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·Original Article·

Efficacy and tolerability of vardenafil in Asian men with erectile dysfunction

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Abstract

Aim: To evaluate the efficacy and tolerability of vardenafil, a phosphodiesterase type-5 (PDE-5) inhibitor, in men of Asian ethnicity with erectile dysfunction (ED). **Methods:** In this prospective, double-blind, multinational study, Asian men were randomized to receive vardenafil (10 mg) or placebo (4:1 ratio) for 12 weeks. The primary efficacy variables were the International Index of Erectile Function erectile function domain (IIEF-EF), and Sexual Encounter Profile (SEP) questions related to penetration and intercourse completion. Significant mean improvements were required in all three measures to show positive benefits of vardenafil treatment. Secondary efficacy variables included the Global Assessment Question (GAQ) on erection improvement. **Results:** Least-squares mean baseline IIEF-EF domain scores (vardenafil 14.6, placebo 13.4) were consistent with moderate ED. After 12 weeks, vardenafil treatment was associated with significant increases from the baseline in IIEF-EF domain scores compared with the placebo (22.4 *vs.* 14.3; $P < 0.001$). Vardenafil was associated with significant improvements from baseline in least squares (LS) mean success rates for SEP-2 (vardenafil 82.2 *vs.* placebo 43.6; $P < 0.001$) and SEP-3 (vardenafil 66.1 *vs.* placebo 24.0; $P < 0.001$). Positive GAQ responses were reported by 81.8% of vardenafil recipients *vs.* 24.3% of placebo recipients. Adverse events were reported by 25.4% of the vardenafil group, the majority mild and transient. **Conclusion:** Vardenafil (10 mg) is a highly effective and well-tolerated treatment for moderate ED in Asian men. These results add to the increasing amount of data demonstrating the safety and efficacy of vardenafil for the treatment of ED in a range of patient populations. *(Asian J Androl 2008 May; 10: 495–502)*

Keywords: Asian males; erectile dysfunction; impotence; phosphodiesterase inhibitors; sexual dysfunction; vardenafil

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1 Introduction

Erectile dysfunction (ED) is a globally prevalent condition, having detrimental effects on overall quality of life, and providing a considerable source of emotional stress for men and their partners [1–3]. The prevalence of ED is expected to rise as populations age, with the largest projected increases anticipated in Asia, Africa and South America [4, 5]. According to age-adjusted predictions made using conservative projections for population growth, the number of men worldwide with ED could increase to 322 million by 2019 [5].

Phosphodiesterase type-5 (PDE-5) inhibitors are the first-line therapeutic option in the treatment of ED. The phosphodiesterase (PDE) group of enzymes terminate cyclic nucleotide signals, and PDE-5 is by far the most active PDE involved in the termination of cyclic guanosine monophosphate (cGMP) signalling in the corpus cavernosum [6]. Inhibition of PDE-5 potentiates the biological activity of cGMP in the corpus cavernosum, increasing smooth muscle relaxation and, therefore, improving erections, in the presence of a sexual stimulus [7].

The PDE-5 inhibitor vardenafil has been introduced for the treatment of ED in various countries worldwide since 2001 [8]. It has been effective and well-tolerated in a broad range of patient populations, including those with diabetes mellitus [9, 10], hypertension [11] and ED following prostatectomy [12] or spinal cord injury [13].

The majority of previously reported clinical studies of vardenafil have involved mostly Caucasian populations [14–17]. Therefore, it is necessary to investigate the safety and efficacy of vardenafil in other ethnic groups. For example, Asian men might differ from Caucasian men with regard to the polymorphic expression of key enzymes responsible for drug metabolism [18, 19], and in particular those that contribute to the metabolism of vardenafil, such as CYP3A and CYP2C9 [18–20]. Moreover, there are differences between ethnic populations with regard to perceptions of, and attitudes towards, ED and cultural trends in medical practice [21, 22]. The study evaluated the efficacy and tolerability of vardenafil in men of Asian ethnicity with ED of broad-spectrum etiology.

