Vardenafil Bayer Yakuhin

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Bayer is developing vardenafil, an orally active phosphodiesterase (PDE) 5 inhibitor for the potential treatment of erectile dysfunction (ED) [314382]. NDAs were filed in September 2001 in the US and Mexico [423096], and vardenafil was submitted for Canadian approval in October 2001. As of November 2001, Bayer was expecting a response from the FDA in the second half of 2002 [429499]; the EMEA accepted a filing in January 2002, following a December 2001 submission [438163]. By October 2000, phase III trials were underway in Japan [384751] and by December 2001, a Japanese NDA had been filed; at the same time an application was filed in South Africa [426526], [433060]. At this time Japanese launch was expected in 2003 [434758]. By February 2001, Bayer was also investigating a nasal formulation of vardenafil for the potential treatment of erectile dysfunction [397608]. In November 2001, Bayer and GlaxoSmithKline signed a worldwide copromotion agreement for vardenafil, under which Bayer was to be responsible for all regulatory work required to obtain approval [429499].

In February 1999, Lehman Brothers predicted a 10% probability that vardenafil would reach the market, with launch in 2002. Peak Japanese sales of US$600 million were predicted for 2014 [319225]. In May 2000, Bayer predicted peak sales of €900 million [397137]. In July 2001, Lehman Brothers predicted a 75% chance that vardenafil would reach the market, and forecast peak sales of US $0.85 billion worldwide; the analyst also speculated that Bayer would seek a comarketing partner [414766].

Originator Bayer Yakuhin Ltd

Licensee GlaxoSmithKline plc

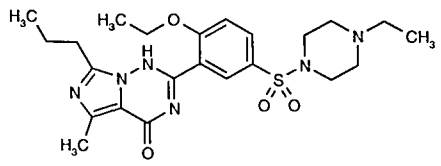
Status Pre-registration

Indication Impotence

Action PDE5 inhibitor

Synonyms & Analogs BAY-38-9456, Nuviva

CAS 1-[[3-(1,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-*f*][1,2,4]triazin-2-yl)-4-ethoxyphenyl]sulfonyl]-4-ethyl
Registry No: 224785-90-4



Introduction

Erectile dysfunction (ED) is a condition defined by the inability to attain or maintain penile erection sufficient for satisfactory sexual intercourse [360733]. There has been growing awareness of the problem of male erectile dysfunction among healthcare providers and an interest in improving therapy for impotence. In 1994 in the US the prevalence of erectile dysfunction in men 40 to 70 years old was 52% [436357]. In Germany, the incidence of severe impotence in the age group from 30 to 80 years is 19.2%, with a decline in sexual function with increasing age [435500]. This German study, the world's most extensive study of ED to date, also demonstrated that the treatment preferred by most patients is oral medication. The advent of the first effective oral agent in the treatment of ED, a PDE5 inhibitor, has had a revolutionary impact on the management of this disorder. Inhibition of PDE5 leads to increased levels of cGMP, which is why PDE5 inhibitors are so successful in the treatment of ED [438026].

Vardenafil is a potent and highly selective PDE5 inhibitor [436730]. It exhibited even higher potency and selectivity for the PDE5 isoform than sildenafil (Pfizer Inc) in preclinical investigations. Preclinical tests have also shown vardenafil to be highly selective for the PDE5 enzyme relative to other phosphodiesterases, an important property if one is to minimize side effects by direct or indirect cross-reactivity with other isoforms.

Phase II studies of vardenafil in men indicated that it was efficacious at improving erections and improved the intercourse completion rate compared to placebo, regardless of whether etiologies were organic or psychogenic, across a range of severity or age [435511], [436731]. Phase III data both in diabetic men and in a broad population confirmed the efficacy seen in the earlier study [435513]. With the exception of ocular disturbances, adverse events have been typical of PDE5 inhibitors, although it is difficult to determine if any of these compounds cause fewer side effects than others.

Vardenafil not only has a high success rate based on the evidence of well-validated questionnaires, but also significantly increases penile rigidity and tumescence in men with mild-to-moderate erectile difficulties when assessed by objective experimental measurements, eg, RigiScan® [408305].

