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Urologic Drugs

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Abstract

The *Annual Review* in this issue of **Drugs of the Future** is dedicated to updated information on urologic drugs. The following table lists 59 drugs under development in this area, some of which have been published in previous issues of the journal and others that have been launched for an indication other than that discussed in the review. Information on 13 of the products is updated here: **darifenacin, duloxetine hydrochloride, dutasteride, finrozole, GYKI-16084, HCT-1026, osaterone acetate, silodosin, solifenacin succinate, suplatast tosilate, tadalafil, tamsulosin hydrochloride** and **vardenafil**.

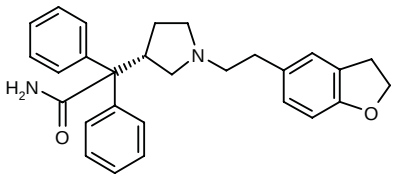
Once again, we remind our readers that all of the information presented in this Review is available in electronic format in our drug discovery portal **Integrity**.

Annual Review 2002: Urologic Drugs

Drug	Source	Indication/Action	Phase
ABT-598	Abbott	Urinary incontinence	I
		Erectile dysfunction	I
AIO-8507L	Ono	Benign prostatic hyperplasia	II
Alibra	Vivus	Erectile dysfunction	III
Aliskiren Fumarate[1]	Speedel	Renal failure	I/II
ALT-711	Alteon	End-stage renal disease	I
Ambrisentan	Myogen	Renal failure	II
AZD-0947	AstraZeneca	Urinary incontinence	I/II
Bimexes	Zonagen	Erectile dysfunction	II
Cetrorelix Acetate[1,2]	Zentaris	Benign prostatic hyperplasia	II
Chondrogel	Curis	Vesicoureteral reflux	III
DA-8159	Dong-A	Erectile dysfunction	I
Darifenacin[1]	Pfizer	Urinary incontinence	III
Deoxyspergualin Hydrochloride[1]	Nippon Kayaku	Glomerulonephritis	II
(*S*)-Didesmethylsibutramine	Sepracor	Erectile dysfunction	II
(*S*)-Doxazosin	Sepracor	Benign prostatic hyperplasia	I
DRP-001	Sosei	Urinary incontinence	I
Duloxetine Hydrochloride[1]	Lilly	Urinary incontinence	III
Dutasteride[1]	GlaxoSmithKline	Benign prostatic hyperplasia	R-2001
Eculizumab	Alexion	Nephritis	II
ERxin	Zonagen	Erectile dysfunction	II
Fasturtec	Sanofi-Synthélabo	Uricosuric	L-2001
Fesoterodine	Schwarz	Urinary incontinence	II
Finrozole[1]	Hormos	Benign prostatic hyperplasia	II
FK-352[1]	Fujisawa	Renal failure	II
Genistein	NIH	Renal failure	II
GYKI-16084[1]	Inst. Drug Res.	Benign prostatic hyperplasia	II
KUL-7211	Kissei	Urethral colic	I
Lanthanum Carbonate	Shire Laboratories	Renal failure	Prereg
ML-04	Milkhaus	Benign prostatic hyperplasia	II
		Chronic prostatitis	II
HCT-1026[1]	Nicox	Urinary incontinence	II
NS-8	Nippon Shinyaku	Urinary incontinence	I
ONO-8025	Kyorin/Ono	Urinary incontinence	II
ONO-8922	Ono	Urinary incontinence	I
OPC-51803	Otsuka	Urinary incontinence	II
Osaterone Acetate[1]	Teikoku Hormone	Benign prostatic hyperplasia	Prereg
(*S*)-Oxybutynin	Sepracor	Urinary incontinence	III
Parvosin	Ranbaxy	Benign prostatic hyperplasia	II
Pirfenidone	Marnac	Renal failure	II
PN-401	Repligen	Renal disease	I
PT-141	Palatin Technologies	Erectile dysfunction	II
R-450	Roche	Urinary incontinence	II
R-701	Roche	Urinary incontinence	I
REC-15/3079	Recordati	Urinary incontinence	I
(+)- Resiniferatoxin	ICOS	Urinary incontinence	II
Ro-70-0004	Roche Bioscience	Benign prostatic hyperplasia	II
Saredutant[1]	Sanofi-Synthélabo	Urinary incontinence	II
Silodosin[1]	Daiichi/Kissei	Benign prostatic hyperplasia	III
Solifenacin Succinate[1]	Yamanouchi	Urinary incontinence	III
SR-121463A	Sanofi-Synthélabo	Diuretic	I
Suplatast Tosilate[1,2]	Taiho	Interstitial cystitis	Prereg
TA-1790	Tanabe Seiyaku/Vivus	Erectile dysfunction	I
Tadalafil[1]	Lilly Icos	Erectile dysfunction	Prereg
Talnetant	GlaxoSmithKline	Urinary incontinence	II
Tamsulosin Hydrochloride[1,2]	Yamanouchi	Lower urinary tract disorder	III
Temiverine Hydrochloride Hydrate	Nippon Shinyaku	Urinary incontinence	Prereg
TF-505	Fujisawa	Benign prostatic hyperplasia	I
UK-294315	Pfizer	Benign prostatic hyperplasia	I
Vardenafil[1]	Bayer/GlaxoSmithKline	Erectile dysfunction	Prereg
WAY-VNA-932[3]	Wyeth	Antidiuretic	I

[1]Previously published in Drugs of the Future. [2]Launched for another indication. [3]Monograph published in March issue of Drugs of the Future.

Darifenacin



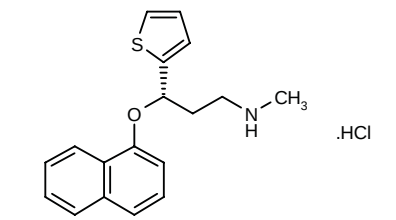
Darifenacin (UK-88525) is a new muscarinic M_3 receptor antagonist from Pfizer in phase III evaluation for the treatment of overactive bladder.

After i.v. administration to anesthetized dogs, darifenacin was found to have 10-fold selectivity for the bladder over the salivary gland and was more selective than tolterodine, oxybutynin and propiverine. The greater selectivity of darifenacin for the muscarinic M_3 receptor could lead to improved treatment of overactive bladder with fewer antimuscarinic side effects (1).

1. Gupta, P., Anderson, C., Carter, A., Casey, J., Newgreen, D. *In vivo bladder selectivity of darifenacin, a new M_3 antimuscarinic agent, in the anesthetised dog*. Eur Urol Suppl 2002, 1(1): Abst 515.

Original monograph - Drugs Fut 1996, 21(11): 1105.

Duloxetine Hydrochloride



Duloxetine (Cymbalta™; Lilly), a potent 5-HT and noradrenaline reuptake inhibitor presently under review at the FDA for the treatment of depression, is expected to be filed for approval for use in stress urinary incontinence later this year (1, 2).

Duloxetine has demonstrated analgesic activity in preclinical and clinical studies (3, 4).

Studies *in vitro* and *in vivo* demonstrated that duloxetine blocks 5-HT and noradrenaline uptake processes and transporter binding more potently than venlafaxine (5).

A randomized study was conducted in 14 healthy volunteers to determine whether elevated gastric pH or coadministration of activated charcoal alters the oral absorption of duloxetine. Subjects were given duloxetine 40 mg alone, with famotidine 40 mg, with 3 doses of Fast Acting Mylanta® 20 ml and with activated charcoal 50 g. Decreased gastric acidity had no significant influence on duloxetine pharmacokinetics. The extent of duloxetine absorption, however, was significantly reduced by coadministration of activated charcoal (6).

A randomized, double-blind, 3-way crossover study performed in 12 healthy male volunteers compared the effect on sleep of duloxetine (80 mg o.d. and 60 mg b.i.d.) and desipramine (50 mg b.i.d.) following multiple oral dosing for 7 days. Based on the Leeds Sleep Questionnaire (LSQ) and polysomnographic recordings, once-daily duloxetine facilitated sleep onset and increased sleep efficiency as opposed to twice-daily duloxetine and desipramine (7).

Another randomized, double-blind, 3-way crossover study conducted in 12 healthy male volunteers evaluated the mechanism of action of desipramine (50 mg b.i.d. p.o.) and duloxetine (60 mg b.i.d. p.o. and 80 mg o.d. p.o.). At steady state (days 5-7), duloxetine but not desipramine decreased 5-HT levels in whole blood. A reduction in the urinary excretion of noradrenaline metabolites was induced by both agents. The i.v. pressor dose of tyramine that increased the systolic blood pressure by 30 mmHg (PD_{30}) was found to be greater for desipramine as compared to duloxetine (+22.84 mg *vs.* < +2 mg) (8) (Table I).

Results from a study conducted in 14 healthy volunteers showed that duloxetine given at the highest proposed dose for clinical purposes is a moderate CYP2D6 inhibitor. Following oral coadministration of desipramine (50 mg) and duloxetine (60 mg b.i.d. for 6 days), C_{max}, $AUC_{0-\infty}$ and $t_{1/2}$ of desipramine increased significantly as compared to administration of desipramine alone (30 ng/ml *vs.* 17.9 ng/ml, 1672 ng·h/ml *vs.* 623 ng·h/ml and 44.0 h *vs.* 24.6 h for C_{max}, AUC and $t_{1/2}$, respectively). Mean t_{max} values of 6.0 h were found for both treatments (9).

The effects of duloxetine on 5-HT and noradrenaline uptake were evaluated in 27 healthy volunteers. Male volunteers with no history of psychiatric disorder were ran-

Table I: Clinical studies of duloxetine (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized, double-blind, crossover	Duloxetine, 60 mg bid x 5-7 d Duloxetine, 80 mg od x 5-7 d Desipramine, 50 mg bid x 5-7 d Placebo	12	The tyramine test may not be the appropriate tool to assess noradrenaline reuptake after subchronic administration of a dual reuptake inhibitor	8
Urinary incontinence	Randomized, double-blind	Duloxetine, 20 mg od x 12 wk (n=138) Duloxetine, 20 mg bid x 12 wk (n=137) Duloxetine, 40 mg bid x 12 wk (n=140) Placebo (n=138)	553	Duloxetine 80 mg was well tolerated and effective in reducing incontinence frequency and improving quality of life in patients with urinary incontinence	11

domized to placebo, clomipramine 100 mg/day, duloxetine 20 mg/day or duloxetine 60 mg/day. Administration of clomipramine and both doses of duloxetine decreased blood 5-HT concentrations, but only clomipramine inhibited the increase in blood pressure following i.v. infusion of tyramine. Duloxetine therefore acted as a selective 5-HT reuptake inhibitor without affecting the noradrenaline reuptake process (10).

