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Annual Update 2003: Urologic Drugs

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Abstract

The Annual Update 2003 of Urologic Drugs is comprised of a Compendium of 72 drugs under development for the treatment of urinary and renal diseases, including urinary incontinence, interstitial cystitis, benign prostatic hyperplasia, prostatatis, erectile dysfunction, ejaculatory dysfunction, female sexual dysfunction, urolithiasis, renal failure, glomerulonephritis, hyperoxaluria, hyperphosphatemia, dilutional hyponatremia and membranous nephritis. The section on monographs offers updated information on the following drugs that were published in previous issues of the journal: darifenacin, duloxetine hydrochloride, dutasteride, finrozole, HCT-1026, lanthanum carbonate, pirfenidone, silodosin, solifenacin succinate, tadalafil and vardenafil hydrochloride hydrate. A table listing the drugs, their manufacturers, indications and developmental phases is also featured.

Introduction

The Annual Update 2003 of Urologic Drugs is comprised of a Compendium of 73 drugs under development for the treatment of urinary and renal diseases, including urinary incontinence, interstitial cystitis, benign prostatic hyperplasia, prostatatis, erectile dysfunction, ejaculatory dysfunction, female sexual dysfunction, urolithiasis, renal failure, glomerulonephritis, hyperoxaluria, hyperphosphatemia, dilutional hyponatremia and membranous nephritis. The section on monographs offers updated information on the following drugs that were published in previous issues of the journal: darifenacin, duloxetine hydrochloride, dutasteride, finrozole, HCT-1026, lanthanum carbonate, pirfenidone, silodosin, solifenacin succinate, tadalafil and vardenafil hydrochloride hydrate. A table listing the drugs, their manufacturers, indications and developmental phases is also featured.

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Drug	Source	Condition	Phase
(+)-Resiniferatoxin	Icos	Cystitis, interstitial	II
SI-7201	Seikagaku/Nippon Shinyaku	Cystitis, interstitial	III
Suplatast Tosilate[1,2]	Taiho/Yamanouchi	Cystitis, interstitial	II
Dapoxetine	Dynogen	Ejaculatory dysfunction	III
VI-0162	Vivus	Ejaculatory dysfunction	I
Alibra	Vivus	Erectile dysfunction	Prereg
Alprox-TD	NexMed	Erectile dysfunction	L-2001
Apomorphine, intranasal	Nastech	Erectile dysfunction	II
DA-8159	Dong-A	Erectile dysfunction	I
EMR-62203	Merck KGaA	Erectile dysfunction	II
PNU-142774	Neurocrine Biosciences	Erectile dysfunction	II
PT-141	Palatin Technologies	Erectile dysfunction	II
TA-1790	Tanabe Seiyaku/Vivus	Erectile dysfunction	I
Tadalafil[2]	Lilly Icos	Erectile dysfunction	L-2003
Topiglan	MacroChem	Erectile dysfunction	III
Vardenafil[2]	Bayer/GlaxoSmithKline	Erectile dysfunction	L-2003
VML-670	Vernalis	Erectile dysfunction	II
Alista	Vivus	Female sexual dysfunction	II/III
Androsorb	Novavax	Female sexual dysfunction	I/II
Apormorphine, intranasal	Nastech	Female sexual dysfunction	II
Femprox	NexMed	Female sexual dysfunction	II
Flibanserin[2]	Boehringer Ingelheim	Female sexual dysfunction	II
LibiGel	BioSante	Female sexual dysfunction	II
PT-141	Palatin Technologies	Female sexual dysfunction	I
ReLibra	Unimed	Female sexual dysfunction	II/III
Tadalafil[2]	Lilly Icos	Female sexual dysfunction	II
Tostrelle	Cellegy	Female sexual dysfunction	II/III
VML-670	Vernalis	Female sexual dysfunction	II
LibiGel E/T	BioSante	Female sexual dysfunction	I
(*R*)-Roscovitine	Cyclacel	Glomerulonephritis	I
Gusperimus Hydrochloride[2]	Nippon Kayaku	Glomerulonephritis	II
IxOC-2	Ixion	Hyperoxaluria	I/II
Colestimide[1]	Mitsubishi Pharma	Hyperphosphatemia	II
Lanthanum Carbonate[2]	Shire Laboratories	Hyperphosphatemia	Prereg
SR-121463A	Sanofi-Synthélabo	Hyponatremia	II
(*S*)-Oxybutynin	Sepracor	Incontinence, urinary	III
AA-10020	Arachnova	Incontinence, urinary	I
Cizolirtine Citrate	Esteve	Incontinence, urinary	II
DRP-001	Sosei	Incontinence, urinary	I
Duloxetine Hydrochloride[2]	Lilly/Boehringer Ingelheim	Incontinence, urinary	Prereg
Fesoterodine[3]	Schwarz	Incontinence, urinary	III
KRP-197	Kyorin/Ono	Incontinence, urinary	II
KUC-7322	Kissei	Incontinence, urinary	I
KUC-7483	Kissei/Boehringer Ingelheim	Incontinence, urinary	I
KW-7158	Kyowa Hakko	Incontinence, urinary	II
NS-8	Nippon Shinyaku	Incontinence, urinary	II
OPC-51803	Otsuka	Incontinence, urinary	II
R-1484	Roche	Incontinence, urinary	I
R-450	Roche/Chugai	Incontinence, urinary	II
R-701	Roche	Incontinence, urinary	I
Rec-15/3079	Recordati/Pharmacia	Incontinence, urinary	I
Temiverine Hydrochloride Hydrate	Nippon Shinyaku	Incontinence, urinary urge	Prereg
Finrozole[2]	Hormos	Lower urinary tract symptoms	II
Eculizumab	Alexion	Nephritis	II
(*S*)-Oxybutynin	Sepracor	Overactive bladder	III
AZD-0947	AstraZeneca	Overactive bladder	II
Darifenacin[2]	Novartis	Overactive bladder	Prereg

Continuation

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Drug	Source	Condition	Phase
Fesoterodine[3]	Schwarz	Overactive bladder	II
HCT-1026[2]	NicOx	Overactive bladder	II
Oxytrol	Watson	Overactive bladder	L-2003
R-701	Roche	Overactive bladder	I
Solifenacin Succinate[2]	Yamanouchi	Overactive bladder	Prereg
Trospium Chloride[+]	Indevus	Overactive bladder	Prereg
AIO-8507L	Ono	Prostatic hyperplasia, benign	II
ANPH-103	Ancile	Prostatic hyperplasia, benign	II
BXL-628	BioXell	Prostatic hyperplasia, benign	II
Cetrorelix Acetate[1,2]	Zentaris (AEterna)	Prostatic hyperplasia, benign	II
Dutasteride[2]	GlaxoSmithKline	Prostatic hyperplasia, benign	L-2003
ML-04	Milkhaus	Prostatic hyperplasia, benign	II
NX-1207	Nymox	Prostatic hyperplasia, benign	I
RBx-2258	Ranbaxy	Prostatic hyperplasia, benign	II
SPM-969	Schwarz	Prostatic hyperplasia, benign	I
TF-505	Taiho	Prostatic hyperplasia, benign	II
Silodosin[2]	Daiichi/Kissei	Prostatic hyperplasia, benign	III
ML-04	Milkhaus	Prostatitis	II
Suplastat Tosilate[1]	Taiho/Yamanouchi	Prostatitis	II
ALT-711	Alteon	Renal failure	I
Ambrisentan	Myogen	Renal failure	I
FK-352[2]	Fujisawa	Renal failure	II
Pirfenidone[2]	InterMune	Renal failure	II
(*S*)-Oxybutynin	Sepracor	Urinary frequency	III
Solifenacin Succinate	Yamanouchi	Urinary frequency	Prereg
KUL-7211	Kissei	Urolithiasis	II