Synthesis and SAR

The synthetic strategy involves cyclization of 2-ethoxybenzamidine with 2-butyramidopropionic acid and ethoxaryl chloride in the presence of DMAP in refluxing pyridine, which gives 2-(2-ethoxyphenyl)-5-methyl-7-propyl-3,4-dihydroimidazo[5,1-*f*][1,2,4]triazin-4-one. This intermediate is sulfinated with chlorosuldonix acid to provide the suldonyl chloride. Finally, this compound is condensed with 1-ethylpiperazine in dichloromethane to produce vardenafil [WO-09924433].

Pharmacology

PDE5 belongs to the group of cyclic nucleotide hydrolyzing enzymes. These include second messengers that stimulate and activate cGMP. PDE5 is the predominant cGMP-hydrolyzing enzyme present in the corpus cavernosum of the penis [438034]. cGMP regulates the smooth muscle tone of the arteries and arterioles in the corpus cavernosum [411380]. Sexual stimulation causes NO to be released from non-adrenergic, non-cholinergic neurons innervating the corpus cavernosum. NO then activates soluble guanyl cyclase to transform GTP into its active form, cGMP [411382]; cGMP activates protein kinase G (PKG), which initiates a phosphorylation cascade. This process finally results in a decrease in the intracellular concentration of calcium, which is followed by a decrease in smooth muscle tone. If appropriate levels of cGMP are reached, vascular muscles relax and allow the sinuses of the penis to be filled. The resultant engorgement allows the penis to become tumescent and rigid. If the concentration of cGMP is insufficient, it may not be possible to achieve an erection. When the release of NO stops, the levels of cGMP decrease due to the continued metabolism of cGMP by PDE5. Inhibition of PDE5, therefore, allows for an enhanced level of cGMP, causing vasodilatation and allowing increased blood flow into the corpus cavernosum, resulting in an increased probability of achieving an erection. As mentioned above, the presence of NO is considered essential. Although PDE5 inhibitors are capable of evoking an erection by themselves at high doses (seen in both *in vitro* and *in vivo* models), they only have a therapeutic effect in combination with sexual stimulation when release of NO occurs [411382].

The effectiveness of PDE5 inhibitors as therapies to treat erectile dysfunction is influenced by their selectivity. This is defined as the inhibitory effect on the target enzyme relative to other PDE isoenzymes. Other factors that have to be examined include the efficacy or potency of the agents. Vardenafil was demonstrated to have a selectivity 257-fold higher for PDE5 than PDE1, and 16-fold higher for PDE5 compared to PDE6. In contrast, sildenafil was only 60-fold more selective in its blocking effect of PDE5 compared with the blockade of PDE1, and 7-fold more selective in terms of PDE6 [436730].

Vardenafil given either intravenously or orally causes a dose-dependent increase in the length of the penis in the conscious rabbit. The lowest effective dose iv was 0.1 mg/kg, which caused a mean increase of 3 mm for about 20 min. Higher doses led to a faster, longer-lasting and greater effect (Figure 1) [435507], [436730]. Figure 2 compares the values obtained for vardenafil as mentioned above to those of sildenafil, used as a standard reference. In this model, vardenafil is more potent than sildenafil; this comparison is based on the same experimental study conducted in the same laboratory using identical techniques.

Metabolism

Vardenafil is metabolized primarily by CYP3A4. In studies with human volunteers, radiolabeled vardenafil was given orally; 4.9% was recovered in urine and 92.5% was recovered in feces over the course of the next several days. Unchanged drug and the major metabolite were the main plasma components and accounted for 33 and 24% of the total radioactivity administered, respectively, at 1.5 h after administration [438197].

Figure 1. Increasing length of the penile mucosa after administration of vardenafil iv to rabbits.

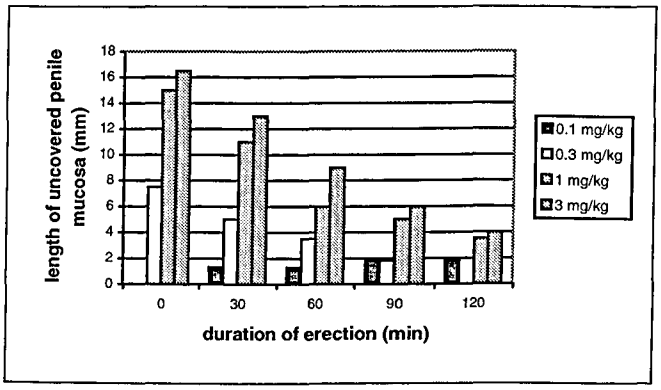
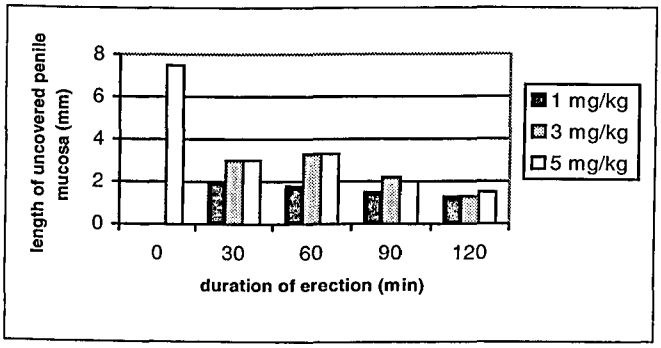


