in patients previously randomised to receive VAR 10 or 20mg or placebo (PL).^[33] In the extension study, PL recipients were switched to VAR 10 or 20mg and other patients continued their previously assigned therapy for an additional 3mo (46–114 patients in each treatment group were evaluable for endpoint [a] and 31–79 were evaluable for endpoint [b]). Statistical analysis was not reported. **GAQ** = Global Assessment Question.

1–2% of vardenafil recipients in the 104-week study.^[63]

Small decreases in mean BP occurred with vardenafil (see section 2.4).^[32–34] Clinically significant ECG abnormalities (sinus bradycardia, first-degree atrioventricular block and abnormalities in ST and/or T waves) were reported with vardenafil 10mg (n = 1), vardenafil 20mg (n = 2) and placebo (n = 1).^[33] In the pooled analysis, ECG abnormalities, oedema, syncope, angina pectoris, hypotension and myocardial ischaemia occurred with an incidence of 0% to <0.6% and were not dose related.^[34] Myocardial infarction occurred in one vardenafil

and one placebo recipient. Another placebo recipient experienced a cerebrovascular accident and a third required cardiovascular surgery.^[34]

There were no reports of abnormal colour vision in vardenafil 5–20mg recipients.^[33,43] Transient vision changes such as mild haziness or an increase in the perceived brightness of light were reported infrequently^[33,43] (incidence of 1% in vardenafil and placebo recipients combined in one study^[43]). Some patients who received vardenafil 40mg in a study examining visual function had impaired colour discrimination in the blue/green and purple ranges 1 hour after drug administration.^[27] However, these changes were mild and transient (changes were no longer present at 24 hours) and most patients did not report subjective visual symptoms.

Sporadic laboratory abnormalities were detected during vardenafil therapy; however, no clear pattern emerged and there did not appear to be a relationship between vardenafil therapy and the occurrence of any laboratory abnormality.^[32]

6. Dosage and Administration

Vardenafil is approved in the the US^[28] and the EU^[27] for the treatment of ED. In adult men, the recommended dose of vardenafil is 10mg; the recommended dose may be increased to 20mg (maximum recommended dose) or decreased to 5mg according to efficacy and tolerability.^[27,28] Vardenafil should be administered orally ≈60 minutes (according to US prescribing information)^[28] or ≈25–60 minutes (according to EU prescribing information)^[27] before sexual activity; sexual stimulation is necessary for the drug to be effective. It is recommended that vardenafil not be taken more than once daily.^[27,28] Vardenafil may be taken with or without food, although the onset of action of the drug may be delayed if it is taken with a high-fat meal (section 3.1).^[27]

A starting dose of vardenafil 5mg should be used in elderly men (aged ≥65 years^[27,28]), as clearance is reduced in this population (section 3.3). No dose adjustment is needed in men with mild to moderate

Table VI. Efficacy of vardenafil (VAR) in men with erectile dysfunction after radical prostatectomy. Results of a randomised, double-blind, fixed-dose, multicentre, 3mo study (available as an abstract and poster)^[49]

Treatment (mg)	No. of randomised patients ^e	Mean IIEF EF domain score (LOCF analysis) ^a		SEP-2 success rate ^{ab} (% of patients)		SEP-3 success rate ^{ac} (% of patients)		GAQ (% of patients) ^d
		baseline	endpoint	baseline	endpoint	baseline	endpoint	
VAR 10	148	9.3	15.3*	21.0	46.6*	6.6	37.2*	59.4*
VAR 20	149	9.2	15.3*	18.3	47.5*	7.0	34.2*	65.2*
PL	145	9.1	9.2	14.2	21.8	6.0	9.9	12.5

a Primary endpoint.

b Percentage of patients responding 'yes' to the question 'Were you able to insert your penis into your partner's vagina?' Endpoint value is the mean for all attempts over the 12wk treatment period.

c Percentage of patients responding 'yes' to the question 'Did your erection last long enough for you to have successful intercourse?' Endpoint value is the mean for all attempts over the 12wk treatment period.

d Percentage of patients responding 'yes' to the question 'Has the treatment you have been taking over the past 4wk improved your erections?' GAQ was assessed in patients completing 12wk treatment using logistic regression analysis (114, 118 and 98 recipients of VAR 10mg, VAR 20mg and PL completed treatment, respectively). Secondary endpoint.

e The no. of evaluable patients varied for each endpoint.