2 Materials and methods

2.1 Study design

This prospective, randomized, double-blind, placebo-controlled, fixed-dose, parallel-group study, conducted between March 2003 and April 2004, assessed the safety and efficacy of vardenafil (10 mg) for the treatment of ED in Asian men. Fourteen centres in six countries participated in the study: Malaysia (4), Singapore (3), Thailand (3), the Philippines (2), Hong Kong, China (1) and Indonesia (1).

The study protocol was approved by the appropriate independent ethics committee at each site, and the study was performed in accordance with the Good Clinical Practice guidelines of the International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use, and the principles of the Declaration of Helsinki. All patients provided written informed consent.

2.2 Patients

Men aged ≥ 20 years with ED of > 6 months' duration were enrolled. Patients were required to have been in a stable heterosexual relationship for > 6 months. At least 50% of attempts to obtain, penetrate with, or maintain an erection must have failed during at least four separate attempts at intercourse during the 4-week baseline period.

The main exclusion criteria were: physiological or psychological disorders that would significantly impair erectile function; history of radical prostatectomy; retinitis pigmentosa; and uncontrolled diabetes mellitus. The following medications were contraindicated: any drugs for the treatment of ED including PDE-5 inhibitors, anticoagulants (except antiplatelet agents), androgens or antiandrogens, nitrates or nitric oxide donor medications; cytochrome P450 3A4 inhibitors; and alpha blocking agents.

2.3 Study medication

After a 4-week baseline period, patients were randomized (in a 4:1 ratio) to receive 12 weeks' treatment with vardenafil (10 mg) or placebo. The 10 mg vardenafil dose was selected as this is the recommended starting dose for the majority of patients. Patients were advised to dispense one tablet per instance of intended sexual intercourse, and to take the study medication at least 30 min before sexual intercourse, with a maximum of one dose daily. The treatment phase was followed by a 7-day observation period. Randomization codes were computer-generated at Bayer Schering Pharma AG (Leverkusen, Germany).

2.4 Efficacy variables

The primary efficacy variables used to assess erec-

tile function were: (i) the International Index of Erectile Function erectile function domain (IIEF-EF) score [23]; (ii) success rates for vaginal penetration, as assessed using the Sexual Encounter Profile question 2 (SEP-2); and (iii) success rates for maintaining penile rigidity for completion of intercourse, as assessed using the Sexual Encounter Profile question 3 (SEP-3). For the efficacy of vardenafil to be satisfactorily demonstrated, significant improvements following vardenafil treatment *vs*. placebo for all three of the primary variables, from baseline to week 12 or last observation carried forward (LOCF) were necessary.

Secondary efficacy variables included IIEF-EF domain scores, penetration success rates (SEP-2) and intercourse completion rates (SEP-3) at 4, 8 and 12 weeks or LOCF. Responses to SEP questions on the achievement of erection (SEP-1), hardness of erection (SEP-4), overall satisfaction with sexual experience (SEP-5), ejaculation (SEP-6) and the Global Assessment Question (GAQ) "Has the treatment you have been taking during the last 4 weeks improved your erections?" were also assessed at 4, 8 and 12 weeks or LOCF.

2.5 Safety assessments

Safety assessments included the reporting of adverse events, laboratory tests (haematology, clinical chemistry, urinalysis), monitoring of vital signs (heart rate and blood pressure) and 12-lead electrocardiography.

2.6 Statistical methods

Sample size estimates were based on the assumptions of Student's independent *t*-test. Assuming a standard deviation of 8.0 for the IIEF-EF domain score, a total of 338 patients were necessary to show a clinically meaningful difference of 5 points between vardenafil and placebo, with an overall power of 90 %.