Figure 2. Increasing length of the penile mucosa after administration of sildenafil iv to rabbits.



Toxicity

No toxicity data are currently available.

Clinical Development

Phase I

Early studies that have been reported include dose-escalation studies to determine vardenafil's tolerability and pharmacokinetic properties. Doses of 20 and 40 mg once a day were well tolerated and no signs of accumulation were observed [408319]. T_{max} was frequently < 1 h and the $t_{½}$ was approximately 4 to 5 h.

Several pharmacokinetic studies have now been reported in healthy men as well as in men with ED. One study evaluated the difference in pharmacokinetic properties between ages 18 to 45 and > 65 years. Fasting men took a single dose of vardenafil (40 mg orally). Plasma concentrations of vardenafil were determined using a validated LC/MS/MS method and pharmacokinetic parameters were calculated using a non-compartmental analysis. Area under the curve (AUC) was measured from time zero to the last measurable time point. Terminal $t_{½}$ was obtained by linear regression analysis. The results indicated a monophasic elimination of vardenafil. The median T_{max} in these men occurred 30 to 40 min after dosing; $t_{½}$ = 4.8 h in the younger group and 6.0 h in the older group. AUC and C_{max} were 52 and 34% greater, respectively in the group aged over 65 years but these results were not statistically or clinically significant. As can be seen in Table 1, T_{max} and $t_{½}$ were not significantly different [438196]. Two pharmacokinetic studies have been performed in men with ED which were part of the RigiScan studies reported later. Similar effects were reported, with T_{max} = 40 min and $t_{½}$ ~ 4.5 h [408305].

Table 1. Pharmacokinetic profiles of vardenafil (40 mg) in young and elderly men.

Parameter (Units)	18 to 45 years (n = 8)	> 65 years (n = 9)
AUC (g.h/l)	125.6 (57.3%)	190.7 (34.3%)
C_{max} (g/l)	36.3 (74.6%)	48.7 (42.0%)
T_{max} (h)	0.6 (63.5%)	0.5 (23.1%)
$t_{1/2}$ (h)	4.8 (26.4%)	6.0 (15.2%)

Studies which examined the effects of potential interactions of vardenafil with other drugs have also been carried out. The effect of 0.4 mg sublingual nitroglycerin (taken 1 h after vardenafil administration) on blood pressure was not potentiated by vardenafil (10 mg) in a study in healthy volunteers. As there is striking evidence for the potentiation of the effects of nitrates as a result of the pharmacodynamic mode of action (effect of vardenafil on the oxide/cGMP-pathway) shown by preclinical experiments, however, these data should be interpreted with extreme caution. Although no special study on concomitant use in patients with ischemic heart disease has been reported, it will be an important component of any regulatory submission. When vardenafil (20 mg) was co-administered with cimetidine (400 mg bid), neither the bioavailability (AUC) nor the maximum plasma concentration (C_{max}) of vardenafil were changed. Similar results were obtained with ranitidine (150 mg bid) which, in contrast to cimetidine, does not act as an unspecific inhibitor of the cytochrome system. The median T_{max} of vardenafil alone was 55 min and $t_{½}$ was 3.9 h in this study [438195].

Elderly volunteers administered vardenafil have shown a kinetic pattern that is sufficiently similar to young volunteers to ensure that no dose adjustment should be necessary because of age.