[1]Launched for another indication. [2]Monograph previously published in Drugs of the Future. [3]Monograph in preparation. [+]Available in Europe from Madaus.

Compendium of Urologic Drugs

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Urinary incontinence

Urinary incontinence is defined as a condition in which the involuntary loss of urine represents a social or hygienic problem. It can and does occur at any age, although the causes tend to vary among different age groups. The overall incidence of urinary incontinence, however, increases progressively with age.

Within the broad classification of urinary incontinence, several subtypes exist. The most frequently reported form is urge urinary incontinence, which accounts for up to 65% of all reported cases. Stress incontinence, another common subtype of urinary incontinence, often results from physical changes occurring in women during pregnancy, childbirth and menopause. Stress incontinence is also commonly associated with obesity. Other subclasses of urinary incontinence include functional incontinence, overflow incontinence, mixed incontinence and transient incontinence.

Urinary incontinence is a common problem, affecting up to 12 million adults in the U.S. It is generally assumed that approximately 6% of the population at any given time suffers from urinary incontinence of sufficient severity to adversely affect quality of life. Overactive bladder, a broader condition that encompasses frequency (needing to urinate more than 8 times over 24 hours) and urgency with or without urge incontinence, is estimated to affect more than 17 million Americans.

Urinary incontinence causes significant financial burdens on individuals, their families and health care providers. In 1995, estimated costs of urinary incontinence were US $26.3 billion. This translates into a cost of US $3,565 per patient affected.

Drugs for the treatment of urinary incontinence act either at the peripheral level, modulating contractions of bladder smooth muscle, or at the central level, affecting neurological control of the process of urination. Peripherally acting agents include anticholinergic drugs (represented by the widely marketed oxybutynin), potassium channel activators, tachykinin receptor antagonists and adrenergic receptor ligands. Neurological control of urination is crucial and involves the central nervous system (cortex, diencephalon, midbrain and medulla), spinal cord and peripheral nerves. Given that reduced inhibitory control in the CNS often contributes to bladder overactivity, centrally acting agents (drugs acting on GABA, opioid, serotonin, noradrenaline, dopamine or glutamic acid receptors) could be useful in treating some types of urinary incontinence.

Anticholinergic agents

During normal as well as abnormal micturition, contraction of the detrusor muscle is mediated by acetylcholine, which is released from postganglionic parasympathetic neurons and acts at muscarinic receptors on detrusor smooth muscle. Anticholinergic drugs, by interfering with this action, reduce detrusor contractions and thus are effective in treating urge incontinence and overactive bladder. In spite of a high incidence of adverse effects, the anticholinergic agent oxybutynin chloride remains the drug of choice for urinary incontinence, and several new formulations of the compound are under development.

The newest of these, Watson's Oxytrol™ (**oxybutynin transdermal** system), was recently launched for the first time in the U.S. for the treatment of patients with overactive bladder and symptoms of urge urinary incontinence, urgency and frequency. Clinical trials in 1,000 subjects at more than 50 U.S. centers demonstrated that Oxytrol™ provides effective control of overactive bladder symptoms over a 3-4-day period. Oxytrol™ is a thin, flexible and clear patch that is applied to the abdomen, hip or buttock twice weekly.

New anticholinergic agents in development for the treatment of urinary incontinence are presented in Table I.

Potassium channel activators

Potassium channel activators increase the efflux of potassium ions from cells, causing membrane

Table I: Anticholinergic agents in development for the treatment of urinary incontinence.

Drug Name	Source	Mechanism of Action	Status (Indication)
Oxybutynin transdermal	Watson	Muscarinic antagonist	Launched-2003 (overactive bladder)
Darifenacin	Novartis	Muscarinic M_3 antagonist	Preregistered (overactive bladder)
Solifenacin succinate	Yamanouchi	Muscarinic M_3 antagonist	Preregistered (overactive bladder)
Temiverine hydrochloride hydrate	Nippon Shinyaku	Muscarinic M_3 antagonist/ Calcium antagonist	Preregistered (urinary urge incontinence)
Trospium chloride	Indevus	Muscarinic antagonist	Preregistered (overactive bladder)
(*S*)-Oxybutynin	Sepracor	Anticholinergic	Phase III (urinary incontinence, overactive bladder, urinary frequency)
Fesoterodine	Schwarz	Muscarinic M_3 antagonist	Phase II (overactive bladder, urinary urge incontinence)
KRP-197	Kyorin/Ono	Muscarinic M_1/M_3 antagonist	Phase II (urinary incontinence)

hyperpolarization and reducing the likelihood that other ion channels will be activated. Several potassium channel activators have been studied for the treatment of urinary incontinence, although most of them do not demonstrate sufficient selectivity for bladder over vascular smooth muscle. Clinical trials are currently under way to determine the potential efficacy of two investigational potassium channel activators in this indication: AstraZeneca's **AZD-0947** is targeted to the treatment of overactive bladder, while Nippon Shinyaku's **NS-8** is being developed for urinary incontinence. Both are in phase II.

Drugs acting on adrenergic receptors

α-Adrenergic receptors, especially α_1-subtype receptors, are present in abundance in the bladder neck and proximal urethra, and stimulation of these receptors by agonists increases maximal urethral closure pressure. This may translate into therapeutic benefit, especially in patients with stress incontinence. Recent studies have shown that the major β-adrenoceptor subtype responsible for detrusor relaxation is the β_3-adrenoceptor. Thus, β_3-adrenoceptor agonists may also have potential in controlling urinary frequency. Drugs in development for the treatment of urinary incontinence that act through adrenergic receptors include the products listed in Table II.

Vasopressin agonists

Vasopressin analogues and agonists such as desmopressin acetate have traditionally been used in the treatment of nocturnal enuresis (bedwetting). A few compounds with this mechanism of action are now being studied for the treatment of urinary incontinence in adults, including **OPC-51803**, in phase II testing at Otsuka.