The safety population included all patients who had received at least one dose of study medication and for whom post-baseline safety data were provided. All patients who received at least one dose of study medication and provided at least one measurement for all three primary efficacy variables were included in the intent to treat (ITT) population. Analysis of IIEF-EF domain scores, assessed at 4, 8 and 12 weeks, was performed using an LOCF approach. For diary questions, mean success rates over the baseline and treatment periods were averaged for all patients, and were reported as the overall mean per patient success rate. These efficacy variables were assessed using analysis of covariance, with baseline response as covariate (ANCOVA), to determine the effects of vardenafil treatment. Statistical analysis of the secondary variable GAQ was performed using logistic regression

3 Results

3.1 Patients

A total of 413 men of Asian ethnicity were screened for eligibility and 358 of these were randomized to treatment (Figure 1). Of these patients, 348 were eligible for

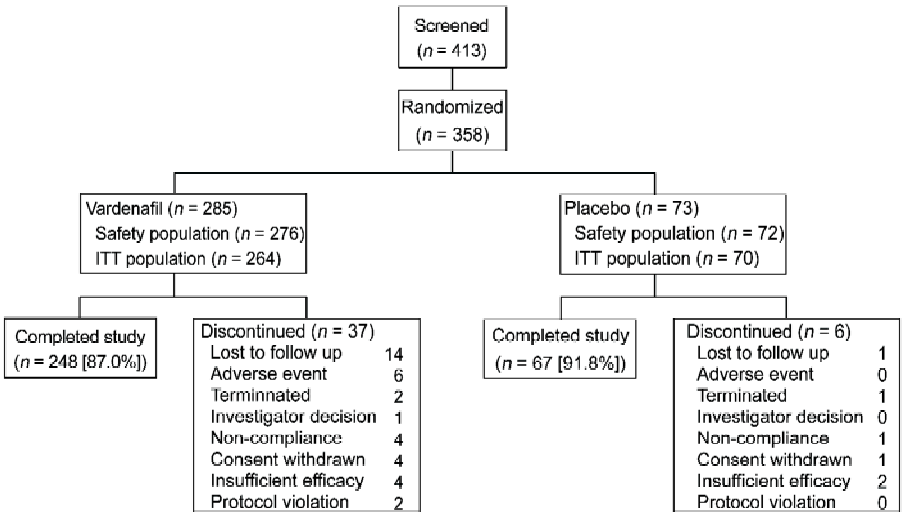

Figure 1. Patient disposition. ITT, intent-to-treat.

inclusion in the safety population (276 vardenafil, 72 placebo). The ITT population comprised 334 patients (264 vardenafil, 70 placebo), who received study medication and provided data for all three major efficacy variables. Forty three patients (12.0%) prematurely discontinued study participation during the 12-week treatment period.

Patients in the study population had a mean age of 54.6 years (range 23–78 years) and a mean weight of 72 kg. There were no relevant differences in demographic characteristics or baseline clinical variables between the two treatment groups (Table 1). The mean baseline erectile function domain scores were 14.6 and 13.4 in the vardenafil and placebo groups, respectively, consistent with a diagnosis of moderate ED (Table 2). A total of 224 patients had previously used sildenafil. The mean (SE) number of study medication doses taken per week was 2.80 (1.38) in the vardenafil group and 2.40 (1.18) in the placebo group.

3.2 Efficacy

Following 12 weeks' treatment, the LS mean

Table 1. Demographic characteristics and medical history of patients (safety population).Percentages are in parentheses. SD, standard deviation. ED, erectile dysfunction.

	Placebo	Vardenafil (10 mg)
Number of patients (%)	72 (100)	276 (100)
Mean age (years, mean ± SD)	55.4 ± 11.0	54.4 ± 10.1
Mean weight (kg, mean ± SD)	72.6 ± 15.3	71.6 ± 11.7
Mean body mass index (kg/m^2, mean ± SD)	26.3 ± 4.7	25.6 ± 3.8
Past or present smoker (%)	34 (47)	92 (33)
Medical history		
Hypertension (%)	28 (39)	98 (36)
Diabetes mellitus (%)	27 (38)	84 (30)
Aetiology of ED		
Organic (%)	44 (61)	149 (54)
Psychogenic (%)	16 (22)	58 (21)
Mixed (%)	12 (17)	69 (25)
Prior sildenafil users (%)	46 (64)	178 (64)

Table 2. Efficacy scores in Asian men with erectile dysfunction (ED) after 12 weeks' treatment with vardenafil (10 mg) or placebo (ITT population). $^*P < 0.001$ *vs.* placebo. EF, erectile function; GAQ, Global Assessment Question; IIEF, International Index of Erectile Function erectile function domain score; ITT, intent to treat; LOCF, last observation carried forward; LS, least square; SE, standard error; SEP, Sexual Encounter Profile.