Phase II

The pharmacodynamic effects of vardenafil on penile rigidity and tumescence, as well as the pharmacokinetics of single doses of vardenafil (10 mg and 20 mg) were analyzed in 21 patients with ED. During this randomized, double-blind, placebo-controlled, crossover study, measurements were recorded during three 20-min periods using the RigiScan technique under visual sexual stimulation. A single dose of vardenafil (10 mg) caused a rigidity of > 60% for about 24 min at the base and tip of the penis. After the single dose of vardenafil (20 mg), the penile rigidity increased to > 60% for about 37 min at the base and 29 min at the tip. The effect on tumescence and rigidity was determined as early as 20 min after the oral administration of vardenafil. Penile rigidity was enhanced under conditions of visual sexual stimulation. Further analysis of the dose response curve in subsequent similar protocols indicated that the 20 mg dose was suitable for 'at home' evaluations [408305].

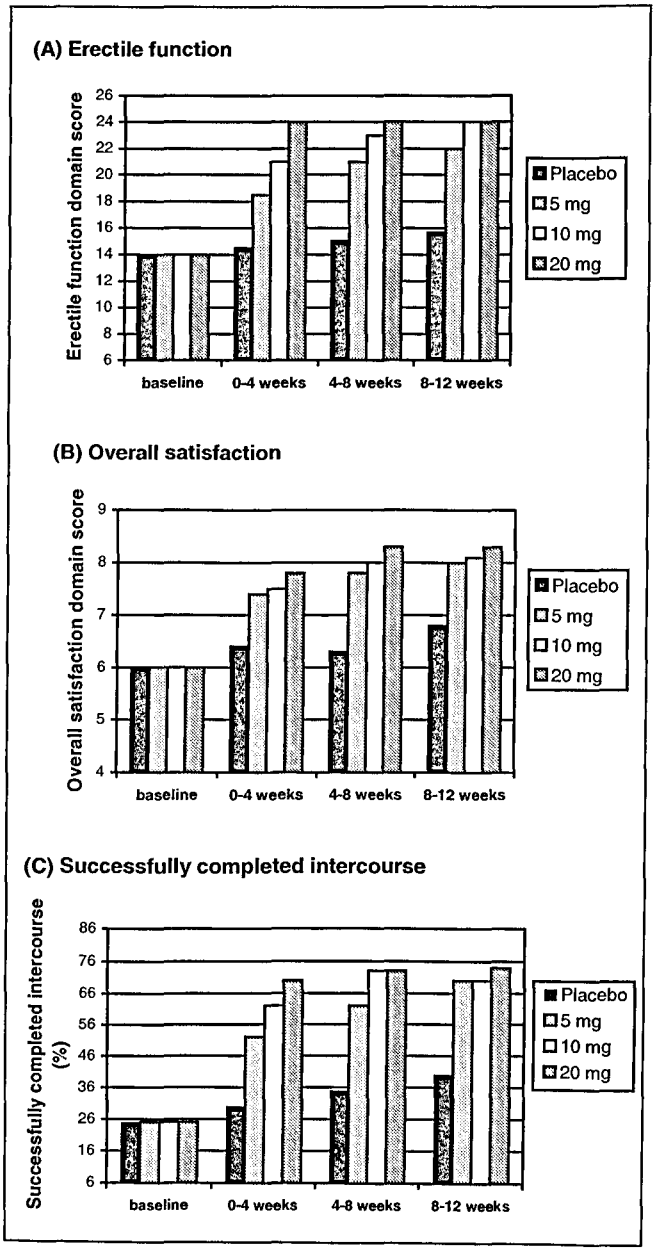
The optimum dose of vardenafil was determined in a double-blind, randomized, multicenter, parallel-group study of males with ED. This consisted of a 4-week unmedicated run-in and a 12-week randomized treatment phase. 601 Patients were accepted, with 580 patients receiving at least one dose and having one efficacy follow up visit. Men were randomized to placebo or vardenafil (5, 10 or 20 mg on demand). The mean age in all groups was approximately 52 years and the mean duration of ED approached three years. The etiologies of ED were approximately evenly divided between organic, psychogenic or mixed. The severity of ED was determined through the IIEF (International Index of Erectile Function) questionnaire [435510]. There were approximately equal proportions of mild, moderate and severe grades of severity and these were distributed equally across all four groups.