EF = erectile function; GAQ = Global Assessment Question; IIEF = International Index of Erectile Function; LOCF = last observation carried forward; PL = placebo; SEP = Sexual Encounter Profile; * $p < 0.0001$ vs PL.

renal impairment.^[27,28] EU prescribing information states that a starting dose of 5mg should be considered in men with mild to moderate hepatic impairment (Child-Pugh A–B) and in men with severe renal impairment (CLCR <1.8 L/h [<30 mL/min]) [section 3.3].^[27] US prescribing information states that no dose adjustment is needed in patients with mild hepatic impairment (Child-Pugh A) or severe renal impairment, although a starting dose of 5mg is recommended in moderate hepatic impairment (Child-Pugh B), with a maximum dose of 10mg (section 3.3).^[28]

Vardenafil is not indicated for use in women or in individuals aged <18 years.^[27]

Due to a lack of data, vardenafil is contraindicated in the EU^[27] and not recommended in the US^[28] in men with severe hepatic impairment (Child-Pugh C); end-stage renal failure needing dialysis; hypotension; a recent history of stroke or myocardial infarction; unstable angina pectoris; or known hereditary degenerative disorders of the retina (e.g. retinitis pigmentosa). In the US, the use of vardenafil is also not recommended in patients with uncontrolled hypertension, a recent history of life-threatening arrhythmia or severe heart failure.^[28] Drugs such as vardenafil should generally not be

used in the treatment of men with ED for whom sexual activity is inadvisable (e.g. men with severe cardiovascular disease such as unstable angina pectoris or New York Heart Association class III–IV heart failure).^[27,28]

Vardenafil should be used with caution in men who have anatomical deformation of the penis or a condition that may predispose them to priapism.^[27,28] Vardenafil should only be administered to men with bleeding disorders or active peptic ulcer disease after careful risk-benefit assessment (high concentrations of vardenafil potentiated the antiaggregatory effects of SNP in *in vitro* studies).^[27,28] The use of vardenafil should be avoided in patients with a history of congenital or acquired QT prolongation.^[28]

Concomitant administration of vardenafil and nitrates or nitric oxide donors is contraindicated.^[27,28] Moreover, in the EU, coadministration of vardenafil and potent CYP3A4 inhibitors such as ritonavir, indinavir, oral ketoconazole or oral itraconazole is contraindicated in men aged >75 years and should be avoided in younger men (section 3.4).^[27] In the US, it is recommended that the dose of vardenafil should not exceed 2.5mg once daily in patients receiving concomitant indinavir, ketoconazole 400

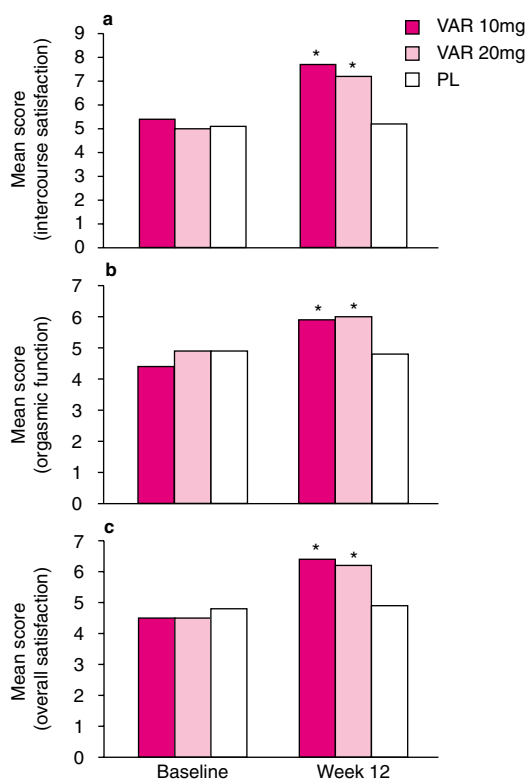


Fig. 6. Efficacy of vardenafil (VAR) in men with erectile dysfunction following nerve-sparing radical prostatectomy. Baseline and 12wk IIEF mean domain scores for (a) intercourse satisfaction, (b) orgasmic function and (c) overall satisfaction. Patients were randomised to receive VAR 10 or 20mg or placebo (PL) to be taken on an as-needed basis (not more than once daily) for 12 weeks.^[50] There were 132–145 patients in each treatment group (intent-to-treat population). IIEF = International Index of Erectile Function; * $p \leq 0.002$ vs PL.