	Placebo (n = 70)	Vardenafil (10 mg, n = 264)
IIEF-EF domain at week 12 (LOCF)		
LS mean baseline	13.4	14.6
LS mean (SE)	14.30 (0.78)	22.40 (0.42)*
SEP-2 (penetration) until week 12 (LOCF)		
LS mean baseline	49.0	51.5
LS mean (SE)	43.6 (3.8)	82.2 (2.0)*
SEP-3 (completion) until week 12 (LOCF)		
LS mean baseline	15.9	19.4
LS mean (SE)	24.0 (4.7)	66.1 (2.5)*
GAQ (has treatment improved your erections?) at week 12 (LOCF)		
Patients responding "yes", n (%)	17 (24.3)	216 (81.8)*

(standard error [SE]) IIEF-EF domain score in men receiving vardenafil (10 mg) was 22.40 (0.42); significantly greater than the score of 14.30 (0.78) observed in men receiving placebo ($P < 0.001$). Vardenafil treatment was also associated with significant improvements in the other two primary efficacy variables after 12 weeks' treatment ($P < 0.001$). The LS mean (SE) SEP-2 per patient success rates were 82.2 (2.0) and 43.6 (3.8) for vardenafil and the placebo, respectively. The LS mean (SE) SEP-3 per patient success rates were 66.1 (2.5) in the vardenafil group and 24.0 (4.7) in the placebo group (Table 2). For all three primary efficacy variables, clinically significant therapeutic effects had occurred by the time of the first assessment (4 weeks after the start of treatment) with small additional improvements noted after this time-point (Figures 2–4).

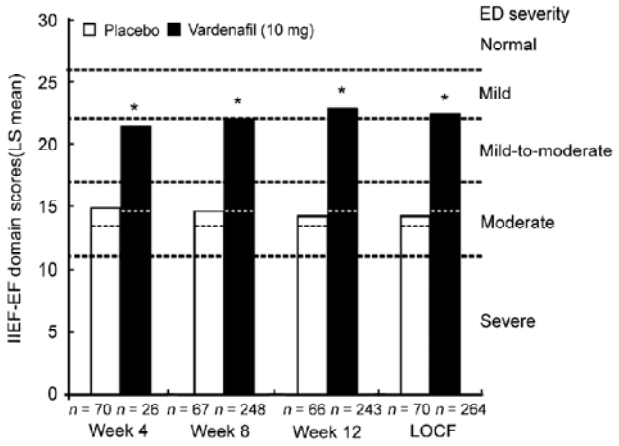

Figure 2. IIEF-EF domain scores at baseline and after 4, 8, and 12 weeks of treatment, and at LOCF with vardenafil (10 mg) or placebo (ITT population; $^{*}P < 0.001$). Dashed lines indicate baseline values at each time-point. ED, erectile dysfunction; IIEF-EF, International Index of Erectile Function erectile function domain score; ITT, intent to treat; LOCF, last observation carried forward; LS, least saquares.

Success rates for SEP-1, SEP-4, SEP-5 and SEP-6 questions at 12 weeks were all significantly improved following vardenafil treatment compared with placebo ($P < 0.001$; Table 3). After 12 weeks, a significantly greater percentage of patients responded positively to the GAQ: 81.8% for vardenafil recipients *vs.* 24.3% for placebo recipients ($P < 0.001$) (Table 2).