For this study, the target variables for efficacy were the responses to the IIEF questions, 'When you attempted sexual intercourse (vaginal penetration) how often were you able to penetrate your partner?' and, 'During sexual intercourse (vaginal penetration) how often were you able to maintain your erection after you penetrated (entered) your partner?'. The placebo group exhibited no significant changes after 12 weeks of treatment on any of the efficacy variables. In contrast, all three vardenafil groups showed a significant increase in erectile capability for both primary endpoints. For the main efficacy parameters no statistically significant differences between the three dosage groups were seen. Key secondary endpoints included the percentage success rate for completed sexual intercourse with ejaculation which was 75% by the study endpoint compared to 40% for placebo. For these variables, the 5-mg group differed significantly from the 20-mg group. The 10-mg dose was almost as effective as the 20-mg dose (Figure 3) [435511]. The improvement at 4 weeks became more established with time at the lower doses of vardenafil and was maintained for the highest dose, as shown in Figures 3A through 3C.

The GAQ global assessment question, 'Has the treatment you received in the last 4 weeks improved your erections?' evaluated the overall impression of patients. The proportion of men in the 20-mg group who reported improved erections was 80% compared to 30% in the placebo population. All vardenafil groups reached significantly higher values than the placebo group ($p < 0.001$). In addition, the 20-mg group responded to the GAQ with 'yes' more often than the 5-mg group ($p < 0.05$).

Vardenafil significantly improved the rate of successful penetration and intercourse. At baseline the success of penetration was given as 25.7% All vardenafil groups subsequently showed a significant increase in this success rate (Figure 4) [435511]. In other analyses of this large phase II study, it has been shown that all erectile function domains improved from the first measurement point onwards with the exception of sexual desire; its score was relatively high even at baseline [436359]. The others: erectile function, orgasmic function, intercourse satisfaction and overall satisfaction, all improved markedly by 4 weeks and were maintained over the course of the 12-week study. There was essentially no change in the placebo group for these domains.

Figure 3. IIEF domain scores for erectile dysfunction were improved by all oral dosages of vardenafil (5, 10 and 20 mg).



Phase III

Two major efficacy studies of vardenafil have been released so far. A double-blind, placebo-controlled study was conducted on 452 men with diabetes, a group known to have a high prevalence of ED and to respond less well than a general population to available oral ED therapies. Diabetes is associated with vascular changes in the penile arteries and microvasculature as well as neuropathies that may contribute to the inability to maintain erections. Diabetic men with ED, 60% of whom had previously used sildenafil, were randomly assigned to either placebo or vardenafil (10 or 20 mg on demand). Results showed that vardenafil as an oral treatment improved erections in up to 72% of patients with type I or type II diabetes mellitus. There was a clinically significant improvement for the 10 and 20 mg doses. In contrast, only a modest improvement was noted in the placebo group. Of the vardenafil group, 64% reported erections hard enough for penetration, versus 36% receiving placebo. The maintenance of erections sufficient to successfully complete intercourse was reported to be 54% at 20 mg in comparison to 23% on placebo [437932].

Results were reported recently from a phase III study in men suffering from ED for at least 6 months and with a wide-ranging severity and etiology [436361]. In this double-blind, placebo-controlled study, 805 men were randomized to placebo or vardenafil (5, 10 or 20 mg) for 26 weeks. The men had a high proportion of comorbid conditions including hypertension (37%), benign prostatic hyperplasia (20%) and diabetes (18%), and some had a previous cardiovascular morbid event, stroke or myocardial infarction (4%), although not within 6 months of the study. In this study, 81% of men at the 20-mg dose reported improved erections at 12 weeks and this had increased to 85% by 26 weeks, indicating a sustained response. This compared to 28% in the placebo group by the 26-week time point [436361].

Side Effects and Contraindications

Apart from the absence of any visual disturbances, side effects were typical of PDE5 inhibitors; headache (7 to 15%), flushing (10 to 11%) and dyspepsia or rhinitis (~ 7%) [435511]. Similar adverse events were found in the diabetes and pivotal studies.

The percentage of patients who were prematurely withdrawn from clinical studies because of adverse events was generally low. No cardiovascular or other serious adverse effects that could be directly linked to vardenafil have been reported [437935]. The incidence of ocular side effects seems to be very low and color vision changes have not been reported in the phase II or III studies to date. Back pain, which has been seen with other agents, was not observed at dosage strengths below 40 mg and, since this dose is not being continued in clinical development, this adverse effect is unlikely to be a concern.

All large-scale studies of vardenafil have excluded the use of nitrates due to the potential of other PDE5 inhibitors to cause hypotension in certain patients. Patients with unstable cardiac conditions have been excluded from these trials as is common in these studies but patients with mild cardiac risk were included if events had occurred 6 months prior. Many of the patients included had significant risk factors.