Based on the efficacy results obtained in 2 pilot studies of duloxetine in patients with stress urinary incontinence, a phase II trial was conducted to compare different doses of duloxetine and placebo in 553 women with urinary incontinence of at least 3 months' duration. The primary endpoint of this double-blind, randomized, placebo-controlled study was incontinence episode frequency (IEF), and the secondary endpoint was to compare changes in quality of life as measured by the Patient Global Impression Improvement (PGI-I) and the Incontinence Quality of Life Questionnaire (I-QOL). Following a 2-week placebo run-in phase, the women were randomized to placebo or duloxetine 20, 40 or 80 mg/day for 12 weeks. Although a high response rate was obtained on placebo, significant and dose-dependent improvement was obtained on duloxetine for IEF, and dose-dependent improvement on the I-QOL and PGI-I reached statistical significance on the highest dose. Of those treated with 80 mg/day duloxetine, half experienced at least a 64% reduction in IEF and 65% had at least a 50% decrease. A subgroup of 148 patients with severe stress urinary incontinence also showed significant improvement at the highest dose. The most frequent adverse event was nausea; 5, 10, 12 and 16% of patients receiving placebo, duloxetine 20, 40 and 80 mg discontinued due to adverse events. Large-scale phase III clinical trials for stress urinary incontinence are in progress (11) (Table I).

1. *Cymbalta relieves emotional and physical symptoms of depression without weight gain*. DailyDrugNews.com (Daily Essentials) May 27, 2002.

2. *Lilly presents detailed update of late- and early-stage product pipeline*. DailyDrugNews.com (Daily Essentials) Nov 2, 2001.

3. Iyengar, S., Bymaster, F., Wong, D.T., Ahmad, L.J., Simmons, R.M.A. *Efficacy of the selective serotonin and norepinephrine reuptake inhibitor, duloxetine, in the formalin model of persistent pain*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 726.

4. Goldstein, D.J., Iyengar, S., Mallinckrodt, C., Lu, Y., Derke, M., Demitrack, M.A. *Duloxetine: A potential new treatment for depressed patients with comorbid pain*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 789.

5. Bymaster, F.P., Dreshfield-Ahmad, L.J., Threlkeld, P.G., Shaw, J.L., Thompson, L., Nelson, D.L., Hemrick-Luecke, S.K., Wong, D.T. *Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, human serotonin receptor subtypes, and other neuronal receptors*. Neuropsychopharmacology 2001, 25(6): 871.

6. Sachirakul, K., Teng, L.L., Yeo, K.P., Chan, C. *Impact of gastric pH and the presence of activated charcoal on the absorption of duloxetine*. Clin Pharmacol Ther 2002, 71(2): Abst MPI-53.

7. Chalon, S., Granier, L.-A., Vandenhende, F., Lainey, E., Potter, W.Z. *Duloxetine affects sleep architecture with antidepressant like pattern*. Clin Pharmacol Ther 2001, 69(2): Abst PII-65.

8. Chalon, S., Granier, L.A., Vandenhende, F., Guillaume, M., Bieck, P.R., Bymaster, F., Potter, W.Z. *Duloxetine: Clinical evidence of serotoninergic and noradrenergic reuptake blockade*. Clin Pharmacol Ther 2001, 69(2): Abst PI-67.

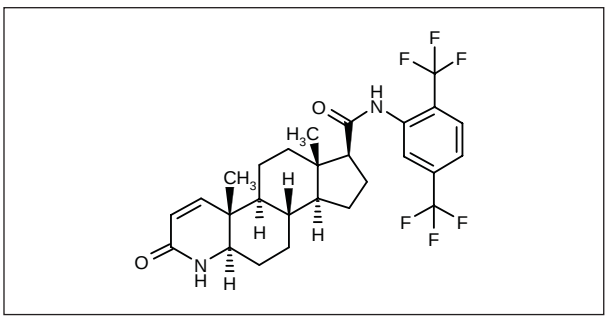
9. Skinner, M.H., Ni, L., Kuan, H.-Y., Knadler, M.P., Gonzales, C. *Effect of duloxetine on CYP2D6*. Clin Pharmacol Ther 2001, 69(2): Abst PIII-59.

10. Turcotte, J.E., Debonnel, G., de Montigny, C., Hébert, C., Blier, P. *Assessment of the serotonin and norepinephrine reuptake blocking properties of duloxetine in healthy subjects*. Neuropsychopharmacology 2001, 24(5): 511.

11. Norton, P., Zinner, N.R., Yalcin, I., Burnp, R.C. *Duloxetine versus placebo in the treatment of stress urinary incontinence*. Neurourol Urodyn 2001, 20(4): Abst 99.

Original monograph - Drugs Fut 2000, 25(9): 907.

Dutasteride



GlaxoSmithKline's dutasteride (GI-198745, GG-745, Avolve) is the first 5α-reductase inhibitor that inhibits both type 1 and 2 isozymes, the enzymes responsible for converting testosterone to dihydrotestosterone in the prostate and proven to play a key role in the development and progression of benign prostatic hyperplasia (BPH). Dutasteride was approved by the FDA late last year for the treatment of symptomatic BPH in men with an enlarged prostate gland. The company has also submitted an MAA to the Swedish regulatory authorities. Clinical trials of dutasteride, involving over 4300 patients suffering from BPH, have demonstrated that it provides long-lasting symptom relief and positively impacts disease progression (1, 2).

Pharmacological experiments have indicated that both dutasteride and finasteride inhibit rat type 2 steroid 5alpha-reductase (r5AR2) in an irreversible fashion but are classical, reversible inhibitors of r5AR1. These and other findings led to the conclusion that dutasteride may more effectively inhibit rat prostate growth than finasteride due to enhanced potency and pharmacokinetics (3).

The effect of DHT suppression on spermatogenesis was investigated in a multicenter, double-blind, randomized, placebo-controlled trial in 76 healthy male volunteers administered dutasteride 0.5 mg, finasteride 5 mg or placebo each day for 1 year. No clinically significant effects of dutasteride on spermatogenesis were seen in the subjects (4).

In a study in 674 patients, treatment with dutasteride 0.5 mg was found to decrease serum total and free prostate-specific antigen (PSA) levels but did not modify the usefulness of the free/total PSA ratio for the detection of prostate cancer (5). Table II summarizes the results of this study and those that follow.

Pooled analysis of results from several 2-year, multicenter, double-blind, placebo-controlled studies in over 4000 BPH patients demonstrated that treatment with dutasteride (0.5 mg/day) had a favorable impact on all the key hallmarks of BPH compared to placebo. The treatment resulted in a nearly complete suppression of DHT levels in serum as compared to placebo starting at 1 month and was sustained throughout the treatment period. Dutasteride improved lower urinary tract symptoms and urinary flow measurements, and decreased the risk of acute urinary retention and BPH-related surgery by 48-57% over the 2-year study period. Significant reductions in both total and transitional zone prostate volume were observed starting at 1 month and increasing with time up to 24 months on dutasteride. Moreover, the results showed that the beneficial effects of dutasteride compared to placebo were greater when the patients also presented with an enlarged prostate. The drug was well tolerated, with a similar incidence of withdrawals related to adverse events on dutasteride and placebo (4% *vs.* 3%) (6-11).

A multicenter, double-blind, parallel-group study found that short-term treatment of BPH patients with a combination of 0.5 mg dutasteride and 0.4 mg tamsulosin once daily, followed by 0.5 mg dutasteride plus placebo once daily, resulted in sustained symptom relief. Of the patients who continued on dutasteride monotherapy, 77% showed BPH symptom control, which was maintained 12 weeks after withdrawal in 93% of them. The combination treatment was well tolerated (12).

1. *First approval obtained for new BPH therapeutic from GSK*. DailyDrugNews.com (Daily Essentials) Dec 4, 2001.

2. *GSK seeks Swedish approval of dutasteride for treatment of BPH*. DailyDrugNews.com (Daily Essentials) Oct 18, 2001.

3. Stuart, J.D., Lee, F.W., Noel, D.S. et al. *Pharmacokinetic parameters and mechanisms of inhibition of rat type 1 and 2 steroid 5α-reductases: Determinants for different in vivo activities of GI198745 and finasteride in the rat*. Biochem Pharmacol 2001, 62(7): 933.

4. Clark, R.V., Huffman, C.S., Haberer, L.J., Swedloff, R.S., Wang, C., Matsumoto, A.M., Bremner, W.J. *Marked suppression of dihydrotestosterone (DHT) by dutasteride has no adverse effect on spermatogenesis in healthy men*. 84th Annu Meet Endocr Soc (June 19-22, San Francisco) 2002, Abst P2-673.

5. Andriole, G., Roehrborn, C.G., Boyle, P. *Effect of the dual 5α-reductase inhibitor, dutasteride, on serum total PSA, free PSA and the ratio of F/T PSA*. J Urol 2002, 167(4, Suppl.): Abst 844.

6. Roehrborn, C.G., Andriole, G., Nickel, C., Boyle, P. *Effect of the dual 5α-reductase inhibitor dutasteride on endocrine parameters*. J Urol 2002, 167(4, Suppl.): Abst 1049.

7. Roehrborn, C.G., Andriole, G., Nickel, C., Boyle, P., Ramsdell, J., Rosenblatt, S. *Effect of dutasteride, a novel dual 5α-reductase inhibitor, on BPH related signs and symptoms*. J Urol 2002, 167(4, Suppl.): Abst 1043.

8. Roehrborn, C.G., Ramsdell, J., Siami, P., Wachs, B.H., Rosenblatt, S. *Prostate volume at baseline predicts the margin of therapeutic response with the 5α-reductase inhibitor, dutasteride*. J Urol 2002, 167(4, Suppl.): Abst 1483.

Table II: Clinical studies of dutasteride for the treatment of benign prostatic hyperplasia (from Prous Science Integrity®).