Nitric oxide donors

Nitric oxide (NO) deficiency has been implicated in many pathological and physiological processes within the mammalian body, including urinary incontinence, providing a plausible biologic basis for the use of NO replacement therapy in the treatment of this condition. Exogenous NO sources have the potential to supplement NO when the body cannot generate enough for normal biological functions. This theory has opened up the possibility of designing nitric oxide donors, a new class of drugs capable of delivering NO into tissues and the bloodstream in a sustained and controlled manner. **HCT-1026**, a nitric oxide-donating derivative of the nonsteroidal antiinflammatory drug flurbiprofen, is currently in phase II clinical testing at NicOx for the treatment of overactive bladder.

Tachykinin antagonists

Esteve is conducting phase II trials evaluating **cizolirtine citrate**, a modulator of substance P and CGRP release, as a treatment for idiopathic unstable human urinary bladder. The drug, which was previously studied for pain indications, has shown good activity in preclinical models of urinary incontinence. Control over tachykinin release is hypothesized to facilitate the regulation of bladder motility.

Table II: Adrenergic receptor-acting drugs in development for the treatment of urinary incontinence.

Drug Name	Source	Mechanism of Action	Status (Indication)
R-450	Roche/Chugai	α_1-Adrenoceptor agonist	Phase II (urinary incontinence)
KUC-7322	Kissei	β_3-Adrenoceptor agonist	Phase I (urinary incontinence)
KUC-7483	Kissei/Boehringer Ingelheim	β_3-Adrenoceptor agonist	Phase I (urinary incontinence)

Centrally acting agents

Neurological control of urination is crucial, and involves the central nervous system (cortex, diencephalon, midbrain and medulla), spinal cord and peripheral nerves. Given that reduced inhibitory control in the CNS often contributes to bladder overactivity, centrally acting agents could be useful in treating some types of urinary incontinence. Theoretically, drugs acting on GABA, opioid, serotonin, noradrenaline, dopamine or glutamic acid receptors could exert therapeutic effects in urinary incontinence, although it is difficult to obtain agents acting selectively on the lower urinary tract.

The greatest success story to date in this area has been the development of **duloxetine hydrochloride**, a dual norepinephrine and serotonin reuptake inhibitor for the treatment of stress urinary incontinence. The drug was codeveloped by Lilly and is licensed to Boehringer Ingelheim for all markets outside Japan, where Shionogi holds rights. Duloxetine oxalate is under regulatory review in the U.S. and E.U. for this indication; it is also in the advanced stages of development as a treatment for depression.

Another centrally acting agent in development is **Rec-15/3079**, a 5-HT_{1A} antagonist from Recordati. Phase I trials are under way evaluating the compound's potential as a treatment for overactive bladder and urinary incontinence. Rec-15/3079 is being codeveloped with Pharmacia.

Anecdotal evidence implies that cannabis may help multiple sclerosis (MS) patients who experience bladder dysfunction, a condition that can affect up to 90% of those afflicted with the disease. Historical references indicate the use of cannabis to treat urinary incontinence, as do several modern case histories. A 1997 survey also finds some MS patients reporting that cannabis mitigates bladder dysfunction. Based on these findings, GW Pharmaceuticals has initiated phase III testing of narrow ratio **THC:CBD** for the improvement of bladder dysfunction in patients with MS.

Miscellaneous drugs

Kyowa Hakko's **KW-7158** acts on the peripheral sensory nerves to control bladder activities. Through this unique mechanism of action, it is expected to be clinically effective against urinary urgency, frequency and urinary incontinence associated with overactive bladder.

Sosei, a Japanese company dedicated to reprofiling underprofiled safe compounds for which development or active marketing has been suspended in Japan, initiated a phase I clinical trial of **DRP-001** (SOU-001) in late 2001. DRP-001 is the first successful demonstration of the company's Drug Reprofiling Programme. Originally developed through to phase IIa clinical trials in Japan for a cardiovascular indication, DRP-001 is under development for the treatment of stress and mixed-type urinary incontinence.

Following a similar strategy of "therapeutic switching", Arachnova is developing **AA-10020**, a drug originally developed by a major pharmaceutical company for a cardiovascular indication, as a potential treatment for stress urinary incontinence. Phase I trials are under way.

Roche is actively investigating new treatments for urinary incontinence. **R-1484**, a GPCR modulator, is in phase I for stress urinary incontinence. The GPCR antagonist **R-701** is in phase I testing for urinary incontinence.

Interstitial cystitis

Interstitial cystitis, one of the chronic pelvic pain disorders, is a chronic inflammatory condition of unknown cause resulting in recurring discomfort or pain in the bladder and surrounding pelvic region. The symptoms of interstitial cystitis vary from case to case and even in the same individual. People may experience mild discomfort, pressure, tenderness or intense pain in the bladder and surrounding pelvic area. Symptoms may include urinary urgency and/or frequency. Pain may change in intensity as the bladder fills with urine or as it empties. Women's symptoms often get worse during menstruation.

Although interstitial cystitis can affect persons of any race, age or gender, it is far more common in women. Of the more than 700,000 Americans estimated to have the condition, 90% are women.

Resiniferatoxin, a potent neuronal desensitizing agent that inhibits the transmission of messages by peripheral sensory neurons to the CNS, is in phase II clinical trials at Icos for the treatment of interstitial cystitis. The drug, a vanilloid receptor agonist related to capsaicin, the hot ingredient in chili peppers, is delivered topically into the bladder via a catheter.

Taiho and Yamanouchi are conducting phase II trials of **suplatast tosilate**, a mediator release inhibitor, in patients with interstitial cystitis. Suplatast is already marketed for the indications of allergic rhinitis, bronchial asthma and atopic dermatitis. In preliminary clinical trials, suplatast tosilate was shown to improve symptoms of frequency, nocturia and suprapubic pain.

Seikagaku and Nippon Shinyaku are codeveloping **SI-7201**, a medical device coated with the glycosaminoglycan hyaluronic acid, as a treatment for interstitial cystitis. Phase III testing is under way in the U.S., with a 2006 launch date projected.

Benign prostatic hyperplasia

Benign prostatic hyperplasia (BPH, also sometimes referred to as benign prostatic hypertrophy), the nonmalignant enlargement of the prostate gland, is a common age-related pathological condition in the aging human male. BPH occurs most frequently in men aged 60 years or more; over 50% of all men in this age group have enlarged prostates. The incidence of BPH, furthermore, increases with age, such that 90% of all men aged

85 years or older are afflicted by the condition. Only half of those, however, are troubled by symptoms.

Given the high incidence of this condition, it is no surprise that the cost of treating BPH is enormous: in the U.S. alone, the annual cost of treating the disorder exceeds US $3 billion. More than 1.7 million office visits and 375,000 hospital stays each year in the U.S. involve a diagnosis of BPH. Drugs marketed for the treatment of BPH collectively generated sales in 1999 of US $2 billion worldwide.