3.3 Safety

In total, 70 (25.4%) patients in the vardenafil group and 12 (16.7%) patients in the placebo group experienced treatment-emergent adverse events. As a result of adverse events, six patients (2.2%) discontinued the study, all of them in the study medication group. The most frequent treatment-emergent adverse events were headache, flushing, nasal congestion and dizziness (Table 4). Adverse events were slightly more frequent in the vardenafil group than in the placebo group; however, the majority were of mild intensity and were transient, resolving spontaneously by the end of the observation period.

Three patients in the vardenafil group reported serious adverse events, one of which was found to be drug-

Table 3. Efficacy scores in Asian men with erectile dysfunction (ED) following 12 weeks' treatment with vardenafil (10 mg) or placebo (ITT population). $^{*}P < 0.001$ *vs* placebo. LOCF, last observation carried forward; LS, least square; SEP, Sexual Encounter Profile; SE, standard error.

	Placebo (n = 70)	Vardenafil (10 mg, n = 264)
SEP-1 (achievement of erection) until week 12 (LOCF)		
LS mean baseline	77.5	78.1
LS mean (SE)	60.6 (3.5)	90.6 (1.9)*
SEP-4 (hardness of erection) until week 12 (LOCF)		
LS mean baseline	9.2	7.1
LS mean (SE)	12.6 (5.0)	61.4 (2.7)*
SEP-5 (satisfaction with sexual experience) until week 12 (LOCF)		
LS mean baseline	10.7	9.9
LS mean (SE)	15.2 (4.9)	62.8 (2.6)*
SEP-6 (ejaculation) until week 12 (LOCF)		
LS mean baseline	47.0	48.8
LS mean (SE)	38.6 (4.1)	7.1 (2.2)*

related. In this reported case the patient suffered moderate chest discomfort, which resolved following discontinuation of treatment.

4 Discussion

ED has substantial negative effects on a patient's quality of life [1, 3] and a considerable emotional impact on the lives of men and their partners, potentially depriving them of intimacy and diminishing their self-esteem [2, 24]. It has been predicted that the prevalence of ED in Asian countries will show greater increases in the future than non-Asian countries [4, 5]. The Asian Men's Attitudes to Life Events and Sexuality (Asian MALES) study confirms that ED is equally prevalent in Asian countries. The prevalence of ED varied by region, and across all regions it was found to increase with age. The study also found that self-reported comorbid illnesses were associated with the presence of ED, and that men with ED exhibited significantly greater dissatisfaction with all assessed aspects of quality of life. Less than half of men with self-reported ED in the Asian MALES Phase I study had sought treatment for their problem [25]. The findings of this study highlight the need to investigate the efficacy and safety of PDE-5 inhibitors in Asian populations.

In the present study, a broad population of men of Asian ethnicity were recruited from Hong Kong (China), Indonesia, the Philippines, Malaysia, Singapore and Thailand. ED was of moderate severity and mostly of organic etiology. Treatment with vardenafil (10 mg) improved ED, as demonstrated by clinically relevant and statistically significant improvements in the IIEF-EF domain score, and vaginal penetration success rates and intercourse completion rates (assessed using the SEP-2

Table 4. Treatment-emergent adverse events with an incidence ≥ 2% in any treatment group (safety population).

Adverse event (*n* [%])	Placebo (*n* = 72)	Vardenafil (10 mg) (*n* = 276)
Any adverse event	12 (16.7)	70 (25.4)
Gastrointestinal disorders	1 (1.4)	7 (2.5)
General disorders	0	6 (2.2)
Musculoskeletal disorders	0	10 (3.6)
Headache	4 (5.6)	20 (7.2)
Dizziness	2 (2.8)	6 (2.2)
Nasal congestion	1 (1.4)	9 (3.3)
Vascular disorders	2 (2.8)	4 (1.4)
Flushing	0	17 (6.2)