Design	Treatments	n	Conclusions	Ref.
Multicenter	Dutasteride, 0.5 mg x 2 y (n=337) Placebo (n=337)	674	Dutasteride was significantly effective in decreasing total, free and free:total PSA ratio in patients with benign prostatic hyperplasia	5
Randomized, double-blind, multicenter, pooled/meta-analysis	Dutasteride, 0.5 mg/d po x 2 y (n=2167) Placebo (n=2158)	4325	Dutasteride was well tolerated and effective in enlarged total and transitional zone prostate volume, decreasing the incidence of acute urinary retention and surgical procedures, increasing urinary flow rate and improving prostatic symptoms in patients with benign prostatic hyperplasia. Moreover, dutasteride produced an early, near total decrease in serum dihydrotestosterone and PSA and an increase in serum testosterone levels	6-11
Randomized, double-blind, multicenter	Dutasteride, 0.5 mg + Tamsulosin, 0.4 mg od x 24 wk → Dutasteride, 0.5 mg od x 12 wk Dutasteride, 0.5 mg + Tamsulosin, 0.4 mg od x 36 wk	327	Dutasteride plus tamsulosin combination therapy relieved prostate symptoms and modified disease progression. Dutasteride alone was able to sustain the benefit in most patients with benign prostatic hyperplasia	12

9. Boyle, P.P., Siami, P., Wachs, B.H., Roehrborn, C.G., Andriole, G., Nickel, C. *Effect of dutasteride on the risk of acute urinary retention and the need for surgical treatment*. J Urol 2002, 167(4, Suppl.): Abst 1479.

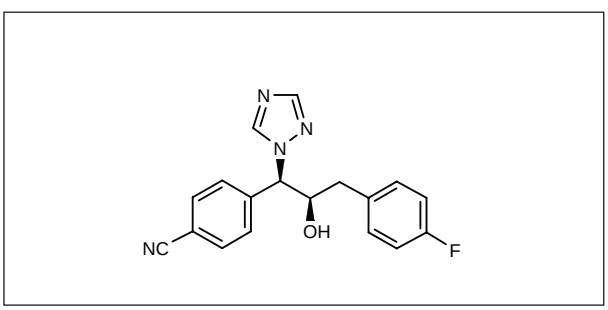
10. Roehrborn, C., Andriole, G., Boyle, P., Höfner, K. *Effect of the dual 5α-reductase inhibitor dutasteride on endocrine parameters and prostate volume*. Eur Urol Suppl 2002, 1(1): Abst 417.

11. Boyle, P. et al. *The impact of dutasteride, a novel 5α-reductase inhibitor, on the hallmarks of BPH. Progression and outcomes*. Eur Urol Suppl 2002, 1(1): Abst 418.

12. Barkin, J., Guimaraes, M., Do Castelo, V., Jacobi, G., Pushkar, D., Taylor, S., Van Vierssen, O. *Dutasteride provides sustained symptom relief following short term combination treatment with tamsulosin*. J Urol 2002, 167(4, Suppl.): Abst 1481.

Original monograph - Drugs Fut 1999, 24(3): 246.

Finrozole



Finrozole (MPV-2213ad) is an aromatase inhibitor in phase II evaluation at Hormos for male obstructive urinary dysfunction (1).

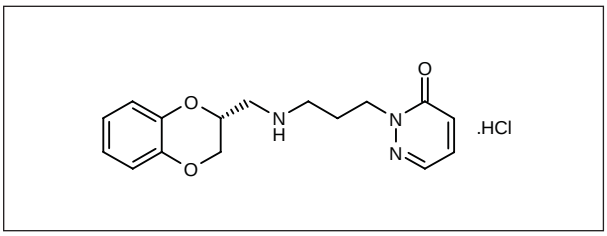
Single doses of finrozole 3, 9 or 30 mg were administered in tablet or solution form to 23 volunteers in an open, partly randomized, crossover pharmacokinetic study. Absorption of the drug from tablets was slower than from the solution but still relatively rapid. The tablet also had a longer elimination half-life, possibly due to overlap of absorption with the elimination phase (2).

1. *Company Profile: Hormos Medical*. DailyDrugNews.com (Daily Essentials) May 16, 2001.

2. Ahokoski, O., Irjala, K., Taalikka, M., Manninen, P., Halonen, K., Kangas, L., Salminen, E., Huupponen, R., Scheinin, H. *Pharmacokinetics of finrozole (MPV-2213ad), a novel selective aromatase inhibitor, in healthy men*. Br J Clin Pharmacol 2001, 52(6): 702.

Original monograph - Drugs Fut 1998, 23(10): 1071.

GYKI-16084



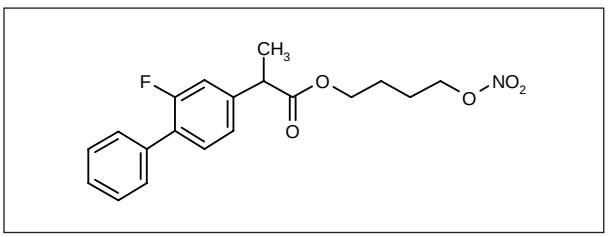
GYKI-16084 (IDR-16084) is a uroselective α_1/α_2-adrenoceptor antagonist under development for the treatment of BPH.

Ivax's Hungarian subsidiary, the Ivax Institute for Drug Research, has received clearance to conduct a multicenter, placebo-controlled phase II study of GYKI-16084 in men with BPH. It is anticipated that 200 patients will be enrolled in the study. Phase I studies demonstrated the compound to be more uroselective, with a greatly reduced incidence of side effects such as dizziness, fainting and sexual dysfunction typical of currently used drugs (1).

1. *Ivax set to begin phase II study of GYKI-16084 for BPH*. DailyDrugNews.com (Daily Essentials) June 14, 2001.

Original monograph - Drugs Fut 1999, 24(10): 1072.

HCT-1026



NicOx's novel patented nitric oxide (NO)-donating flurbiprofen derivative HCT-1026 (NO-flurbiprofen) represents a new approach to the treatment of lower urinary tract symptoms (LUTS), a condition characterized by overactive bladder with symptoms of urgency, urge incontinence and pain on micturition, based on the hypothesis that inhibition of prostaglandin synthesis may reduce instability of the bladder muscle, a leading cause of urinary urge incontinence.

HCT-1026 has an improved gastric tolerability compared to the conventional nonsteroidal antiinflammatory drug (NSAID) flurbiprofen, potentially allowing administration for extended periods at fully active doses. It is thought that the pharmacological activity of NO will also enhance the drug's performance. NicOx recently announced positive phase IIa results for HCT-1026. The U.K. study evaluated the efficacy and safety of HCT-1026 in 24 female patients with symptoms of overactive bladder, with or without incontinence and with or without detrusor instability. The patients received placebo or HCT-1026 100 mg as capsules twice daily for 14 days per treatment period in a crossover design. There was a statistically significant improvement compared to placebo in symptoms of urinary urgency and dysuria and in the sensation of complete bladder emptying. Overall safety was excellent. The results indicate potential for HCT-1026 in the treatment of LUTS, in particular sensory urgency and interstitial cystitis. In a previous phase IIa study in this indication, HCT-1026 provided increased bladder volume and improvement in bladder contractility in patients with neurogenic bladder and detrusor instability. In phase I trials, HCT-1026 showed good oral absorption, potent prostaglandin inhibition, dose linearity, excellent overall safety and reduced gastric toxicity after oral dosing. The FDA has accepted NicOx's IND application for HCT-1026 for the treatment of urinary incontinence, which will allow the company to move the drug forward in clinical trials in the U.S., expanding on the first phase I and II trials conducted in Europe. HCT-1026 is also under development in a wide range of therapeutic areas such as Alzheimer's disease, dermatological conditions and bone metabolism diseases (1, 2).

The effect of HCT-1026 on bladder hyperactivity was evaluated in rats treated with cyclophosphamide to produce bladder irritation. After treatment, a transurethral catheter was used to fill the bladder with continuous infusions of saline. Increasing concentrations of HCT-1026 were then infused intravesically and were found to rapidly reduce the frequency of voiding in these animals, without altering voiding pressure (3).

The antinociceptive effect of HCT-1026 was examined in rats with cyclophosphamide-induced cystitis. In this inflammatory vesical pain model, administration of cyclophosphamide alters certain behavioral parameters taken as indices of pain, *i.e.*, it decreases breathing rate and induces eye closure and certain postures. Pretreatment with HCT-1026 (10 mg/kg i.v.) resulted in more gradual effects following cyclophosphamide, indicating a strong antinociceptive effect in this model and suggesting potential in the treatment of interstitial cystitis (4).

1. *Positive phase IIa results achieved by HCT-1026 in overactive bladder*. DailyDrugNews.com (Daily Essentials) April 2, 2002.

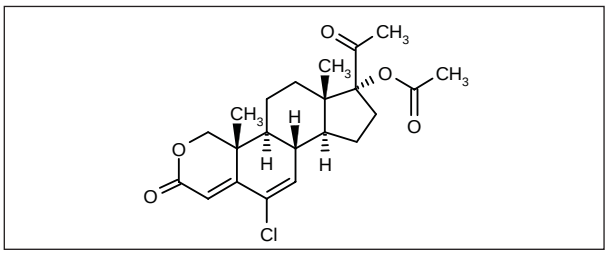
2. *IND approval for NicOx's HCT-1026 for urinary incontinence*. DailyDrugNews.com (Daily Essentials) Jan 8, 2002.

3. *Positive results obtained for HCT-1026 as treatment for contact urticaria*. DailyDrugNews.com (Daily Essentials) April 20, 2001.

4. Coudoré, M.M.M.-A., Eschalier, A., Riffaud, J.-P., Boucher, M. *Antinociceptive effects of the nitro-derivative of flurbiprofen (HCT 1026) on a newly-developed inflammatory vesical pain model in the rat*. Inflamm Res 2001, 50(Suppl. 3): Abst 068.

Original monograph - Drugs Fut 1999, 24(8): 858.

Osaterone Acetate



The steroidal antiandrogen osaterone acetate (TZP-4238, Hipros; Teikoku Hormone) is under regulatory review in Japan for the treatment of BPH.

Researchers assessed the pharmacokinetics and biliary excretion of osaterone in intact dogs and biliary fistula dogs. Biexponential disposition and a very long half-life were noted in intact dogs. Biliary recycling was also significant in this species (1).

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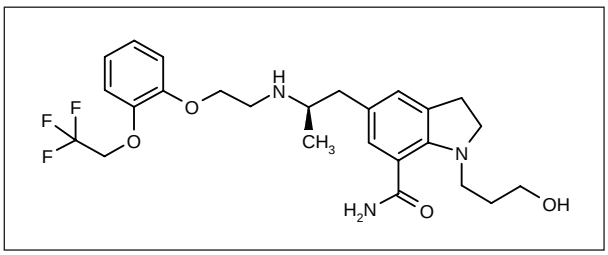
Original monograph - Drugs Fut 1993(6), 18: 516.

Silodosin



Silodosin (KMD-3213, KAD-3213) is an α_1-adrenoceptor antagonist with potential for the treatment of urinary disturbances associated with BPH. Kissei has entered into an agreement with Daiichi Pharmaceutical under which they will codevelop silodosin starting in phase III trials. The companies will comarket the product in Japan under different brand names, while Kissei retains development and marketing rights overseas. The compound has completed phase II studies in Japan and is currently in U.S. phase II trials (1).