Current Opinion

Vardenafil has a higher selectivity compared with sildenafil and is also much more potent, having an IC_{50} less than one-fifth that of sildenafil. Selectivity is calculated by comparing an inhibitor's potency against PDE5 in comparison with other PDEs. A comparison of sildenafil and vardenafil shows that the newer drug is much more selective than sildenafil; particularly so for PDE1 and PDE6. Sildenafil is likely to exert a blocking effect at therapeutic doses, at least on PDE6, which may explain the color vision disturbances which are commonly reported by many patients receiving sildenafil. This has not been observed during the clinical studies with vardenafil (Figure 5).

Figure 4. % Of successful intercourse for placebo and vardenafil-treated patients.

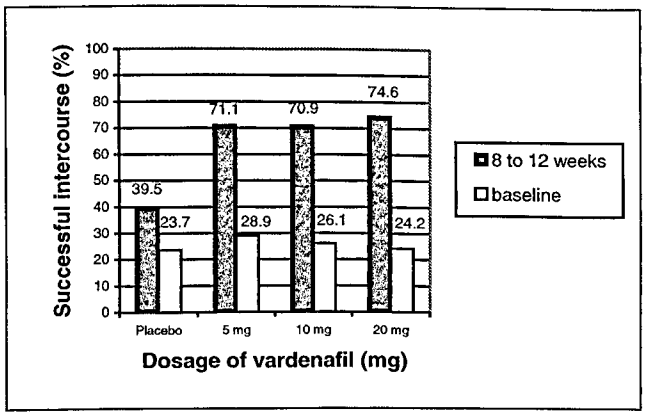
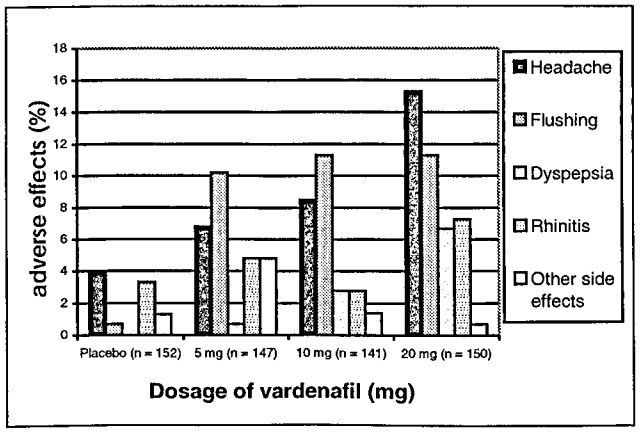


Figure 5. % Of patients who noticed side effects during 12 weeks of treatment.



Pharmacokinetics of the PDE5 inhibitors (especially $t_{½}$ and T_{max}) are likely to correlate with their onset and the duration of action, respectively. T_{max} for sildenafil is 1.16 h and for vardenafil it appears to be below 1 h, ranging from 0.66 to 0.9 h according to the data presented so far. This difference in T_{max} may translate into a quicker onset of action of vardenafil [408305]. The terminal $t_{½}$ for both vardenafil and sildenafil is about 4 h. On this basis, theoretically, vardenafil is the PDE5 inhibitor with the most appropriate pharmacokinetic profile, the shortest T_{max} and the most appropriate $t_{½}$ giving men the optimal window of opportunity to initiate and complete successful intercourse.

Side effects reported under vardenafil appear to be less frequent and less pronounced than those of sildenafil. Relative to sildenafil the incidence of headache reported in the earlier studies seems to be comparatively low. At therapeutic doses severe episodes of back pain are lacking. Vardenafil, at a dose range from 5 to 20 mg, shows a statistically significant improvement on ED. Compared with ED patients who are relatively healthy, patients suffering from diabetes mellitus responded comparatively well to vardenafil. This population of diabetics is more difficult to treat and is 3-times more likely to develop ED. Positive results have been reported regardless of age, severity or cause of ED; 72% reported positive results with vardenafil (20 mg) compared with only 55% of diabetic patients given sildenafil (100 mg).

Vardenafil provides a clear benefit even after 4 weeks of treatment (earliest point of measurements), which was consistently maintained over 12 weeks as shown in the phase II and phase III diabetic studies. Vardenafil, in comparison with placebo, not only improves erectile functioning but also allows patients with ED to complete intercourse with orgasm and improves their overall satisfaction. All efficacy parameters have shown the same effects for vardenafil in a statistically significant manner irrespective of the dose used (5 up to 20 mg). Asked if erections had improved, up to 85% of ED patients in the latest study responded with 'yes', while just 28% from the placebo group gave a positive answer. This clearly shows a significant benefit for the patients.