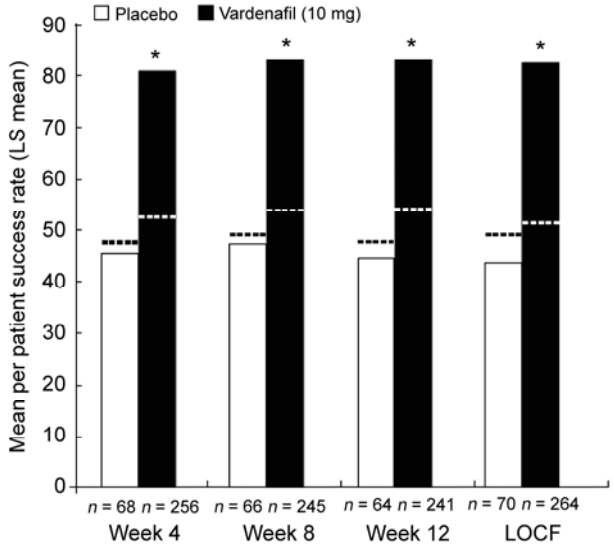

Figure 3. Mean positive response rates to the Sexual Encounter Profile (SEP)-2 question "Were you able to insert your penis in your partner's vagina?" at baseline and after 4, 8 and 12 weeks of treatment, and at LOCF with vardenafil (10 mg) or placebo (ITT population; $^{*}P < 0.001$). Dashed lines indicate baseline values at each time-point. ITT, intent to treat; LOCF, last observation carried forward; LS, least squares.

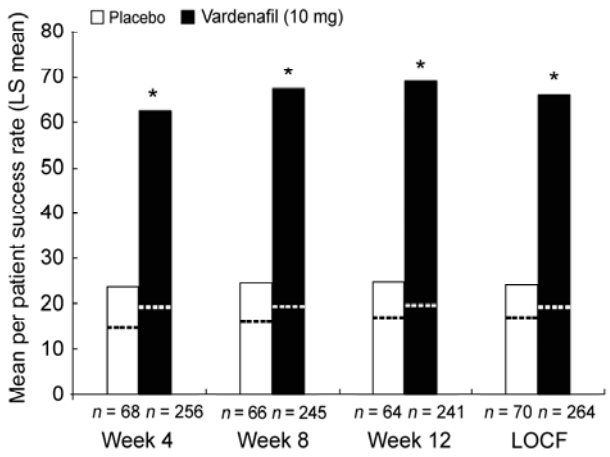

Figure 4. Mean positive response rates to the Sexual Encounter Profile (SEP)-3 question "Did your erection last long enough for you to have successful intercourse?" at baseline and after 4, 8 and 12 weeks of treatment, and at LOCF with vardenafil (10 mg) or placebo (ITT population; $*P < 0.001$). Dashed lines indicate baseline values at each time-point. ITT, intent to treat; LOCF, last observation carried forward; LS, least squares.

and SEP-3 diary questions). Early treatment effects were evident, with most of the beneficial effects of vardenafil therapy observed after 4 weeks of treatment. After 12 weeks' treatment with vardenafil, the mean IIEF-EF domain score increased from 14.7 to 22.8. This change represents an improvement of the classification of the mean score from "moderate ED" to "mild ED". By comparison, the mean IIEF-EF domain score in placebo recipients showed only a small increase (from 13.5 to 14.3), and remained within the category of moderate ED. Major clinical improvement was also demonstrated by the number of positive answers to the GAQ, provided by 81.8% of men receiving vardenafil, and 24.3% of placebo recipients ($P < 0.001$).

In previous double-blind, randomized studies performed in Caucasian populations, mean IIEF-EF domain scores were 22.1 following 12 weeks' treatment with vardenafil 10 mg, and the number of positive answers to the GAQ was 76%. Per-patient success rates for SEP-2 and SEP-3 were 77.8% and 70.3%, respectively [14, 16]. Recently, vardenafil has been demonstrated to be effective and well tolerated in men of Eastern Asian ethnicity [24]. In that particular double-blind, randomized study in an Eastern Asian population, a mean IIEF-EF domain score of 24.2 was achieved following treatment with vardenafil, with the number of positive responses to the GAQ being 85.1%. Mean per-patient response success rates for SEP-2 and SEP-3 were 88.2 and 69.4, respectively [24]. Therefore, a comparison of the present results with other published data confirms that the efficacy of vardenafil is similar among Asian and Caucasian men with ED. Moreover, the magnitude of effect on the EF domain is similar to that observed in double-blind studies of sildenafil [26].