Continuous i.v. infusion of silodosin for 70 or 100 min in rats resulted in significantly greater α_1-adrenoceptor binding in the prostate than after a 10-min infusion. Additionally, continuous infusion for 70 or 100 min significantly reduced phenylephrine-induced increases in mean blood pressure and intraurethral pressure. The specific binding properties of silodosin in the rat prostate may therefore be related to the drug's effect on the lower urinary tract (2).

A study providing the first *in vivo* evidence for higher binding affinity for silodosin at the α_{1A}-adrenoceptor *versus* the α_{1B}- and α_{1D}-adrenoceptor subtypes was recently published. Initial *in vitro* studies demonstrated saturable and reversible, specific binding of [^{3}H]-silodosin and [^{3}H]-prazosin in rat prostate (K_d = 49.3 and 73.4 pM, respectively; B_{max} = 17.8 and 22.2 fmol/mg protein, respectively) and rat submaxillary gland (K_d = 55.0 and 84.9 pM, respectively; B_{max} = 111 and 130 fmol/mg protein, respectively). However, in spleen preparations, only [^{3}H]-prazosin exhibited a considerable degree of binding. Following i.v. injection to rats, a significant degree of specific [^{3}H]-silodosin binding was detected in all tissues except the cerebral cortex, spleen and liver. However, the degree of specific binding was markedly different in different tissues, with a rank order of kidney > heart > lung > submaxillary gland > prostate > aorta, and significant differences in the time course of specific binding were also seen; specific binding in the lung, kidney and spleen achieved maximum levels at 10 min and declined rapidly, whereas levels in the submaxillary gland, vas deferens and prostate reached a maximum at 60 min and decreased gradually. Compared with [^{3}H]-prazosin, the

AUC_{0-120} values for [^{3}H]-silodosin were significantly lower in the aorta, spleen and liver, but higher in the prostate, submaxillary gland and lung. The specific binding of [^{3}H]-silodosin (1.4-13.6 nmol/kg) and [^{3}H]-prazosin (1.2-10.6 nmol/kg) at doses previously reported to dose-dependently inhibit phenylephrine-induced increases in intraurethral pressure in rats was dose-dependent in rat prostate, indicating a close correlation between prostatic α_1-adrenoceptor binding and functional activity; specific binding of [^{3}H]-silodosin was also dose-dependent in submaxillary gland, but not spleen, whereas that of [^{3}H]-prazosin was dose-dependent in all tissues examined. Furthermore, the specific binding of [^{3}H]-silodosin was attenuated in a dose-dependent manner by low i.v. doses of prazosin, but not yohimbine, an alpha$_2$-adrenoceptor-selective antagonist. Overall, these *in vivo* findings indicate that [^{3}H]-silodosin, unlike prazosin, has substantially higher affinity for the α_{1A}-adrenoceptor found predominantly in submaxillary gland and prostate compared with the α_{1B}-adrenoceptor located mainly in the spleen and liver. These findings thus support the development of silodosin for the treatment of BPH (3).

The uroselectivity of silodosin, prazosin and tamsulosin was compared in decerebrate dogs by evaluation of the inhibitory effects of the drugs on the increase in urethral pressure induced by electrical stimulation of the hypogastric nerve. Silodosin was found to be 12- and 7.5-fold more uroselective than prazosin and tamsulosin, respectively, when the drugs were administered i.v. (4).

Both silodosin and tamsulosin were found to reduce unstable bladder contractions in a rat model of BPH (5).

The effects of silodosin were evaluated in a rat BPH model. In this model, testosterone- and 17β-estradiol-treated rats developed significant increases in prostate and bladder weights compared to normal animals, as well as bladder overactivity and increases in micturition volume and threshold pressure, after 4 weeks. Treatment with silodosin produced dose-dependent reductions in bladder overactivity and elevated threshold pressure. The investigators concluded that silodosin may not only improve bladder function, but also irritative symptoms associated with BPH (6).

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2. Akiyama, K., Tatemichi, S., Katayama, S., Nakajima, M., Oki, T., Okura, T., Yamada, S., Kimura, R. *Relationship between prostatic α_1-adrenoceptor binding and reduction in intraurethral pressure following continuous infusion of KMD-3213 in rats*. Pharmacology 2002, 64(3): 140.

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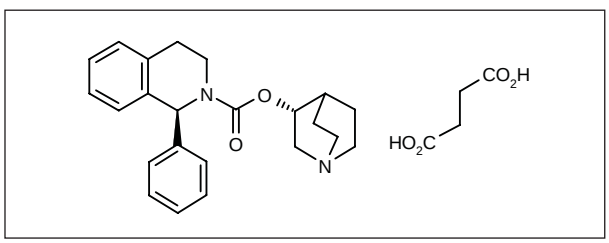
Solifenacin Succinate



The muscarinic M_3 receptor antagonist solifenacin succinate (YM-905, YM-53705; Yamanouchi) is in phase III trials for pollakiuria and urinary incontinence in the U.S. and Europe (1).

The binding characteristics of solifenacin to muscarinic receptors were examined *ex vivo* following oral administration (30 and 100 mg/kg) to mice. A significant dose-dependent increase in the K_d value for [^{3}H]-scopolamine was observed, with little change in the B_{max} in the bladder, prostate, submaxillary gland, heart, colon and lung, indicating competitive binding of solifenacin to receptors. The increased K_d seen in the bladder, prostate, submaxillary gland and colon was sustained for 6 or 12 h (2).

Bladder-selective anticholinergic agents have received much attention as potential therapeutic agents for urinary incontinence with reduced side effects. The binding characteristics of the antimuscarinic agent solifenacin were recently compared to oxybutynin *in vitro* and after oral administration to mice. In an *in vitro* binding assay, a concentration-dependent inhibition of specific *N*-methyl-[^{3}H]-scopolamine ([^{3}H]-NMS) binding was seen for solifenacin (3-1000 nM) and oxybutynin in submaxillary gland, bladder and heart, in descending order. In mice treated with oral solifenacin (20.8, 62.4, 208 mol/kg), K_d values for specific [^{3}H]-NMS binding were significantly increased in a dose-dependent manner in the bladder, prostate, submaxillary gland, heart, colon and lung, with peak effect at 2 h and significant effects lasting for up to 12 h. This was in contrast to the rapid achievement of peak plasma

levels for solifenacin (0.5 h after administration). On the other hand, although similar muscarinic receptor blockade was seen with oxybutynin, the peak effect was reached much sooner (0.5 h) and the duration of its effect was shorter, disappearing by 6 h. It is suggested that the slow kinetics of muscarinic receptor binding may contribute to the slow onset and prolonged duration of action of solifenacin in overactive bladder, as well as its reduced incidence of side effects (3).

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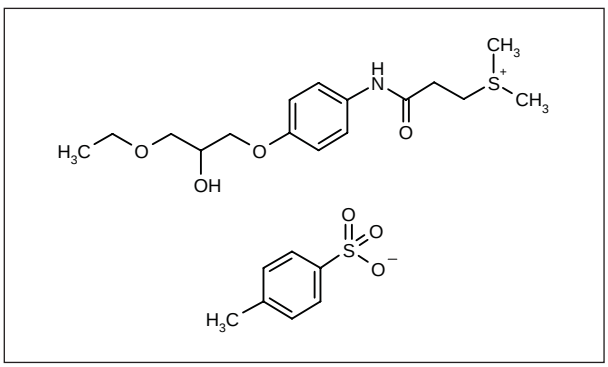
Suplastat Tosilate



The mediator release inhibitor suplatast tosilate (IPD-1151T) is currently marketed in Japan by Taiho for the treatment of asthma and studies are under way to evaluate its efficacy in interstitial cystitis.

A study has compared the effect of several different drugs (pentosan polysulfate, hydroxyzine hydrochloride, prednisolone and suplatast) on the bladder function of HCl-IC rats with interstitial cystitis. The disorder was induced by injection of HCl into the bladder and on the following day the animals started receiving a single daily dose of one of the study drugs for 7 days. The results indicated that suplatast tosilate might be more effective for treating interstitial cystitis than the other study drugs, as it improved bladder function parameters to a greater extent (1).

The effect of suplatast (0.1-100 mg/kg) was assessed in rat models of HCl-induced interstitial cystitis and cyclophosphamide-induced hemorrhagic cystitis. Suplatast improved bladder function and histopathology in the interstitial cystitis model and improved bladder function in the hemorrhagic cystitis model (2).

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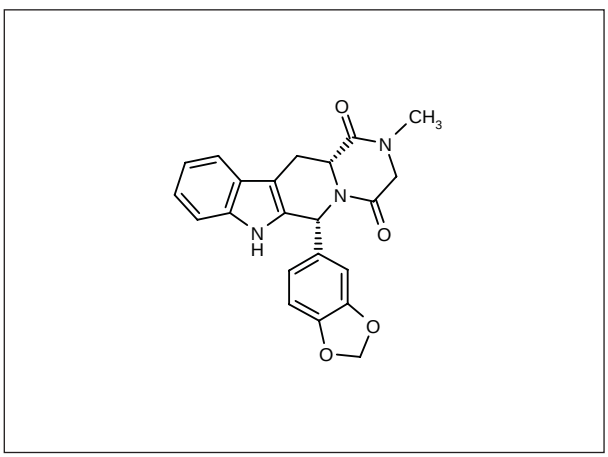
Tadalafil



Lilly Icos, a joint venture between Icos and Lilly, has received an approvable letter from the FDA for the phosphodiesterase type 5 (PDE5) inhibitor tadalafil (Cialis™, IC-351) for the treatment of erectile dysfunction (ED). Approval is dependent on successful completion of additional pharmacology studies, labeling discussions and manufacturing inspections. Based on these requirements, a U.S. launch for Cialis™ is expected in 2003. The joint venture has also received a positive opinion from the European Committee for Proprietary Medicinal Products (CPMP) for approval of tadalafil for ED. The PDE5 inhibitor is also in phase II evaluation for the treatment of female sexual dysfunction (1-7).

An *in vitro* study using various recombinant PDEs, PDE6 from human retina and human corpus cavernosum tissue and penile arteries collected from men with ED showed that tadalafil potently and selectively inhibited PDE5 (IC_{50} = 0.9 nM) and enhanced NO-mediated responses in penile smooth muscle via potentiation of cGMP accumulation. Higher concentrations of the agent were needed to inhibit other PDEs (*e.g.*, IC_{50} for PDE6 = 730 nM). Tadalafil (30 nM) also enhanced neurogenic relaxation of trabecular smooth muscle, significantly increased sodium nitroprusside-induced cGMP accumulation in human cavernosal tissue and enhanced acetylcholine-induced relaxation of penile smooth muscle (8-10).