According to current treatment standards, BPH is treated only when symptoms are severe enough to be troublesome to the patient, if kidney function is affected or if other complications (*e.g.*, kidney infection, bleeding) have developed. The standard conservative approach used in the patient who does not suffer symptoms of his enlarged prostate, or who is not bothered by his symptoms, is "watchful waiting." Drug therapy of symptomatic BPH typically involves the administration of α_1-adrenoceptor antagonists or 5α-reductase inhibitors. Nonpharmacological therapy, principally surgery or minimally invasive treatment, may be required for those patients whose symptoms are not adequately controlled on pharmacotherapy alone.

α_1-Adrenoceptor antagonists

α_1-Adrenoceptor antagonists have been used widely since the mid-1980s in the treatment of BPH. These compounds act by blocking sympathetic activity and thus relax the smooth muscle component of prostatic obstruction. The first nonselective blockers were associated with undesirable systemic side effects, but with the arrival of more uroselective blockers such as terazosin, tamsulosin and alfuzosin, the treatment of BPH has improved significantly.

Several α_1-adrenoceptor antagonists are under active development, as shown in Table III.

5alpha-Reductase inhibitors

In 1992, finasteride (Proscar®) became the first 5alpha-reductase inhibitor marketed for the treatment of BPH. Most of finasteride's effects at clinical doses are obtained through inhibition of type 2 5α-reductase; its activity against type 1 isoenzyme is much less potent. Although it is a highly potent enzyme inhibitor with an excellent safety profile, finasteride has proven to be only moderately effective in treating symptomatic BPH.

Thus, there is a clear need for improved (dual-acting) 5α-reductase inhibitors. A dual inhibitor of both isozymes may decrease circulating dihydrotestosterone (DHT) to a greater extent than a single isozyme inhibitor like finasteride.

In March 2003, GlaxoSmithKline announced the international launch of **dutasteride** (Avodart®) for the treatment of moderate to severe symptoms in patients with BPH and for reducing the risk of acute urinary retention and surgery in these patients. The product was launched in the U.S. in January and in the U.K. in February. Dutasteride is a novel 5α-reductase inhibitor that inhibits both type 1 and type 2 isozymes of 5α-reductase, the enzyme responsible for converting testosterone to DHT. Dutasteride treatment has been shown to reduce DHT by 90% within 2 weeks and begins to shrink the prostate as early as 1 month, as well as reducing the risk of acute urinary retention by 57% and BPH-related surgery by 48% over 2 years.

TF-505 (FK-687), another dual-acting type 1 and type 2 5α-reductase inhibitor, is in phase II testing in Japan. The drug was originally discovered by Fujisawa, but development is being carried out by Taiho.

Table III: α_1-Adrenoceptor antagonists in development for treatment of BPH.

Drug Name	Source	Status
Silodosin	Daiichi Pharmaceutical/Kissei	Phase III
AIO-8507L	Ono	Phase II
RBx-2258	Ranbaxy	Phase II

Other hormonal agents

Cetrorelix acetate, a GnRH antagonist that is already marketed for the treatment of female infertility, is being codeveloped in phase II by Zentaris (AEterna) as a treatment for BPH.

Milkhaus recently announced that enrollment had been completed in the company's phase IIb trial of **ML-04** for the treatment of BPH. A total of 546 patients have been enrolled in this study, the primary endpoint of which is the change in the symptoms of BPH, as measured by the American Urological Association Symptom Index. Previous phase II studies revealed positive results with ML-04, for which statistical significance in the relief of BPH and a side effect profile similar to placebo were observed. Additionally, patients suffering from sexual dysfunction at the beginning of the trial experienced significant improvement following treatment with ML-04. The product, a patented oral form of human chorionic gonadotropin (hCG), is also in development for the indication of prostatitis (see below).

BioXell has commenced enrollment for a phase II trial of its novel lead compound **BXL-628**, a vitamin D analogue, in BPH. The double-blind, randomized, placebo-controlled trial will be coordinated by the Division of Urology at the Università Vita e Salute-San Raffaele, Milan, and will enroll 120 patients across 12 Italian sites. BXL-628 appears to inhibit the growth of prostate cells by impairing the activity of several growth factors that are involved in prostate growth, as well as in the pathogenesis of BPH.

Age-related prostate enlargement due to BPH is considered to be the main cause of lower urinary tract symptoms (LUTS) in the aging male. However, development of LUTS may also be related to age-related decline in androgen levels resulting in a shift of androgen/estrogen ratio towards estrogen dominance. This hormonal imbalance may cause disturbance in the coordination of urethral and bladder musculature and thus cause urinary symptoms. All current medical treatment options are developed for the treatment of LUTS related to BPH. The nonsteroidal competitive aromatase inhibitor **finrozole** is the first compound under development to treat LUTS related to decreased androgen/estrogen ratio. Finrozole is currently in clinical phase II studies at Hormos Medical.

Miscellaneous drugs

Although most drugs in development for the treatment of BPH possess one or more of the clearly defined mechanisms of action described above, a few compounds are known to be in development for which the mechanism of action has not been discerned or has not been disclosed.

In February 2003, Nymox announced the initiation of U.S. phase I safety studies of **NX-1207** in men with BPH. Schwarz's **SPM-969**, another potential treatment for BPH, is also currently in phase I testing.

ANPH-103, a botanical drug from Ancile Pharmaceuticals, is in phase II testing for the treatment of BPH.

Prostatitis

Prostatitis, an inflammatory condition of the prostate gland, is extremely painful and significantly decreases quality of life. Men suffering from prostatitis often experience significant pelvic pain, have difficulty urinating and experience sexual dysfunction. Current therapies are not adequate and represent a largely unmet medical need.

Prostatitis may be acute, often caused by a bacterial infection, or chronic. Chronic prostatitis evolves gradually in association with or following a bout of acute prostatitis, urethritis, epididymitis or urinary tract infection. Acute prostatitis is diagnosed in approximately 2 of every 10,000 outpatient visits. Chronic prostatitis affects as many as 35% of men over the age of 50. The cause(s) of nonbacterial prostatitis, which accounts for nearly 65% of all cases of chronic prostatitis, have not yet been discerned but may involve a fungal or viral infection, trichomonads or irritation by a reflux of urine flowing into the prostate gland.

Milkhaus is evaluating **ML-04** as a regulator of cell growth and as an antiinflammatory agent in the treatment of nonbacterial chronic prostatitis/chronic pelvic pain syndrome. The company has initiated a phase IIa proof of concept trial with ML-04, evaluating pain reduction and improvement in both sexual function and overall quality of life. Preliminary results from this trial indicate a significant level of improvement from baseline for all patients against primary endpoints with greater improvement in both moderate and severe patients. Results from this trial will be available in early 2003. The product is also in development for the indication of BPH, as mentioned above.

Taiho and partner Yamanouchi are evaluating the potential efficacy of **suplatast tosilate**, a mediator release inhibitor that is already marketed for the indications of asthma, rhinitis and atopic dermatitis, in phase II trials for the treatment of nonbacterial prostatitis.