The present study also confirms the favorable tolerability profile of vardenafil previously established in Caucasian and other populations [8, 15, 17, 24, 27–29]. Vardenafil was well-tolerated, with the most frequently-occurring adverse events (headache, flushing, nasal congestion and dizziness), consistent with the vasodilatory activity of PDE-5 inhibitors [7, 8].

Vardenafil was effective and well-tolerated in the treatment of ED of moderate severity in a male population of Asian ethnicity. Vardenafil significantly improved erectile function, as measured by IIEF-EF domain scores, responses to SEP diary questions and the GAQ, following 12 weeks' treatment. Significant improvements were observed after 4 weeks' treatment compared with the placebo. These results add to the increasing amount of data indicating that vardenafil is suitable for the treatment of ED in a broad range of patient populations.

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References

1 Sanchez-Cruz J J, Cabrera-Leon A, Martin-Morales A, Fernandez A, Burgos R, Rejas J. Male erectile dysfunction and health-related quality of life. Eur Urol 2003; 44: 245–53.

2 Martin-Morales A, Meijide F, Garcia N, Artes M, Munoz A. Efficacy of vardenafil and influence on self-esteem and self-confidence in patients with severe erectile dysfunction. J Sex Med 2007; 4: 440–7.
3 Mallis D, Moisidis K, Kirana PS, Papaharitou S, Simos G, Hatzichristou D. Moderate and severe erectile dysfunction equally affects life satisfaction. J Sex Med 2006; 3: 442–9.
4 McKinlay JB. The worldwide prevalence and epidemiology of erectile dysfunction. Int J Impot Res 2000; 12 (Suppl 4): S6–S11.
5 Aytac IA, McKinlay JB, Krane RJ. The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. BJU Int 1999; 84: 50–6.
6 Lin CS, Lin G, Lue TF. Cyclic nucleotide signaling in cavernous smooth muscle. J Sex Med 2005; 2: 478–91.
7 Eardley I. Vardenafil: a new oral treatment for erectile dysfunction. Int J Clin Pract 2004; 58: 801–6.
8 Montorsi F, Salonia A, Briganti A, Barbieri L, Zanni G, Suardi N, *et al*. Vardenafil for the treatment of erectile dysfunction: a critical review of the literature based on personal clinical experience. Eur Urol 2005; 47: 612–21.
9 Ziegler D, Merfort F, van Ahlen H, Yassin A, Reblin T, Neureither M. Efficacy and safety of flexible-dose vardenafil in men with type 1 diabetes and erectile dysfunction. J Sex Med 2006; 3: 883–91.
10 Valiquette L, Montorsi F, Auerbach S; Vardenafil Study Group. First-dose success with vardenafil in men with erectile dysfunction and associated comorbidities: RELY-I. Int J Clin Pract 2006; 60: 1378–85.
11 Rubio-Aurioles E, Porst H, Eardley I, Goldstein I; Vardenafil-Sildenafil Comparator Study Group. Comparing vardenafil and sildenafil in the treatment of men with erectile dysfunction and risk factors for cardiovascular disease: a randomized, double-blind, pooled crossover study. J Sex Med 2006; 3: 1037–49.
12 Nehra A, Grantmyre J, Nadel A, Thibonnier M, Brock G. Vardenafil improved patient satisfaction with erectile hardness, orgasmic function and sexual experience in men with erectile dysfunction following nerve sparing radical prostatectomy. J Urol 2005; 173: 2067–71.
13 Giuliano F, Rubio-Aurioles E, Kennelly M, Montorsi F, Kim ED, Finkbeiner AE, *et al*; Vardenafil Study Group. Efficacy and safety of vardenafil in men with erectile dysfunction caused by spinal cord injury. Neurology 2006; 66: 210–6.