mg/day or itraconazole 400 mg/day, and that ritonavir recipients should receive no more than one dose of vardenafil 2.5mg within a 72-hour period.^[28] The vardenafil dose should not exceed 5mg once daily in patients receiving ketoconazole 200 mg/day or itraconazole 200 mg/day.^[28] Coadministration of vardenafil and grapefruit juice (which weakly inhibits CYP3A4 gut wall metabolism) should be avoided as it may result in increased plasma vardenafil concentrations, and the vardenafil dose should not exceed 5mg when it is coadministered with the CYP3A4 inhibitor erythromycin (section 3.4).^[27] Concomitant therapy with vardenafil and α -blockers

is not recommended in the EU^[27] and is contraindicated in the US (section 2.4.1).^[28]

7. Place of Vardenafil in the Management of Erectile Dysfunction

ED is a common medical disorder; in the Massachusetts Male Aging Study (conducted between 1987 and 1989), 52% of men aged 40–70 years reported ED.^[69] ED often has a negative effect on a patient's quality of life, particularly in terms of personal well being and family and social relationships.^[53]

Given that ED may be the presenting symptom of an underlying disease (e.g. diabetes mellitus, coronary artery disease, spinal cord compression), a detailed history should be taken and a physical examination and appropriate laboratory investigations (e.g. testosterone, blood glucose and lipid levels) performed in order to identify any underlying cause.^[1,3,5,7,70] It may emerge that the patient would benefit from psychosexual therapy, that lifestyle modifications (e.g. stopping smoking, reducing alcohol intake, exercising, losing weight) are needed or that the patient is receiving a drug known to be associated with ED (e.g. β -blockers, selective serotonin reuptake inhibitors, carbamazepine, risperidone, gemfibrozil, clofibrate, phenytoin, levodopa, phenothiazine antipsychotics, antihistamines and antiemetics).^[3,5,7]

Oral therapy (e.g. a PDE5 inhibitor or sublingual apomorphine [a dopaminergic agonist]) is recommended as first-line pharmacological treatment for ED.^[5,7,70,71] If oral therapy is not associated with satisfactory results, second-line options include transurethral therapy (e.g. alprostadil [synthetic prostaglandin E1]), intracavernous therapy (e.g. alprostadil or a mixture of papaverine [a nonspecific phosphodiesterase inhibitor], phentolamine [an α -adrenergic antagonist] and/or alprostadil) or the use of vacuum constriction devices.^[7,71] Penile implants remain an option for men who are not satisfied with medical treatment, and vascular surgery is an option in young men with congenital or traumatic ED.^[7,71]

With regards to second-line therapy, intraurethral and intracavernosal alprostadil (alone or in combination with papaverine and phentolamine) are suitable for use in a wide range of patients and have proven efficacy in ED;^[3,7] intracavernosal and intraurethral alprostadil are reported to be effective in ≈ 60 – 85% and ≈ 30 – 50% of men, respectively (reviewed by Costabile^[72]). In addition, both therapies have a rapid onset of action (sexual stimulation is not needed for these drugs to take effect) and few systemic effects.^[3,7] Despite these positive features, long-term continuation rates with these therapies are low.^[73,74] A disadvantage of both intraurethral and intracavernosal therapies is that patients need to have good manual dexterity and good eyesight in order to self-administer them correctly.^[3] In addition, adverse effects associated with both routes of administration include discomfort and penile pain; intracavernosal therapy is also associated with penile fibrosis and priapism.^[70,72,73] Vacuum devices have a number of beneficial features in that they are suitable for long-term use in a wide range of patients and are associated with a low incidence of adverse events.^[3] However, some patients find such devices inconvenient and awkward to use, as well as being associated with a lack of spontaneity and partner nonacceptance.^[3,73]

PDE5 inhibitors and sublingual apomorphine are the oral therapies recommended for first-line use in ED (although apomorphine is currently only available in Europe). As with the oral PDE5 inhibitors, sexual stimulation is needed for apomorphine to produce an erection.^[10] Response rates (percentage of intercourse attempts resulting in an erection firm enough for sexual intercourse) were $\approx 46\%$ with apomorphine 2 and 3mg (reviewed by Altwein and Keuler).^[75] The most commonly occurring adverse events associated with apomorphine were nausea, dizziness and yawning.^[75] Apomorphine is infrequently associated with a transient vasovagal syndrome (incidence of $<0.2\%$).^[76]