Erectile dysfunction

Erectile dysfunction (ED) is the inability of a man to achieve or maintain an erection sufficient for his sexual needs or the needs of his partner. Most men experience this inability at some point in their lives, usually by age 40, and are not psychologically affected by it. Some men experience chronic, complete ED (impotence) and others achieve partial or brief erections. Frequent ED can cause emotional and relationship problems, and often leads to diminished self-esteem. It has many causes, most of which are treatable, and is not an inevitable consequence of aging.

An estimated 30 million men in the U.S. – 10% of the male population – experience chronic ED, although as few as 5% seek treatment. It may affect 50% of men between the ages of 40 and 70. Transient lost or inadequate erection affects men of all ages.

If a patient is sufficiently motivated and disciplined, ED can and most often does improve with treatment. Treatments for ED include psychotherapy and/or drug therapy and lifestyle modifications. The goal of pharmacotherapy for ED is to simultaneously enhance proerectile pathways while suppressing antierectile pathways. Drugs to treat ED generally act by inducing smooth muscle relaxation, thus improving blood flow into the penis (*i.e.*, peripherally acting agents), or by acting on brain centers associated with libido and penile erection (*i.e.*, centrally acting agents).

Prostaglandin E_1

Alprostadil (prostaglandin E_1) has been available in injectable (Pharmacia's Caverject®) and intraurethral pellet formulations for some years. The drug acts almost immediately – and without sexual stimulation – by relaxing smooth muscle to enhance blood flow into the penis, thereby producing an erection. Although highly effective, existing administration methods of alprostadil are not particularly attractive, and several companies have dedicated their efforts in recent years to developing improved drug delivery systems for alprostadil.

NexMed's alprostadil cream formulation **Alprox-TD®** was launched in China under the trade name Befar® in 2001 and is in phase III development in the U.S.

Table IV: PDE5 inhibitors recently launched and in active development for the treatment of erectile dysfunction.

Drug Name	Source	Status
Tadalafil	Lilly Icos	Launched-2003
Vardenafil	Bayer/GlaxoSmithKline	Launched-2003
EMR-62203	Merck KGaA	Phase II
DA-8159	Dong-A	Phase I
TA-1790	Tanabe Seiyaku/Vivus	Phase I

Also in late-stage clinical testing is **Topiglan®**, a SEPA®-enhanced gel formulation of alprostadil from MacroChem.

Vivus is developing **Alibra®**, a combination product incorporating alprostadil and the α_1-adrenoceptor antagonist prazosin. In 1999, the company submitted a New Drug Application to the U.S. Food and Drug Administration to market Alibra®, which it subsequently withdrew in October 2000. The company is in discussions with the FDA and continues to pursue regulatory approval for the drug in the U.S.

PDE5 inhibitors

The 1998 launch of sildenafil (Viagra™) had a tremendous impact on the treatment of sexual dysfunction in both men and women. In its first year on the market, Viagra™ generated US $1 billion in sales in the U.S. alone. Seventeen million Americans reportedly have used the drug. The implications of this success story are much broader, however. With a patient-friendly alternative now available, more men have become willing to report and seek treatment for their condition.

Two new PDE5 inhibitors reached the market in 2003: Lilly Icos's **tadalafil** (Cialis™) and Bayer/GlaxoSmithKline's **vardenafil hydrochloride hydrate** (Levitra™).

The pharmaceutical industry continues to dedicate significant resources to the study of PDE5 inhibitors for the treatment of ED, as reflected in Table IV.

Centrally acting agents

Over the course of searching for effective centrally acting erectogenic agents, multiple therapeutic targets have been identified in the CNS. Serotonin (5-HT), dopamine, nitric oxide, epinephrine, norepinephrine, opioids, acetylcholine, histamine and γ-aminobutyric acid (GABA) have been identified as CNS factors influencing sexual function in humans, although these factors appear to work in harmony.

TAP Pharmaceticals launched **apomorphine sublingual** tablets as Ixense® in France and Germany in June 2001. Ixense® (marketed in some countries as Uprima®) is the first centrally acting oral treatment working at sites in the brain and spinal cord that control the erectile response, thereby replicating how the body would normally achieve an erection. After sublingual administration, an erection is produced quickly with a median onset time of 18-19 min. Abbott has nonexclusive rights to the product outside the U.S. and Canada from TAP Pharmaceuticals. TAP originally licensed the drug from Pentech.

Centrally acting drugs in active development for the treatment of ED are summarized in Table V.

Ejaculatory dysfunction

Ejaculatory dysfunction, ranging from premature ejaculation through retarded ejaculation to the complete inability to ejaculate, affects up to 70% of all men at some point in their lives. Premature ejaculation is by far the most common form of ejaculatory dysfunction. Premature ejaculation is nearly always psychogenic in origin, although recent evidence suggests that it may in some cases have a biogenic basis. Prompt treatment is recommended in order to avoid development of secondary erectile dysfunction.

As with other sexual disorders, anxiety is a significant contributing factor to premature ejaculation, and behavioral therapy is considered the gold standard of treatment. An estimated 60-95% of all cases can be corrected with behavioral therapy and counseling. In other cases drug therapy is required. Tricyclic antidepressants, primarily clomipramine, have been the most extensively studied for this indication. Selective serotonin reuptake inhibitors (SSRIs) are less effective than clomipramine, but are also associated with fewer side effects.

A newer compound in development for premature ejaculation is **dapoxetine**, an SSRI originally developed by Lilly. The compound was first licensed to the Lilly/PPD joint venture PPD GenuPro, then to Alza (subsequently acquired by Johnson & Johnson), and finally to Dynogen, which is testing dapoxetine in phase III trials.

Table V: Centrally acting agents in development for the treatment of erectile dysfunction.

Drug Name	Source	Mechanism of Action	Status
Apomorphine sublingual	Takeda/Abbott	Dopamine D_2 agonist	L-2001
Apomorphine intranasal	Nastech	Dopamine D_2 agonist	Phase II
VML-670	Vernalis	5-HT_{1A} agonist	Phase II
PNU-142774	Neurocrine Biosciences	Dopamine D_2 agonist	Phase II
PT-141	Palatin Technologies	Melanocortin agonist	Phase II

Table VI: Drugs in development for the treatment of female sexual dysfunction.