14 Porst H, Rosen R, Padma-Nathan H, Goldstein I, Giuliano F, Ulbrich E, *et al*. The efficacy and tolerability of vardenafil, a new, oral, selective phosphodiesterase type 5 inhibitor, in patients with erectile dysfunction: the first at-home clinical trial. Int J Impot Res 2001; 13: 192–9.
15 Hellstrom WJ, Gittelman M, Karlin G, Segerson T, Thibonnier M, Taylor T, *et al*. Vardenafil for treatment of men with erectile dysfunction: efficacy and safety in a randomized, double-blind, placebo-controlled trial. J Androl 2002; 23: 763–71.
16 Hellstrom WJ, Gittelman M, Karlin G, Segerson T, Thibonnier M, Taylor T, *et al*; Vardenafil Study Group. Sustained efficacy and tolerability of vardenafil, a highly potent selective phosphodiesterase type 5 inhibitor, in men with erectile dysfunction: results of a randomized, double-blind, 26-week placebo-controlled pivotal trial. Urology 2003; 61 (Suppl): 8–14.
17 Cheng E. Real-life safety and efficacy of vardenafil in the treatment of erectile dysfunction-results from 30,010 US Patients. J Sex Med 2007; 4: 432–9.
18 Kim K, Johnson JA, Derendorf H. Differences in drug pharmacokinetics between East Asians and Caucasians and the role of genetic polymorphisms. J Clin Pharmacol 2004; 44: 1083–105.
19 Chowbay B, Zhou S, Lee EJ. An interethnic comparison of polymorphisms of the genes encoding drug-metabolizing enzymes and drug transporters: experience in Singapore. Drug Metab Rev 2005; 37: 327–78.
20 Lamba JK, Lin YS, Schuetz EG, Thummel KE. Genetic contribution to variable human CYP3A-mediated metabolism. Adv Drug Deliv Rev 2002; 54: 1271–94.
21 Crimmel AS, Conner CS, Monga M. Withered Yang: a review of traditional Chinese medical treatment of male infertility and erectile dysfunction. J Androl 2001; 22: 173–82.
22 Nicolosi A, Moreira ED Jr, Shirai M, Bin Mohd Tambi MI, Glasser DB Epidemiology of erectile dysfunction in four countries: cross-national study of the prevalence and correlates of erectile dysfunction. Urology 2003; 61: 201–6.
23 Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 1997; 49: 822–30.
24 Chen KK, Paick JS, Ishii N. The efficacy and safety of vardenafil in East Asian men with erectile dysfunction. J Sex Med 2007; 4: 753–61.
25 Tan HM, Low WY, Ng CJ, Chen KK, Sugita M, Ishii N, *et al*. Prevalence and correlates of erectile dysfunction (ED) and treatment seeking for ED in Asian men: the Asian Men's Attitudes to Life Events and Sexuality (Asian MALES) study. J Sex Med 2007; 4: 1582–92.
26 Rosen RC, Cappelleri JC, Gendrano N 3rd. The International Index of Erectile Function (IIEF): a state-of-the-science review. Int J Impot Res 2002; 14: 226–44.
27 Rosen R, Shabsigh R, Berber M, Assalian P, Menza M, Rodriguez-Vela L, *et al*; Vardenafil Study Site Investigators. Efficacy and tolerability of vardenafil in men with mild depression and erectile dysfunction: the depression-related improvement with vardenafil for erectile response study. Am J Psychiatry 2006; 163: 79–87.
28 Goldstein I, Young JM, Fischer J, Bangerter K, Segerson T, Taylor T; Vardenafil Diabetes Study Group. Vardenafil, a new phosphodiesterase type 5 inhibitor, in the treatment of erectile dysfunction in men with diabetes: a multicenter double-blind placebo-controlled fixed-dose study. Diabetes Care 2003 26: 777–83.
29 Brock G, Nehra A, Lipshultz LI, Karlin GS, Gleave M, Seger M, *et al*. Safety and efficacy of vardenafil for the treatment of men with erectile dysfunction after radical retropubic prostatectomy. J Urol 2003 170: 1278–83.

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