The pharmacokinetic properties of tadalafil (10 or 20 mg) were compared in several studies involving healthy male and female young (19-45 years) and elderly (65-78 years) subjects and subjects with diabetes, renal insufficiency or hepatic insufficiency. Systemic tadalafil exposure was 25% greater in elderly as compared to young subjects and steady-state concentrations were 13% higher in women compared to men. Systemic exposure to the agent was 19% in subjects with diabetes compared to healthy age- and gender-matched subjects. While similar systemic exposure was observed between healthy subjects and subjects with mild and moderate hepatic insufficiency, subjects with mild and moderate renal insufficiency had higher AUC values. Overall, it was concluded that differences in age, gender and the presence of diabetes had no significant effects on the pharmacokinetics, and that dose adjustment for patients with hepatic insufficiency would not be necessary. Ingestion of a standard high-fat breakfast before dosing did not alter the rate and extent of tadalafil absorption. The most common treatment-related adverse events were mild to moderate back pain and headache (11, 12).

Data from 13 studies were pooled to evaluate the pharmacokinetic parameters of single doses of tadalafil 10 or 20 mg given to 237 healthy, fasted subjects. Analysis of the data indicated rapid absorption, tissue distribution and elimination primarily by the liver. The $t_{1/2}$ of 17.5 h corresponded well to clinical trial findings of a 24-h period of responsiveness to tadalafil (13, 14).

The potential interactions between tadalafil and sublingual nitroglycerin were examined and compared to those between sildenafil and SL nitroglycerin in a double-blind, randomized, crossover study in healthy volunteers. In contrast to sildenafil, tadalafil demonstrated no significant effect compared to placebo on the mean blood pressure changes caused by SL nitroglycerin, but no significant difference was seen when the two PDE5 inhibitors were directly compared. However, further analysis indicated that both agents increased the blood pressure decrease induced by nitrates in a subset of patients and the investigators recommended that tadalafil, like sildenafil, not be used in subjects taking nitrates (15). Table III summarizes these results and those from some of the studies that follow.

Analysis of data from 5 double-blind, randomized, placebo-controlled phase III trials in 1112 normotensive and hypertensive men with ED taking tadalafil (2.5-20 mg) as needed up to once daily have been reported. Tadalafil consistently and significantly improved all erectile function endpoints compared to placebo across different patient populations, with improved erections in 81% and an increase in the percentage of successful intercourse attempts of up to 75%. The efficacy of the agent was the same regardless of blood pressure status. Adverse events, mostly headache and dyspepsia, were generally mild or moderate and transient, and the discontinuation rate due to adverse events was similar in tadalafil and placebo patients (16-19).

Phase III data demonstrated impressive results for tadalafil in one of the most difficult-to-treat populations of men with ED. In this study, 216 men with mild to severe diabetes-related ED were randomized to receive either placebo or tadalafil on demand at doses of up to 20 mg for 12 weeks. The results showed that 64% of men on the highest dose of tadalafil had improved erections compared to only 25% on placebo. Treatment with tadalafil significantly improved sexual function compared to placebo across all primary and secondary study endpoints, regardless of patient age, duration and severity of ED or diabetes. Study participants reflected a broad cross-section of men with diabetes and included those with poor glucose control, diabetic retinopathy and diabetic kidney disease. Despite these diabetes-related complications, few side effects were reported, with headache and dyspepsia being the only effects reported in more than 5% of study participants; the majority of adverse events were mild to moderate and appeared to diminish with continued treatment. Moreover, no clinical laboratory, ECG or blood pressure changes were seen, and tadalafil was not associated with disturbances in color vision (20-25).

Further clinical trial results have demonstrated that tadalafil improved the ability of men to achieve erections up to 24 h after drug administration. Two trials measured the responsiveness to tadalafil. In the first trial, 61 men with mild to severe ED were randomized to receive tadalafil 10 mg or placebo in a clinical setting. After taking tadalafil, RigiScan™ evaluations, a measure of the firmness and duration of erections, during exposure to visual sexual stimulation were conducted. Men in the tadalafil group were significantly more successful in achieving erections than men in the placebo group, even when evaluated at 24 h. The second trial observed responsiveness in a more natural setting. In this trial, 223 men received tadalafil (up to 20 mg) or placebo in a home-based study. The men participating in the study took the medication immediately before engaging in sexual activity and used a stopwatch to record the elapsed time until they achieved an erection sufficient for successful intercourse. In this trial, the ability to achieve an erection after sexual stimulation was statistically superior in the group taking tadalafil compared with the placebo group at 16 min postdosing. Subjects who received tadalafil also recorded statistically significantly more

Table III: Clinical studies of tadalafil for the treatment of erectile dysfunction (from Prous Science Integrity®).

Design	Treatments	n	Conclusions	Ref.
Randomized, double-blind, crossover	Tadalafil, 10 mg po → + Nitroglycerin s.l. Sildenafil, 50 mg po → + Nitroglycerin s.l. Placebo → + Nitroglycerin s.l.	49	Although tadalafil did not show any significant effect on mean blood pressure changes induced by nitrates and sildenafil increased it in comparison with placebo, neither drug should be used in combination with nitrates due to the potentiation in the decrease of blood pressure	15
Randomized, double-blind, multicenter, pooled/meta-analysis	Tadalafil, 2.5-20 mg od PRN x 12-24 wk Placebo	1112	Tadalafil was well tolerated and significantly effective in increasing the percentage of successful intercourse attempts in patients with erectile dysfunction	16-18
Randomized, double-blind, multicenter	Tadalafil, 10 mg po PRN x 12 wk (n=72) Tadalafil, 20 mg po PRN x 12 wk (n=73) Placebo (n=71)	216	Tadalafil 10 and 20 mg was well tolerated and effective in improving erectile function when administered on demand for the treatment of mild to severe erectile dysfunction in patients with diabetes	20-24
Randomized, double-blind, crossover, multicenter	Study 1: (n=61) Tadalafil, 10 mg po Placebo Study 2: (n=223) Tadalafil, 10 mg po 1x/8-10 d x 4 doses Tadalafil, 20 mg po 1x/8-10 d x 4 doses Placebo	284	Tadalafil 20 mg was well tolerated and effective in improving erectile function, enabling the completion of intercourse as early as 16 min postdosing. The effect was maintained for at least 2 h postdosing, enabling multiple successful intercourse attempts	26, 28
Randomized, double-blind, multicenter	Tadalafil, 2 mg po PRN x 8 wk (n=42) Tadalafil, 5 mg po PRN x 8 wk (n=44) Tadalafil, 10 mg po PRN x 8 wk (n=42) Tadalafil, 25 mg po PRN x 8 wk (n=43) Placebo (n=41)	212	Tadalafil at doses of 5-25 mg was well tolerated and effective in improving penetration ability and maintaining erection during intercourse when administered on demand for the treatment of mild to severe erectile dysfunction	31, 32
Multicenter, pooled/meta-analysis	Tadalafil, 20 mg (n=949) Placebo (n=379)	1328	Tadalafil was safe, had little effect on systemic arterial pressure and was not associated with an increased incidence of cardiovascular events in patients with erectile dysfunction	33, 34
Randomized, double-blind, multicenter	Tadalafil, 20 mg po (before intercourse) Placebo	348	Tadalafil was well tolerated and more effective than placebo, enabling men with mild to severe erectile dysfunction to have successful intercourse up to 36 h after one 20-mg dose	35
Randomized, double-blind, multicenter	Tadalafil, 2 mg po PRN x 3 wk (n=35) Tadalafil, 5 mg po PRN x 3 wk (n=37) Tadalafil, 10 mg po PRN x 3 wk (n=36) Tadalafil, 25 mg po PRN x 3 wk (n=36) Placebo (n=35)	179	On-demand tadalafil was well tolerated and improved erectile dysfunction at doses up to 25 mg	36

success at second sexual encounters than patients who received placebo for a period of up to 24 h after dosing. No adverse effects were reported. Good tolerability was also observed over the entire duration of the drug's effect (26-29).

Results from an exploratory placebo-controlled trial of tadalafil showed no conclusive treatment effect relative to placebo in women with female sexual arousal disorder (FSAD). The study was designed to evaluate the efficacy and safety of tadalafil at different doses in treating FSAD. The randomized, double-blind, placebo-controlled study involved a total of 214 premenopausal women who received up to 20 μg of tadalafil or placebo on demand. They were evaluated using diary reports and a standardized recall questionnaire called the Female Sexual Dysfunction Index to assess change from baseline in sexual functioning, including degree of genital and subjective arousal, lubrication, orgasmic function and satisfaction. Tadalafil was well tolerated in these subjects, and the most frequently reported side effect was headache (30).

Men with mild to severe ED (n=212) were randomized to on-demand placebo or tadalafil 5-25 mg in an 8-week, multicenter, double-blind trial. Tadalafil was well tolerated and significantly better than placebo in improving measures of penetration ability and the ability to maintain an erection during intercourse, as well as other measures of sexual function (31, 32).

Analysis of the results of several large phase III clinical trials on the safety and efficacy of tadalafil as a treatment for ED concluded that the treatment is not associated with an increase in the incidence of cardiovascular events and has little effect on systemic arterial pressure (33, 34).

In a randomized, double-blind, placebo-controlled study, 348 men with mild to severe ED received tadalafil 20 mg or placebo and attempted intercourse 2 times 24 h after a dose and 2 times 36 h after a dose. At both time intervals, tadalafil significantly increased the percentage of successful intercourse attempts compared to placebo (57.3% *vs*. 31.3% and 60.4% *vs*. 29.9% at 24 and 36 h, respectively) (35).

The efficacy and safety of on-demand tadalafil (2, 5, 10 or 25 mg for 3 weeks) were confirmed in a multicenter, randomized, double-blind, placebo-controlled trial involving 179 men (mean age = 56 years) with ED. Treatment was well tolerated, with no changes in laboratory parameters, ECG or blood pressure seen. The most common adverse events were dyspepsia and headache. All doses of the agent resulted in significant improvements in question 3 scores of the International Index of Erectile Function (IIEF) as compared to placebo. Doses of 5 mg and higher also significantly improved question 4 as compared to placebo (36).