Drug Name	Source	Mechanism of Action	Status (Indication)
Alista (topical alprostadil)	Vivus	Prostaglandin	Phase II/III (female sexual arousal disorder)
ReLibra (testosterone gel)	Unimed	Testosterone	Phase II/III (to improve libido and well-being in postmenopausal women)
Tostrelle (testosterone transdermal gel)	Cellegy	Testosterone	Phase II/III (decreased libido)
Apomorphine intranasal	Nastech	Dopamine D_2 agonist	Phase II (female sexual dysfunction)
Tadalafil	Lilly Icos	PDE5 inhibitor	Phase II (female sexual dysfunction)
Femprox (alprostadil cream)	NexMed	Prostaglandin	Phase II (female sexual arousal disorder)
Flibanserin	Boehringer Ingelheim	5-HT_{1A} agonist/ 5-HT_{2A} antagonist	Phase II (female sexual dysfunction)
LibiGel (testosterone gel)	BioSante	Testosterone	Phase II (female sexual dysfunction)
VML-670	Vernalis	5-HT_{1A} agonist	Phase II (antidepressant-related sexual dysfunction)
Androsorb (testosterone lotion)	Novavax	Testosterone	Phase I/II (testosterone deficiency in postmenopausal women)
LibiGel E/T (estradiol/testosterone gel)	BioSante		Phase I (female sexual dysfunction in postmenopausal women)
PT-141	Palatin Technologies	Melanocortin agonist	Phase I (female sexual dysfunction)

Vivus has initiated a clinical trial to evaluate the safety and efficacy of **VI-0162**, its proprietary, oral, on-demand treatment for premature ejaculation. The at-home, double-blind, placebo-controlled, crossover trial should be completed during the second quarter of 2003. The company is also evaluating **VI-0134** in early clnical trials as another oral, on-demand treatment for premature ejaculation.

Female sexual dysfunction

Female sexual function involves various anatomical, physiological, psychological, social and emotional factors that, until recent years, were not well understood in spite of the fact that up to 60% of all women are affected by sexual dysfunction at some point in their lives. The pathogenic causes of female sexual dysfunction may be psychogenic, endocrinologic, neurogenic, vasculogenic or myogenic. The most common forms of sexual dysfunction affecting women include female sexual arousal disorder, female orgasmic disorder, vaginismus, hypoactive sexual desire disorder, sexual aversion disorder and dyspareunia.

Female sexual dysfunction has traditionally been treated with psychotherapy and hormone replacement therapy, but the lack of a well-defined, broadly accepted diagnostic framework and system of classification has been a major barrier to the study and treatment of sexual dysfunction in women. In the wake of discoveries made in the area of male sexual dysfunction, enabled by advances in modern technology and inspired by a recent surge of interest in women's health issues, the study of female sexual function – and dysfunction – is now evolving rapidly.

The discovery that PDE5 inhibitors and other vasoactive drugs increase blood flow in the male sexual organs has inspired the evaluation of drugs to increase blood flow in the female genitalia as well, and currently both PDE inhibitors and α-adrenoceptor antagonists are being studied for female sexual dysfunction.

Testosterone plays an essential role in the female sexual response, although much lower levels are required in women than in men. Abnormally low testosterone levels may cause decreased sexual arousal, responsiveness, libido, genital sensation and orgasm. Methyltestosterone replacement therapy may be effective in women with symptoms of inhibited desire, dyspareunia or insufficient vaginal lubrication, especially in the postmenopausal period.

Compounds with these and other mechanisms of action under active development for the treatment of female sexual dysfunction are presented in Table VI.

Urolithiasis

Urolithiasis (also known as kidney stones, renal stones and renal calculi) occurs when urine becomes too concentrated. This causes minerals and other substances in the urine to form crystals on the inner surfaces of the kidneys. Over time these crystals may combine to form a small, hard mass. Sometimes this mass, or stone, breaks off and passes into the ureter. About 80% of stones are a combination of calcium and oxalate (oxalic acid). Most other stones are composed of uric acid. A few are made of ammonia crystals (struvite) and result from chronic urinary tract infections. About 1% of stones are composed of the amino acid cystine and occur in people who have the inherited disorder cystinuria.

The β_2/β_3-adrenoceptor agonist **KUL-7211** is in phase I testing at Kissei, where it is targeted to the relief of colic caused by urolithiasis.

Renal failure

Acute renal failure is sudden loss of the ability of the kidneys to excrete wastes, concentrate urine and conserve electrolytes. The condition, which is more common in adults than children, can be caused by a variety of illnesses and conditions including low blood flow (*i.e.*, in trauma, septic shock, hemorrhage or burns), injury to the kidneys, overexposure to toxic metals, infections such as acute pyelonephritis or septicemia, urinary tract obstruction, autoimmune disorders such as scleroderma, *etc*. Acute renal failure often resolves with treatment, although some patients may progress to chronic renal failure.

Chronic renal failure, in contrast, results from the slowly progressive loss of renal function such as that caused by hypertension or diabetes. It can range from mild dysfunction to severe kidney failure, and may progress to end-stage renal disease. Chronic renal failure usually occurs over a number of years as the internal structures of the kidney are slowly damaged. In the early stages, there may be no symptoms. In fact, progression may be so gradual that symptoms do not occur until kidney function is less than one-tenth of normal. Chronic renal failure and end stage renal disease affect more than 2 out of 1,000 people in the U.S.

Pirfenidone, a TNF-α production inhibitor, is in phase II testing at InterMune, where it is targeted to the treatment of focal segmental glomerulosclerosis. This condition, which results from the buildup of scar tissue in the glomeruli (structures of the kidney that filter out harmful substances), in most cases progresses to chronic renal failure.

Myogen, under license from Abbott, is evaluating the endothelin ETA receptor antagonist **ambrisentan** (BSF-208075) in phase I trials for several indications, including the treatment of patients with chronic renal failure. In late 2003 the company plans to begin phase II clinical testing of ambrisentan in patients with advanced chronic renal disease and poorly controlled hypertension. Myogen's strategy for registration of ambrisentan in chronic renal disease is focused on the control of blood pressure in patients with advanced disease and coexisting hypertension.

ALT-711, a novel A.G.E. crosslink breaker from Alteon, is designed to reverse the progressive stiffening of the cardiovascular system. The company has initiated phase I testing of ALT-711 in patients with end-stage renal disease who are undergoing peritoneal dialysis.

Glomerulonephritis

Glomerulonephritis is a group of kidney diseases caused by inflammation of the internal kidney structures, or glomeruli. Glomerulonephritis may be a temporary and reversible condition or may be progressive, resulting in destruction of the kidney glomeruli, chronic renal failure and end-stage renal disease. The disease may be caused by specific problems with the body's immune system, but the precise cause of most cases is unknown.

Cyclacel is evaluating its lead drug **(*R*)-roscovitine** (CYC-202)as a potential treatment for glomerulonephritis. CYC-202 is a small-molecule cyclin-dependent kinase inhibitor with potential in the treatment of diseases characterized by abnormal cell proliferation. CYC-202 previously completed a phase I study in healthy volunteers, as well as preclinical studies in models of glomerulonephritis, in preparation for advanced clinical trials. Preclinical results suggested that CYC-202 causes cellular responses and improvement of kidney function in multiple disease models of glomerulonephritis. CYC-202 is currently in multicenter phase Ib trials in patients with cancer to determine its safety, maximum tolerated dose and pharmacokinetic profile. Previous phase Ia studies in cancer showed it to be well tolerated and orally available.