Vardenafil, sildenafil and tadalafil are the three oral PDE5 inhibitors currently available for use in

ED. Sildenafil was the first PDE5 inhibitor to be approved and is widely available. The newer PDE5 inhibitors vardenafil and tadalafil are both available in the EU, although only vardenafil is currently approved in the US. An obvious advantage of these agents is that compared with many other ED treatment options, oral PDE5 inhibitors are noninvasive.^[3]

Vardenafil is a potent and highly selective PDE5 inhibitor and has excellent efficacy in men with mild to severe ED of varying aetiology. Compared with placebo, vardenafil significantly improved erectile function domain scores and responses to questions concerning penetration and the ability to maintain an erection in 12- and 26-week studies (section 4.1).^[32,43] In addition, 73–85% of vardenafil 10 or 20mg recipients reported improvement in their erections (GAQ) [section 4.1].^[32,43] Early results of a 104-week analysis show that the efficacy of vardenafil is maintained in the longer term (section 4.1).^[63] Men with ED associated with diabetes mellitus or ED after radical prostatectomy have historically been considered difficult to treat. Vardenafil demonstrated efficacy in both these populations, with significantly greater improvements in erectile function domain scores and responses to SEP-2 and SEP-3 questions in vardenafil 10 or 20mg recipients versus placebo recipients, as well as 57–72% of vardenafil recipients reporting an improvement in their erections (GAQ) [sections 4.2 and 4.3].^[33,49] It should be noted that these studies excluded patients who had not responded to prior sildenafil therapy^[32,43,49] or who had discontinued sildenafil because of a lack of response or adverse effects.^[33,49] Thus, results of these studies may not be representative of those obtained in the general population. However, vardenafil was also more effective than placebo in a study conducted in patients with moderate to severe ED who had an inadequate response to prior sildenafil therapy (section 4.1.2).^[48]

Vardenafil was generally well tolerated in 12- or 26-week clinical trials; adverse events were transient and of mild to moderate intensity (section

5).^[32,33,43] The most frequently occurring adverse events were typical of those seen with PDE5 inhibitors (e.g. headache and flushing). Small decreases in BP were seen in men with ED who received vardenafil (section 2.4.3)^[32-34] and ECG abnormalities occurred infrequently (section 5).^[34] Slight increases in the corrected QT interval occurred in healthy volunteers receiving vardenafil 10 or 80mg (section 2.4.1).^[28] An FDA advisory committee report notes that to date, no clinical cardiovascular adverse effects and no cases of torsade de pointes have been reported with vardenafil use during post-marketing surveillance.^[77] It also states that no clinically important arrhythmogenic effects are likely to occur in clinical practice.^[77] Abnormalities of colour vision have been reported with sildenafil use.^[78] There were no reports of abnormal colour vision in patients receiving vardenafil at clinically recommended doses, although transient vision changes (e.g. haziness) were reported infrequently (section 5).^[33,43] Transient impairment of blue/green and purple colour discrimination was reported with vardenafil 40mg (section 5).^[27] The good tolerability of vardenafil appears to be maintained in the longer term, according to the results of a 104-week analysis (section 5).^[63] although there is still a need for more data concerning the long-term tolerability of the drug.

Oral PDE5 inhibitors are not suitable for use in all patients.^[3] In particular, there has been concern over the use of oral PDE5 inhibitors in patients with cardiovascular disease. However, the authors of a recent UK consensus statement say that based on available data, sildenafil does not appear to increase cardiovascular risk and is effective in patients with ED and cardiovascular disease.^[79] They suggest that the potential for a cardiovascular event is actually associated with the reinitiation of sexual activity, hence, the risk associated with increased levels of activity should be carefully assessed in patients with ED before treatment is started.^[79] It is assumed that this advice will also apply to vardenafil and tadalafil, although data in patients with cardio-

vascular disease receiving these agents are currently limited^[79] (the results of treadmill testing showed that vardenafil did not impair the ability of men with stable coronary artery disease to exercise to a level similar to or greater than that associated with sexual intercourse [section 2.4.2]).^[29,30] In line with a lack of data, vardenafil is currently contraindicated (EU) or not recommended (US) in patients with hypotension, unstable angina pectoris or a recent history of stroke or myocardial infarction, and is not recommended for use in men with ED for whom sexual activity is inadvisable (section 6).^[27,28] In the US, additional populations in which vardenafil use is not recommended include patients with uncontrolled hypertension, a recent history of life-threatening arrhythmia or severe heart failure.^[28] It is also important to note that oral PDE5 inhibitors are contraindicated in patients with ED receiving nitrates (co-administration of sildenafil and nitrates has been associated with significant hypotension).^[27,28,79-81]