Results from a phase III placebo-controlled trial of tadalafil showed that 85% of men taking 20 mg reported improved erections. Two additional studies demonstrated an improved ability to achieve erections up to 24 h after taking the drug. The phase III study examined the safety and efficacy of on-demand tadalafil treatment in 196 men with mild to severe ED. Men were randomized to receive up to 20 mg of tadalafil or placebo over 12 weeks and were free to have sex with their partners at any time after each dose. In the study, 85% of men taking tadalafil 20 mg reported significantly improved erections compared to baseline. In addition, 78% of all intercourse attempts recorded by the men on this dose were successful. Also, 63% of men treated with tadalafil 20 mg achieved an erectile function score considered normal for healthy men, as measured by the IIEF. On the lower dose of 10 mg, 92% of men reported improved erections and 70% of intercourse attempts were successful. Normal IIEF scores were achieved by 42% of these men. For comparison, on placebo, 54% of patients reported improved erections, 43% of intercourse attempts were successful and 20% of patients attained IIEF scores in the normal range. Side effects were mild to moderate and the incidence decreased with continued treatment. The most commonly reported adverse events were backache, muscle aches and upset stomach. No clinically significant changes in blood pressure, heart rate, ECG or laboratory tests were seen (37).

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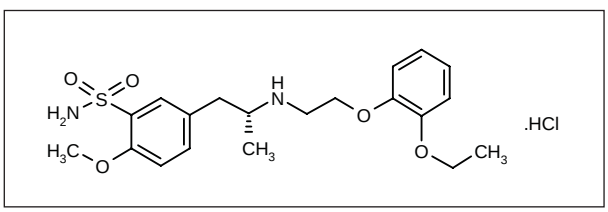
Tamsulosin Hydrochloride



Tamsulosin hydrochloride was discovered and developed by Yamanouchi, which launched it in Japan in 1993 as Harnal(R) for the treatment of BPH. The product was subsequently introduced in a number of other countries, including the U.S., Canada and several European countries, in some cases by licensee Boehringer Ingelheim.

Researchers reported that the highly selective retention of tamsulosin in the prostate and bladder of dogs could be the cause of the higher uroselectivity of the drug in this species as compared to rats (1).

In a rabbit model of bladder outlet obstruction, pretreatment with tamsulosin prevented increases in bladder weight and bladder wall thickness and improved bladder dome responsiveness to methoxamine (2).

The relationship between the pharmacokinetics and pharmacodynamics of tamsulosin (30 and 100 μg/kg orally) was explored in conscious dogs. The elevation in prostatic intraurethral pressure (IUP) induced by phenylephrine administration was inhibited by tamsulosin, with a peak inhibition at 1-2 h after dosing. With the 100 μg/kg dose, plasma concentrations of tamsulosin peaked at

Table IV: Clinical studies of tamsulosin hydrochloride for the treatment of benign prostatic hyperplasia (from Prous Science Integrity®).

Design	Treatments	n	Conclusions	Ref.
Open, multicenter, pooled/meta-analysis	Tamsulosin x 12 mo Alfuzosin Finasteride Placebo	1031	Tamsulosin, alfuzosin and finasteride were effective in decreasing the long-term risk of acute urinary retention in patients with benign prostatic obstruction or lower urinary tract symptoms	5
Randomized, double-blind, multicenter	Tamsulosin, 0.4 mg po od x 52 wk (n=161) Tamsulosin, 0.4 mg po od + Permixon, 160 µg po bid x 52 wk (n=168)	329	Tamsulosin plus Permixon combination therapy did not provide any additional benefit over tamsulosin alone for the treatment of benign prostatic hyperplasia	6, 7
Randomized, double-blind, multicenter	Tamsulosin, 0.4 mg po od x 12 mo (n=354) Permixon, od x 12 mo (n=350)	704	Tamsulosin and Permixon showed similar efficacy for the treatment of benign prostatic hyperplasia	9
Randomized, double-blind, multicenter	Tamsulosin, 0.4 mg od x 3 - 7 day x 6 mo (n=71) Placebo (n=70)	141	Tamsulosin reduced the rate of urinary recatheterization after an episode of acute urinary retention in elderly patients	10
Randomized, double-blind, multicenter	Tamsulosin, 0.4 mg od x 3-7 d (n=75) Placebo (n=74)	149	Tamsulosin was effective in decreasing the need for recatheterization after an episode of acute urinary retention in elderly patients with benign prostatic hyperplasia	11
Randomized, double-blind	Tamsulosin + Finasteride x 6-12 mo → Finasteride Tamsulosin x 12 mo → Placebo	120	Finasteride was effective in sustaining the subjective and objective improvements after tamsulosin discontinuation in patients with enlarged prostates and lower urinary tract symptoms	19
Randomized	Tamsulosin + Finasteride x 6-12 mo → Finasteride	75	Tamsulosin discontinuation was tolerated by most patients with enlarged prostates and lower urinary tract symptoms treated with finasteride plus tamsulosin combination	20

0.4 h after dosing, while peak prostatic and urethral levels were reached at 2 h. Peak drug concentrations showed the following rank order: prostate > urethra > plasma > bladder > aorta > mesenteric artery > carotid artery. At specific points in time, drug concentrations in the prostate were 3.7-18.0 times higher than in the plasma and 3.8-6.6 times higher than in the mesenteric artery. Therefore, the effects of tamsulosin on IUP appear to be due, at least in part, to selective retention of this drug in prostatic and urethral tissues (3).

Tamsulosin hydrochloride is used in the treatment of patients with BPH. A pooled analysis of results from 2 European open-label long-term studies in patients with LUTS/BPH treated for up to 4 years was reported. These extension trials enrolled a total of 516 patients from 3 double-blind, controlled phase III studies comparing tamsulosin 0.4 once daily with placebo or alfuzosin 2.5 mg t.i.d. The significant improvement in maximum urine flow and total Boyarsky symptom score obtained during the controlled trials was sustained throughout the duration of the extension study, and the percentage of treatment responders, defined as having at least a 25% decrease in total symptom score, also remained stable at 74-81% for up to 4 years. A total of 91 (18%) patients had the dose increased to 0.8 mg/day, but this had no substantial beneficial effect. Possibly drug-related side effects, including dizziness and abnormal ejaculation, were reported by about one-fourth of the patients, and only 5% withdrew from the studies due to side effects. No clinically relevant changes in blood pressure or pulse rate were seen. It was concluded that tamsulosin induces a rapid and sustained response in symptoms in LUTS/BPH patients and is well tolerated over the long term. While it appears to have comparable efficacy to other drugs in this class, it has a much better safety profile, particularly as regards dizziness, asthenia and postural hypotension (4).

A pooled analysis of 2 open-label trials showed that patients with benign prostatic obstruction treated with tamsulosin had a lower incidence of acute urinary retention than patients treated with placebo, thus suggesting a role for tamsulosin in the prevention of acute urinary retention (5). Results from this study and some that follow are summarized in Table IV.

In 329 patients with LUTS and BPH, the combination of tamsulosin and an extract of the plant *Serenoa repens* over 1 year did not improve storage/filling, voiding and symptom scores compared to tamsulosin alone (6, 7).

Data from a randomized, double-blind, parallel-group trial comparing the safety and efficacy of tamsulosin 0.4 mg/day with phytotherapy with a lipidosterolic extract of *Serenoa repens* (LSESr, Permixon®) 320 mg/day in patients with LUTS due to BPH were reported. About 84% of the 704 patients randomized (354 patients to tamsulosin and 350 to LSESr) completed the 52-week comparative treatment period. Both treatments showed similar efficacy, including a 27% decrease in IPSS. However, prostate volume increased in patients receiving tamsulosin and decreased in those receiving LSESr. Although both treatments were well tolerated, ejaculation disorders occurred in 4.2% of patients in the tamsulosin arm, as compared to only 0.4% of those in the LSESr arm (8, 9).

A multicenter, randomized, double-blind, placebo-controlled trial evaluated treatment with tamsulosin 0.4 mg once daily or placebo for up to 6 months in 149 elderly males with acute urinary retention (AUR) due to BPH. Tamsulosin reduced the need for recatheterization following a trial without catheter after an AUR episode (10, 11).

The antidepressant drug reboxetine, a selective noradrenaline reuptake inhibitor, has been shown in clinical trials to cause an increase in urinary hesitancy and retention, primarily in male patients. It has been postulated that this side effect may be caused by a peripheral noradrenergic mechanism. The effectiveness of tamsulosin hydrochloride in relieving these symptoms was assessed in 6 male patients. Symptoms were evaluated using the American Urological Association symptom index; patients were then started on tamsulosin treatment and the questionnaire was repeated 1 week later. Total symptom scores between first and second symptom assessments decreased significantly. The researchers concluded that an α_{1A}-adrenoceptor antagonist such as tamsulosin may be effective in the treatment of LUTS associated with reboxetine (12).

In a multicenter, open-label phase IIIB extension study, 609 patients with LUTS due to BPH received a 0.4-mg maintenance dose of tamsulosin once or twice daily. Of these patients, 418 completed 5 years of treatment and 109 completed 6 years of treatment. The number of patients who responded – defined as a decrease of 25% or more in TAUASS (Total AUA Symptom Score) from baseline – was greatest during the first year, and response was generally maintained throughout the extension period. Therefore, tamsulosin appears to have sustained beneficial effects in patients with BPH-associated LUTS (13, 14).

The long-term efficacy and safety of tamsulosin were assessed in a randomized, placebo-controlled study in patients with neurogenic lower urinary tract dysfunction (NLUTD) due to suprasacral spinal cord lesions. A total of 263 patients were randomized to 0.4 or 0.8 mg of tamsulosin once daily or placebo for 4 weeks; 134 of these continued on open-label therapy for 1 year. Tamsulosin therapy led to a nonsignificantly greater reduction in maximum urethral pressure (MUP) at 4 weeks as compared to placebo, and patients receiving the drug for 1 year showed an even more pronounced reduction. In addition, patients receiving tamsulosin had significantly reduced maximum urethral closure pressure and improved cystometric parameters related to bladder storage and emptying, as well as increased mean voided volume according to the micturition diary. IPSS-QoL score and urinary leakage also showed improvement over baseline. Autonomic dysreflexia symptoms improved significantly with tamsulosin therapy and the drug was well tolerated at both doses (15).

The randomized, multicenter, double-blind MICTUS (Multicenter Investigation to Characterize the effect of Tamsulosin on Urinary Symptoms) trial compared once-daily tamsulosin 0.4 mg with finasteride 5 mg begun after a 2-week placebo run-in in 403 patients with LUTS suggestive of BPH. After 26 weeks, it was determined that patients receiving tamsulosin had a more rapid increase in urinary flow, with a greater improvement in the level of discomfort (16).