Parameters tested in the phase II and III studies demonstrated the sustained benefit of vardenafil for a wide range of patients with ED of diverse etiologies and severities. Although it remains to be confirmed in larger studies, there is some evidence that side effects appear to be less frequent and less pronounced than with sildenafil, and easier to control. The high selectivity of vardenafil in terms of PDE5 widely excludes effects on vision which are caused by the inhibition of PDE6 or on the CNS (PDE1). As phase II and phase III studies have shown, vardenafil is a safe and well-tolerated medication with minimal side effects. Not only mild or moderate, but even severe, ED can be treated successfully with vardenafil. In conclusion, vardenafil may be the long-awaited solution for ED of any origin, even in hard-to-treat populations such as diabetics.

Licensing

GlaxoSmithKline plc

In November 2001, Bayer and GlaxoSmithKline signed a worldwide copromotion agreement for vardenafil. Under the terms of this deal, Bayer was to manufacture the product and be responsible for all regulatory work required to obtain approval. The company was to account for all sales of the product and both parties were to share selling and future development expenses, as well as profits. In addition, the companies were to form a joint steering committee to oversee marketing and future development [429499].

Development history

Developer	Country	Status	Indication	Date	Reference
Bayer AG	Canada	Pre-registration	Impotence	16-NOV-01	429499
Bayer AG	Mexico	Pre-registration	Impotence	26-SEP-01	423096

Development history (continued)

Developer	Country	Status	Indication	Date	Reference
Bayer AG	US	Pre-registration	Impotence	26-SEP-01	423096
Bayer AG	Western Europe	Pre-registration	Impotence	01-JAN-02	438163
Bayer AG	South Africa	Pre-registration	Impotence	11-DEC-01	433060
Bayer Yakuhin	Japan	Pre-registration	Impotence	11-DEC-01	433060
GlaxoSmithKline	Western Europe	Pre-registration	Impotence	01-JAN-02	438163

Literature classifications

Biology

Study Type	Effect Studied	Experimental Model	Result	Reference
In vivo	Effective dose.	Conscious rabbit administered varying doses of vardenafil.	The lowest effective dose was 0.1 mg/kg, which caused a mean increase in penis length of 3 mm for ~ 20 min.	435507

Metabolism

Study Type	Effect Studied	Experimental Model	Result	Reference
In vivo	Pharmacokinetics.	Radiolabeled vardenafil administered orally.	4.9% recovered in urine and 92.5% in feces over several days. Unchanged drug (33%) and major metabolite (24%) were main plasma components after 1.5 h.	438197

Clinical

Effect Studied	Model Used	Results	Reference
Tolerance.	Vardenafil (20 and 40 mg) given once daily to healthy volunteers.	Doses were well tolerated and no signs of accumulation were seen.	408319
Efficacy on penetration and duration of intercourse.	Randomized, double-blind, multicenter, parallel-group study in 601 patients with ED. Vardenafil administered at 5, 10 or 20 mg on demand.	Significant increase in erectile capability in all drug-treated groups. The 5-mg group significantly differed from the 20-mg group on the % success rate for completed intercourse with ejaculation.	435511
Efficacy.	Phase III, double-blind, placebo-controlled study in 452 patients with diabetes and ED. Vardenafil administered at 10 and 20 mg.	Hardness of erections was improved in 72% of patients, and 54% of erections were maintained long enough for complete intercourse in the 20-mg group.	437932

Associated patent

Title 2-Phenyl substituted imidazotriazinones as phophodiesterase inhibitors.

Assignee Bayer AG

Publication WO-09924433 31-OCT-98

Priority DE-1998198402899 04-SEP-98

Inventors Niewohner U, Es-Sayed M, Haning H, Schenke T, Schlemmer KH, Keldenich J, Bischoff E, Perzborn E, Dembowsky K, Serno P, Nowakowski M.

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• *Important study which demonstrated the safety profile and efficacy of vardenafil.*

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411380 **Phosphodiesterase type 5 inhibitors: Discovery and therapeutic utility.** Rotella DP *DRUGS FUTURE* 2001 **26** 2 153-162

411382 **IC-351.** Sorbera LA, Martin L, Leeson PA, Castaner J *DRUGS FUTURE* 2001 **26** 1 15-19

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