Nippon Kayaku's angiogenesis inhibitor **gusperimus hydrochloride**, currently in phase II testing, is being developed for the treatment of glomerulonephritis as well as several other indications.

Hyperoxaluria

Primary hyperoxaluria is a rare, autosomal recessive disease, caused by deficiency of an enzyme in the liver, affecting approximately 3,000-4,000 children and adolescents in major populations worldwide. Primary hyperoxaluria is bimodal, with two peaks of mortality. Many primary hyperoxaluria patients will be diagnosed and die of renal failure before their first birthday, with the remainder typically diagnosed in early adolescence.

Because the kidneys are the main pathway for reducing oxalate, hyperoxaluria leads to calcium oxalate kidney stones and nephrocalcinosis, nearly always resulting in renal failure. Up to 50% of patients suffering from primary hyperoxaluria reach end-stage renal failure by 15 years of age. The decline in renal function results in an accumulation of oxalate within various organs and tissues, such as bones, heart, arteries, retina and nerves, leading to severe morbidity and mortality.

The principal treatment for hyperoxaluria is large fluid intake, large daily doses of vitamin B_6 (pyridoxine), phosphate and/or citrate and magnesium supplements, and often an oxalate-restricted diet. In patients who maintain kidney function, a significantly increased fluid intake helps keep the kidneys flushed out and limits crystal formation. In patients who have lost kidney function, aggressive dialysis is an appropriate treatment until a living-related kidney can be transplanted. However, it is recommended that a kidney be transplanted as soon as possible after renal failure occurs, since dialysis does not adequately remove oxalate. Furthermore, kidney transplantation alone offers only a temporary solution, because the replacement kidney is attacked by the disease. While combined kidney-liver transplantation appears to give good results, availability is limited, and

the effect of life-long immune suppression is severe, particularly in children.

On September 6, 2002, Ixion Biotechnology announced the initiation of treatment in a pilot study of its oral oxalate therapy, **IxOC-2**. IxOC-2 is a frozen cell paste of live *Oxalobacter formigenes*, a naturally occurring beneficial gut-dwelling bacteria. The only known function of *O. formigenes* is to break down oxalate and prevent it from being absorbed from the diet. Robust colonization with *O. formigenes* may also enhance elimination of endogenous oxalate via enteric elimination. The study is being conducted in three patient groups: children with confirmed diagnosis of primary hyperoxaluria type I, subjects with cystic fibrosis, and other subjects with secondary, absorptive hyperoxaluria due to other reasons. In addition to safety, the pilot study will assess the drug's efficacy in terms of colonization of the GI tract with *O. formigenes* and its effect on 24-h urinary oxalate levels in patients with various forms of hyperoxaluria

Hyperphosphatemia

Hyperphosphatemia, a condition often encountered in patients with chronic renal failure who are undergoing dialysis, is characterized by the presence of abnormally high concentrations of phosphate in the blood. Hyperphosphatemia is a strong risk factor for cardiovascular mortality in this patient group.

Standard therapy for hyperphosphatemia consists of the administration of calcium-containing phosphate binders. In March 2003, Shire received an approvable letter from the FDA for Fosrenol® (**lanthanum carbonate**), a potent noncalcium, nonaluminium phosphate binder, requesting additional data and analysis to address several remaining questions. Shire remains on track to launch Fosrenol® before the end of 2003 for the treatment of high phosphate levels in the blood which occur in patients undergoing dialysis as a result of chronic kidney failure. The company has also filed regulatory submissions in Europe and Canada, while development continues in Japan. Shire acquired an exclusive worldwide license to develop, manufacture, use and sell Fosrenol® from AnorMED in 1998.

Mitsubishi Pharma is conducting phase II clinical trials evaluating the potential efficacy of **colestimide**, a bile acid sequestrant that has been marketed for some years for the treatment of hypercholesterolemia, in this new indication.

Dilutional hyponatremia

Dilutional hyponatremia, also known as syndrome of inappropriate antidiuretic hormone secretion (SIAHS), is a disorder of fluid and electrolyte balance caused by excessive retention of antidiuretic hormone. Fluid and electrolyte imbalance in SIAHS results from the body's inability to secrete dilute urine, water retention within the body and low levels of sodium. Small cell lung cancer, which induces the secretion of excessive amounts of antidiuretic hormone, is the most common cause of this condition. Other causes include pancreatic cancer, prostate cancer, Hodgkin's disease, CNS disorders, pulmonary disorders and psychosis.

Sanofi-Synthélabo is conducting a phase II study designed to assess the efficacy of **SR-121463A**, a vasopressin receptor antagonist, in the treatment of low levels of sodium in the blood associated with SIADH.

Membranous nephritis

In February 2002, Alexion announced that it had completed enrollment in the company's first phase II trial evaluating the antiinflammatory complement C5 inhibitor

Table VII: Drugs formerly in development for renal and urologic disorders discontinued in the past year.

Drug Name	Source	Status (indication)	Reason
Osaterone acetate	Teikoku Hormone	Preregistered (benign prostatic hyperplasia)	No development reported
Chrondrogel	Curis	Phase III (vesicoureteral reflux)	Refocusing of company R&D priorities
IDR-16084	Institute for Drug Research	Phase II (benign prostatic hyperplasia)	No development reported
Ro-70-0004	Roche Bioscience	Phase II (benign prostatic hyperplasia)	Negative results in clinical trials
Saredutant	Sanofi-Synthélabo	Phase II (urinary incontinence)	Development redirected to other indications
Talnetant	GlaxoSmithKline	Phase II (urinary incontinence)	Development redirected to other indications
Aliskiren fumarate	Speedel	Phase I/II (chronic renal disease)	Lack of efficacy (development continues for another indication)
(*S*)-Doxazosin	Sepracor	Phase I (benign prostatic hyperplasia)	No development reported
ABT-598	Abbott	Phase I (urinary incontinence, erectile dysfunction)	No development reported
Ono-8922	Ono	Phase I (pollakiuria)	No development reported
PN-401	Repligen	Phase I (kidney disease in patients with mitochondrial disease and renal tubular acidosis)	No development reported
UK-294315	Pfizer	Phase I (benign prostatic hyperplasia)	No development reported

antibody 5G1.1 (**eculizumab**) in patients suffering from membranous nephritis, a severe form of kidney disease. The multicenter, double-blind, randomized, placebo-controlled trial is examining the safety and clinical efficacy of repeated doses of eculizumab over four months in approximately 115 membranous nephritis patients enrolled in the U.S. The company has received orphan drug designation from the FDA for the use of eculizumab in patients with this disorder. Alexion is also conducting phase II trials evaluating eculizumab in the treatment of lupus nephritis.

Discontinued products

Several products that were mentioned in the 2002 edition of the Annual Review on Renal and Urologic Drugs, published in *Drugs of the Future*, have been dropped from the pipeline in the intervening period. Information on these drugs, together with the reason why each product has not been included in this year's review, is summarized in Table VII.