A single-center, open-label study explored whether outlet obstruction influences the efficacy of tamsulosin therapy for LUTS. Men over 45 years of age with an IPSS score over 13 and an independent flow rate of 4-16 ml/s were given 0.4 mg/day of tamsulosin for 12 weeks. Of the 42 participants, 30 had proven obstruction. IPSS scores showed similar reductions of 37 and 34% in the obstructed and nonobstructed groups, respectively. Moreover, mean free flow rate increased in both the obstructed and nonobstructed groups. Thus, the efficacy of tamsulosin in LUTS appears to be similar in patients with and without proven obstruction (17).

The feasibility of administering tamsulosin to patients with nonbacterial prostatitis was confirmed by a double-blind, placebo-controlled pilot study in 58 patients. The prostatitis symptom index improved more with tamsulosin than with placebo. The beneficial effects of tamsulosin over placebo were more evident in patients with severe prostatitis and seemed to increase after longer treatment periods (18).

Results of a placebo-controlled study in 120 patients with enlarged prostates and LUTS showed that men who were initially treated with tamsulosin, followed by combination with finasteride, were more likely to tolerate discontinuation of tamsulosin treatment than those treated only with placebo (19, 20).

The National Institutes of Health (NIH) has initiated a clinical trial to evaluate the efficacy, safety and tolerability of tamsulosin hydrochloride and ciprofloxacin as combination treatment for nonbacterial prostatitis. The multisite, double-blind, randomized, placebo-controlled trial is the first to study the combination as compared to each agent alone. Approximately 184 patients will be treated for 6 weeks and followed for an additional 6 weeks. The study is also the first to use the newly developed and validated NIH-Chronic Prostatitis Symptom Index (NIH-CPSI) to measure symptom severity, the primary study outcome.

Other secondary endpoints will include a participant-reported global response assessment at 6 weeks or withdrawal, and laboratory measures including white blood cells in expressed prostatic secretions. Study enrollment is to be completed by the summer of 2002 and results are expected by the end of 2002 (21).

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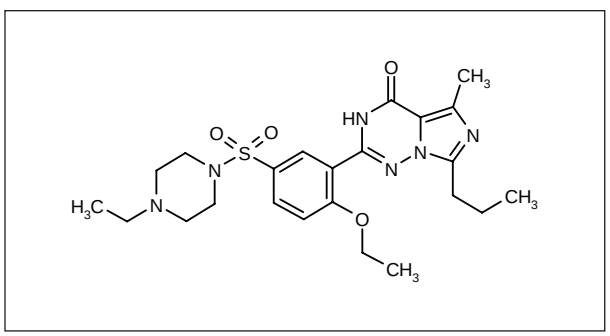
Original monograph - Drugs Fut 1986, 11(4): 293.

Vardenafil



Vardenafil (Bay-38-9456) is a potent and highly selective PDE5 inhibitor developed by Bayer and subsequently licensed to GlaxoSmithKline for copromotion. The compound was evaluated in multiple phase III trials involving some 4000 patients prior to regulatory submissions in the E.U., the U.S., Canada, Mexico and Japan seeking its approval for the treatment of male ED. The companies have received an approvable letter from the FDA and the product is now expected to be launched in 2003 (1-5).

In soluble extracts of human corpus cavernosum smooth muscle cells, vardenafil more potently inhibited PDE5 than sildenafil. In the presence of NO in intact cells, vardenafil led to a greater increase in cGMP, indicating that it may be more effective than sildenafil at lower doses (6, 7).

In vitro studies using various PDEs (bovine aortic PDE1, bovine heart PDE2, PDE3 and PDE4, human platelet PDE5 and bovine retina PDE6) and human corpus cavernosum tissue collected from men with ED showed that vardenafil potently inhibited PDE5 (IC_{50} = 0.7 nM). The agent was 224-, 257- and 3600-fold less active against PDE6, PDE1 and other PDEs, respectively. The compound produced a concentration-dependent (0.1-10 μM) increase in cGMP levels in rabbit corpus cavernosum, while cAMP levels were not affected. In addition, it significantly and concentration-dependently (1 nM-100 μM) relaxed phenylephrine-contracted corpus cavernosum, relaxed sodium nitroprusside (SNP)-induced responses in trabecular smooth muscle, improved acetylcholine-induced relaxation of trabecular smooth muscle, enhanced neurogenic relaxation of trabecular smooth muscle and concentration-dependently enhanced SNP-induced cGMP accumulation in human cavernosal tissue (8, 9). The inhibition of various PDEs with vardenafil was also investigated in bovine tissues, SF9 cells transfected with human recombinant PDEs and in enzymes of murine origin. Vardenafil demonstrated strong inhibition of PDE5 and weak inhibition of other PDEs (10). Other experiments confirmed the selectivity of vardenafil for PDE5 and the drug's ability to potentiate NO-mediated relaxation and to alter cGMP levels in human corpus cavernosum strips. *In vivo*, orally administered vardenafil dose-dependently (starting at 0.1 mg/kg) potentiated erectile responses to i.v. doses of SNP in rabbits (11). The pharmacological activities of vardenafil and sildenafil were investigated in human corpus cavernosum tissue and in conscious rabbits. Vardenafil demonstrated greater potency in increasing cGMP accumulation produced by SNP, as well as in inducing relaxation in human penile smooth muscle and in enhancing erectile responses in rabbits (12).

In conscious rabbits, oral vardenafil 1-30 mg/kg dose-dependently induced erections. Sodium nitroprusside potentiated this effect and reduced the effective doses of vardenafil. Sildenafil was also effective, although less potent than vardenafil (13, 14).

In rabbits, i.v. administration of 1, 3, 10 and 30 μg/kg vardenafil proved more effective than the same doses of sildenafil in facilitating pelvic nerve-mediated penile erection, assessed through monitoring of intracavernosal pressure (15-19). In conscious rabbits, vardenafil (0.1-3 mg/kg i.v.) induced erections, an effect potentiated by concomitant administration of SNP. Intravenous sildenafil and phentolamine 0.1, 0.3 and 1 mg/kg also induced erections in this model while less efficacy was demonstrated with milrinone 1 mg/kg (20).

In rabbit corpus cavernosum, vardenafil was found to dose-dependently increase cGMP levels, while not affecting cAMP levels. Erectile responses induced by electrical stimulation in rats were also increased by vardenafil 0.1 and 1 mg/kg (21).

An *in vivo* study using an anesthetized rat model of penile erection (*i.e.*, stimulation of the cavernous nerve 3, 13 and 23 min after dosing) compared the efficacy of vardenafil with sildenafil (0.1 or 1 mg/kg i.v.). The higher dose of both agents significantly increased the AUC/diastolic blood pressure (DBP) values (+25 and +22%, respectively) and the maximum intracavernous pressure (ICP_{max})/DBPx100 values (+20 and +18%, respectively) of the 3 erectile responses measured as compared to controls. In contrast to 0.1 mg/kg sildenafil which had no effect on ICP_{max}/DBP and only significantly increased AUC/DBP of the erectile responses at 3 min (+15%), vardenafil significantly increased the ICP_{max}/DBPx100 value for erectile responses at 3 (+20%) and 13 (+18%) min and significantly increased the AUC/DBP value for erectile responses at 3 (+26%) and 13 (+21%) min (22).

Vardenafil demonstrated greater potency than sildenafil in inducing penile erections in a study in conscious rabbits. Vardenafil appeared to be well absorbed and distributed and may be effective in humans at lower doses than sildenafil (23).

A randomized, placebo-controlled study examined the interaction between a single dose of nitroglycerin 400 μg taken after a series of doses of vardenafil 10 mg or placebo. The subjects evaluated were 18 healthy males 40-65 years of age. Changes in blood pressure and heart rate seen in patients taking vardenafil and nitroglycerin were similar to those observed in patients taking nitroglycerin and placebo at 1, 4, 8 and 24 h (24). These results and those from some of the studies that follow are summarized in Table V.

The efficacy of vardenafil (5, 10 or 20 mg) taken on demand for 12 weeks was analyzed in demographic and diagnostic subgroups of patients participating in a randomized, placebo-controlled phase IIb study involving at total of 601 men with ED of various etiologies for at least 6 months. All doses of the agent were well tolerated and resulted in significant improvements over placebo in all levels of erectile dysfunction severity in the IIEF. The rate of successful sexual intercourse was significantly greater with vardenafil as compared with placebo at the end of the study (74.6 and 39.5% for vardenafil 20 mg and placebo, respectively). The agent was effective regardless of patient etiology (*i.e.*, organic or psychogenic), baseline severity, age and whether the patients were taking antihypertensive medications. A low adverse event profile (headache 7-15%, flushing 10-11%, dyspepsia 7%, rhinitis 7%) was also reported (25-30).

The results of a multicenter, randomized, double-blind, placebo-controlled trial of vardenafil (10 and 20 mg) in 452 males with ED and type 1 or type 2 diabetes were evaluated for changes in IIEF scores and adverse events. The treatment was found to provide early and sustained improvement in erectile function and sexual satisfaction. The group receiving 20 mg vardenafil had a significantly greater responder rate (72%) at 12 weeks as compared to placebo (13%). Both the 10- and 20-mg dose resulted in improved erectile function domains of the IIEF, improved rates of successful penetration and maintenance to intercourse completion that were significantly better than placebo. The most common adverse events related to treatment were flushing, headache and rhinitis (31-33).

Table V: Clinical studies of vardenafil for the treatment of erectile dysfunction (from Prous Science Integrity®).