In clinical trials in men with ED, ≈60–90% of patients reported that sildenafil improved their erections (reviewed by Langtry and Markham)^[82] and ≈70–90% of patients reported that tadalafil improved their erections (reviewed by Porst).^[83] Currently, there are no data from trials directly comparing the efficacy and tolerability of vardenafil with sildenafil or tadalafil. This lack of comparative data precludes comment on the relative efficacy and tolerability of the agents. The greater *in vitro* and *in vivo* potency of vardenafil (sections 2.1 and 2.2) means that it has a lower recommended starting dose than sildenafil (10mg vs 50mg), although whether this translates into tolerability benefits remains to be seen.

There are some pharmacokinetic differences between the drugs. Tadalafil 20mg has a longer median t_{max} (2 hours) and mean $t_{1/2}$ (17.5 hours)^[81,83] than sildenafil (60 minutes and 3–5 hours)^[78,82] or vardenafil 10–20mg (0.7–0.9 hours and ≈4 hours),^[22,23] suggesting that tadalafil may have a longer time to onset of effect and a longer duration of action than vardenafil or sildenafil (60% of inter-

course attempts were successful 36 hours after tadalafil administration in one study).^[84] In men with ED being monitored with Rigiscan, the time to onset of effect with vardenafil 20 or 40mg was \approx 26 minutes (visual sexual stimulation commenced 20 minutes after drug administration; section 2.3).^[23] Data are limited concerning the duration of action of vardenafil in men with ED, although it has been suggested that the duration of effect of the drug may be much longer than its measured $t_{1/2}$ (section 2.2).^[20]

Whether certain *in vitro* properties of vardenafil translate into clinical benefits is yet to be determined. For example, it is not known if the higher *in vitro* potency of vardenafil versus tadalafil and sildenafil (section 2.1) results in greater clinical efficacy. The high selectivity of vardenafil for PDE5 over other PDE isoenzymes (section 2.1) theoretically limits the possibility of certain adverse effects (e.g. increased heart rate and vasodilation are attributed to PDE1 and PDE3 inhibition).^[26] Blue-green vision disturbances are attributed to PDE6 inhibition;^[10,26] relative to PDE5, selectivity ratios for rod PDE6 were 25 with vardenafil and 11 with sildenafil, and for cone PDE6 were 4 and 10, respectively (section 2.1).^[15] Consistent with PDE6 inhibition in rods and cones, transient impairment of blue/green colour discrimination has been reported with supratherapeutic doses of vardenafil (40mg) [section 5].^[27] Relative to PDE5, the selectivity ratio of vardenafil for PDE11A was 1160 versus 5 for tadalafil (section 2.1);^[15] the clinical significance of the relatively low PDE11A selectivity ratio associated with tadalafil is not yet known.^[11,26]

There are no data directly comparing vardenafil with other ED treatments or examining the use of vardenafil in combination with other treatments for ED (the use of vardenafil in combination with other ED therapies is not recommended).^[27] Data are also lacking in certain patient groups (e.g. men aged >75 years; patients with spinal cord injury or severe hepatic impairment, patients with ED secondary to pelvic trauma, hypoactive sexual desire or penile

anatomical deformities; and patients requiring dialysis).^[27]

In conclusion, vardenafil is a potent and highly selective oral PDE5 inhibitor. It is effective and generally well tolerated in men with mild to severe ED of varying aetiology, as well as in men with ED associated with diabetes mellitus or ED after radical prostatectomy. Vardenafil should be considered a first-line treatment option in men with ED who are suitable candidates for oral PDE5 inhibitor therapy.

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Correspondence: *Gillian M. Keating*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 1311, New Zealand.
E-mail: demail@adis.co.nz