Design	Treatments	n	Conclusions	Ref.
Randomized, crossover	Vardenafil, 10 mg po + Nitroglycerin, 400 µg s.l. Placebo + Nitroglycerin, 400 µg s.l.	18	No interaction between vardenafil and nitroglycerin was found in terms of blood pressure and heart rate; the combination of both agents was well tolerated in all cases	24
Randomized, double-blind, multicenter	Vardenafil, 5 mg po x 12 wk (n=147) Vardenafil, 10 mg po x 12 wk (n=141) Vardenafil, 20 mg po x 12 wk (n=150) Placebo (n=152)	590	Vardenafil was safe, well tolerated and effective in improving sexual function and satisfaction, resulting in up to 80% improvement in erection and 76% successful intercourses in patients with erectile dysfunction	25, 29
Randomized, double-blind	Vardenafil, 5 mg po PRN x 12 wk Vardenafil, 10 mg po PRN x 12 wk Vardenafil, 20 mg po PRN x 12 wk Placebo	601	Vardenafil was generally well tolerated and effective in improving erectile function independently of baseline severity and etiology and whether or not patients were taking antihypertensive medications	26, 30
Randomized, double-blind	Vardenafil, 5 mg po PRN x 12 wk Vardenafil, 10 mg po PRN x 12 wk Vardenafil, 20 mg po PRN x 12 wk Placebo	576	All doses of vardenafil were well tolerated and improved all aspects of erectile dysfunction compared to placebo, with the effect maintained for 8 wks	27
Randomized, double-blind, multicenter	Vardenafil, 10 mg po PRN x 12 wk Vardenafil, 20 mg po PRN x 12 wk Placebo	452	Vardenafil was well tolerated and effective in improving erectile function and other measures of sexual experience for the treatment of erectile dysfunction in diabetic patients	31-33
Randomized, double-blind, crossover	Vardenafil, 10 mg po Vardenafil, 20 mg po Placebo	25	Vardenafil was well tolerated and increased penis rigidity and tumescence and their duration in patients with erectile dysfunction	36
Randomized, double-blind, crossover	Vardenafil, 20 mg po Vardenafil, 40 mg po Placebo	24	Vardenafil was more effective than placebo in achieving a longer duration of penis erection in patients with erectile dysfunction	37
Randomized, double-blind, crossover, pooled/meta-analysis	Study 1: Vardenafil, 10 mg po Vardenafil, 20 mg po Placebo Study 2: Vardenafil, 20 mg po Vardenafil, 40 mg po Placebo	42	Vardenafil 20 and 40 mg induced an improvement in erectile function with a fast onset of action	38
Randomized, double-blind, crossover, multicenter, pooled/meta-analysis	Vardenafil, 5 mg po PRN x 12 wk Vardenafil, 10 mg po PRN x 12 wk Vardenafil, 20 mg po PRN x 12 wk Placebo	1401	Vardenafil at doses of 5, 10 and 20 mg was well tolerated and effective in improving erectile function irrespective of the use of antihypertensive medications	40
Randomized, double-blind, multicenter, pooled/meta-analysis	Vardenafil, 5 mg x 12 or 26 wk Vardenafil, 10 mg x 12 or 26 wk Vardenafil, 20 mg x 12 or 26 wk Placebo	1385	Vardenafil 5-20 mg was effective in improving or restoring normal erectile function in a significant proportion of men with erectile dysfunction, irrespective of etiology and severity, being especially effective in the most severe cases	41-44

Continued

Table V (Cont.): Clinical studies of vardenafil for the treatment of erectile dysfunction (from Prous Science Integrity®).

Design	Treatments	n	Conclusions	Ref.
Randomized, double-blind, multicenter	Vardenafil, 5 mg po PRN x 26 wk Vardenafil, 10 mg po PRN x 26 wk Vardenafil, 20 mg po PRN x 26 wk Placebo	736	Vardenafil was generally well tolerated and effective in improving erection in up to 85% of men	45
Randomized, double-blind, multicenter	Vardenafil, 10 mg PRN x 3 mo (n=146) Vardenafil, 20 mg PRN x 3 mo (n=149) Placebo (n=145)	440	Vardenafil 10-20 mg was well tolerated and more effective than placebo in improving erectile function, erections, rate of successful intercourses and rates of vaginal penetration in patients with erectile dysfunction due to nerve-sparing radical retropubic prostatectomy	47
Randomized, double-blind, crossover, multicenter	Vardenafil, 10 mg po Placebo	41	Vardenafil 10 mg did not affect the ability of patients with stable coronary artery disease to exercise at a level exceeding that usually required for sexual intercourse	48, 49
Randomized, multicenter	Vardenafil, 5 mg po PRN x 12 wk Vardenafil, 10 mg po PRN x 12 wk Vardenafil, 20 mg po PRN x 12 wk Placebo	489	Vardenafil was safe, well tolerated and effective in increasing the number of successful attempts at intercourse by improving erectile function in patients with mild to severe erectile dysfunction	50

A randomized phase II study in men with ED assessed the efficacy of on-demand vardenafil (5, 10 or 20 mg) or placebo in patients under 45 and those over 65 years of age. A separate phase I study examined the safety, tolerability and pharmacokinetics of a single dose of vardenafil 40 mg in healthy male volunteers 18-45 and over 65 years of age. The results of the trials revealed that older men had slightly higher drug plasma levels and experienced similar improvements in erectile function as younger men (34, 35).

The efficacy of single-dose vardenafil (10 or 20 mg p.o.) was examined using RigiScan™ penile plethysmography during visual sexual stimulation in a randomized, double-blind, placebo-controlled, crossover trial in 21 men with ED. Treatment was safe and well tolerated. A slight reduction in blood pressure with a compensatory rise in heart rate was observed with treatment but was concluded to be clinically insignificant. No changes in ECG or laboratory parameters were seen with treatment. Vardenafil resulted in significantly greater and dose-dependent erectile responses as compared to placebo on all measures, including duration of rigidity, rigidity and degree of tumescence. Single 10- and 20-mg doses resulted in rapid increases in plasma levels of the agent and AUC (normalized for body weight and dose) and C_{max} values were dose-proportional (36, 37).

The efficacy of oral vardenafil (10, 20 or 40 mg) was examined using RigiScan™ penile plethysmography in 2 randomized, double-blind, placebo-controlled, crossover studies involving 42 men with erectile dysfunction. Treatment was safe and well tolerated. Vardenafil resulted in significantly greater and dose-dependent erectile responses as compared to placebo on all measures including duration of rigidity, rigidity and degree of tumescence (38).

Treatment of mild to severe ED with vardenafil 5, 10 or 20 mg was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial in 805 patients. The study lasted 26 weeks. Measures of erectile function were dose-dependently improved and maintained by vardenafil, and most men with mild ED and many with severe ED regained normal erectile function with treatment (39).

A pooled analysis of data from 2 double-blind, randomized pivotal phase III trials in men with ED treated with vardenafil (5, 10 or 20 mg/day) or placebo assessed the efficacy and safety of the drug in subjects on antihypertensive therapy. Of 1401 men evaluable for safety, 545 had received antihypertensive therapy during the treatment period (12-26 weeks). All doses of vardenafil were significantly superior to placebo on all measures of erectile function, regardless of antihypertensive therapy. Adverse events in men on vardenafil occurred with a similar or lower incidence in those receiving antihypertensive therapy and minimal blood pressure changes were seen in both subgroups. It thus appears that neither the safety nor the efficacy of vardenafil is compromised in subjects being treated for hypertension (40).

Analysis of 2 randomized, double-blind phase III trials in which a total of 1357 men with ED received vardenafil 5, 10 or 20 mg or placebo for 12 weeks revealed that the drug significantly improved erectile dysfunction regardless of etiology or baseline severity. Patients with severe ED benefited the most from treatment (41).

Researchers evaluated the efficacy of as-needed vardenafil 5, 10 or 20 mg in 1385 men with ED using data from 2 randomized, double-blind, placebo-controlled

studies. The data were broken down according to subgroups of patients with hyperlipidemia, those with diabetes mellitus and those taking antihypertensive medications. Vardenafil was well tolerated and significantly improved ED domain scores in all of these patients compared to placebo, regardless of comorbidities (42). Data were pooled to assess the percentage of men with ED who regained normal erectile function after treatment with vardenafil. The 10-mg dose of vardenafil restored normal erectile function in 71% of men with mild ED and in 51% of men with mild to moderate ED, while the 20-mg dose restored normal function in 47% of men with moderate ED and in 39% of men with severe ED (43). The influence of age on the efficacy and safety of vardenafil was assessed. In the trials, men with ED were given vardenafil 5, 10 or 20 mg or placebo for 12 or 26 weeks. Erectile function scores and positive general assessment question response rates were improved with vardenafil treatment compared with placebo regardless of the patient's age. The adverse event profile was not altered by age (44).

Vardenafil (5, 10 and 20 mg) or placebo was administered in a randomized fashion to men with ED in a double-blind phase III trial. Vardenafil treatment was well tolerated and significantly improved penetration and maintenance of erections. Erections were improved in 85% of men given the 20-mg dose (45).

The results from the first large-scale patient trial of vardenafil showed that the PDE5 inhibitor not only improved erections in up to 80% of men, but also increased their ability to complete sexual intercourse with ejaculation. The analyses involved 580 male patients aged 21-70 years from centers in the U.S., Europe and South Africa. The patients had experienced difficulty with erectile function of organic, psychogenic or mixed etiology for an average of 2.8 years. They were randomized to receive placebo or vardenafil at a dose of 5, 10 or 20 mg, on demand but not more than once daily. Vardenafil produced statistically and clinically significant improvement in erectile function regardless of the cause of the problem, age of the patient or severity of the condition. Improved erections were reported in 80% of those on the highest dose of vardenafil compared to about 30% of those on placebo, and the rate of complete intercourses with ejaculation was 75% on the highest dose of vardenafil compared to about 40% on placebo. The treatment was well tolerated, with the most common side effects consisting of headache, flushing, rhinitis and dyspepsia, which were generally mild in intensity and dose-related (46).

A multicenter, double-blind, randomized trial was conducted in 440 men with ED after nerve-sparing radical prostatectomy to compare the effects of vardenafil 10 or 20 mg and placebo, as needed for 3 months, on measures of erectile function. Most of the patients had severe ED. Treatment with vardenafil significantly improved scores on the IIEF erectile function domain compared to placebo and was associated with increases in success in terms of penetration (46.6-47.5% *vs*. 21.8% on placebo) and maintenance of erection (34.2-37.2% *vs*. 9.9% on placebo). In the subgroup of subjects with bilateral prostatectomy, erections were rated as improved on the Global Assessment Questionnaire in 12% on placebo, 60% on vardenafil 10 mg and 71% on vardenafil 20 mg. Adverse events were mostly mild to moderate and included headache, flushing and rhinitis (47).

The cardiac effects of vardenafil during physical exercise exceeding that usually necessary for sexual intercourse in patients with stable ischemic coronary artery disease (CAD) have been evaluated. Forty-one men were enrolled in a multicenter, double-blind, randomized, crossover study to receive single doses of vardenafil 10 mg or placebo prior to an exercise treadmill test. The results indicated that vardenafil should not increase the risk of developing exercise-induced ischemia during intercourse in patients with CAD (48, 49).

A total of 489 men with ED were included in a randomized, multicenter study comparing treatment with oral vardenafil 5, 10 or 20 mg or placebo taken as needed. After 12 weeks of treatment, patients reported that 75% of attempts at intercourse were successfully completed *versus* 25% before treatment. Vardenafil treatment also increased scores on the IIEF questionnaire to a greater extent than placebo (50).

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