Internet resources

American Urological Association
www.auanet.org

Interstitial Cystitis Association
www.ichelp.com

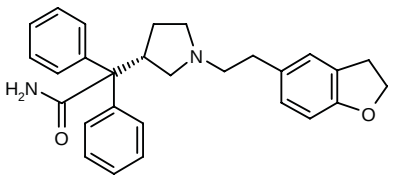
National Institute of Diabetes and Digestive and Kidney Disorders
www.niddk.nih.gov

National Kidney Foundation
www.kidney.org

Monograph Updates of Urologic Drugs

N.E. Mealy, M. Bayés, P.A. Leeson
Prous Science, P.O. Box 540, 08080 Barcelona, Spain

Darifenacin



Darifenacin (Enablex®) is a muscarinic M_3 receptor antagonist for the treatment of urinary incontinence that was developed by Pfizer and recently acquired by Novartis. Pfizer divested the drug in order to comply with regulatory requirements related to its recent merger with Pharmacia. An NDA was filed in December 2002 and the drug is expected to be launched in 2004. European approval is expected in 2004 (1-3).

The muscarinic receptor subtype that mediates the contraction of human urinary bladder was identified to be predominantly, if not exclusively, the M_3 subtype. In the presence of the nonselective muscarinic receptor antagonist atropine, the M_1-selective agent pirenzepine, the M_2-selective agent methoctramine, and the M_3-selective compound darifenacin, carbachol concentration-response curves were shifted towards higher concentrations. The responses to carbachol, however, were significantly affected only in the presence of darifenacin, where the maximal response was significantly reduced (4).

The binding affinity of darifenacin for human recombinant muscarinic receptor subtypes (M_1-M_5) was compared with tolterodine, oxybutynin, propiverine and trospium. Respective pK_i values for the M_3 receptor were 9.1 ± 0.1, 8.5 ± 0.1, 8.9 ± 0.1, 6.4 ± 0.1 and 9.3 ± 0.1. Darifenacin demonstrated the greatest selectivity for the M_3 receptor over other muscarinic receptor subtypes (K_i M_3/M_1 = 9.3, M_3/M_2 = 59.2, M_3/M_4 = 59.2, M_3/M_5 = 12.2). Muscarinic M_3 receptor selectivity was not observed for current treatments for overactive bladder and it was suggested that this property might confer superior clinical efficacy for darifenacin (5).

1. *Novartis acquires Enablex*. DailyDrugNews.com (Daily Essentials) May 13, 2003.

2. *Major step forward in Pfizer-Pharmacia merger*. DailyDrugNews.com (Daily Essentials) March 4, 2003.

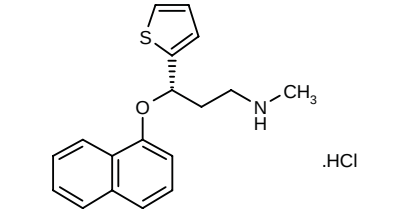
3. *Novartis to acquire Pfizer incontinence drug*. DailyDrugNews.com (Daily Essentials) March 20, 2003.

4. Fetscher, C., Fleichman, M., Schmidt, M., Krege, S., Michel, M.C. *M_3 muscarinic receptors mediate contraction of human urinary bladder*. Br J Pharmacol 2002, 136(5): 641.

5. Napier, C., Gupta, P. *Darifenacin is selective for the human recombinant M_3 receptor subtype*. 32nd Annu Meet Int Continence Soc (Aug 28-31, Heidelberg) 2002, Abst 444.

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

Duloxetine Hydrochloride



Duloxetine hydrochloride (Lilly) is undergoing regulatory review in the U.S. for both stress urinary incontinence (SUI) and depression (brand name Cymbalta™). Lilly and Boehringer Ingelheim recently signed a long-term agreement to jointly commercialize duloxetine for the treatment of SUI on a worldwide basis, excluding Japan. The two companies also agreed to jointly commercialize the drug for the treatment of depression outside the U.S., excluding Japan (1, 2).

A randomized, placebo-controlled phase III clinical trial provided new data on the efficacy and safety of duloxetine in 494 women with stress urinary incontinence. The patients were randomized to receive either placebo or duloxetine (40 mg b.i.d.) for 12 weeks. The drug was significantly more effective than placebo in reducing the incontinence episode frequency (median decrease of 50% *vs*. 29%), increasing the voiding intervals (15 min *vs*. 4 min) and improving the patients' quality of life. Discontinuation rates due to adverse events were 22% and 8% for duloxetine and placebo, respectively, the most common being transient, mild to moderate nausea (3).

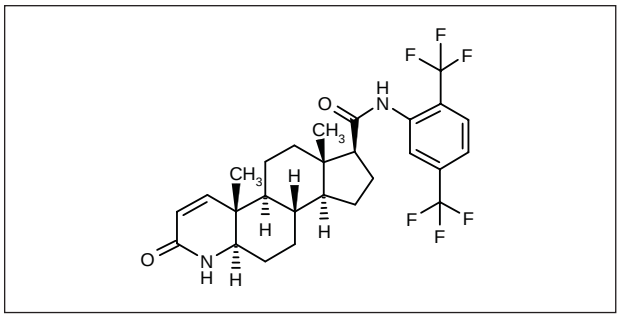
1. *Cymbalta deemed approvable by FDA*. DailyDrugNews.com (Daily Essentials) Sept 19, 2002.

2. *Lilly and Boehringer Ingelheim sign cocommercialization agreements for duloxetine*. DailyDrugNews.com (Daily Essentials) Dec 10, 2002.

3. Van Kerrebroeck, P., Abrams, P., Lange, R., Slack, M., Wyndaele, J., Yalcin, I., Bump, R. *Duloxetine vs. placebo in the treatment of stress urinary incontinence: Phase 3 results from Europe and Canada*. Eur Urol Suppl 2003, 2(1): Abst 107.

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

Dutasteride



GlaxoSmithKline's azasteroid dutasteride, the first 5α-reductase inhibitor that inhibits both type 1 and 2 isozymes responsible for converting testosterone to dihydrotestosterone (DHT) in the prostate and other tissues, was introduced in the U.S. in January (as Avodart®) and in the U.K. in February for the treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH) and for the prevention of acute urinary retention and surgery in BPH patients. The drug was approved by the Swedish regulatory authorities as Avolve® last year, followed by E.U.-wide approval under the mutual recognition procedure (1-6).

The actions of dutasteride on prostate cancer cell lines were investigated. Incubation with the drug at a concentration of 10 μM reduced the proliferation rate and inhibited both the 5α-reductase activity and the action of testosterone on prostate cancer LAPC-4 and LNCaP cell lines, which express a wild-type and a mutated form of the androgen receptor, respectively. Higher dutasteride levels (50 μM) were necessary to induce similar effects on cell line PC-3, which does not express the androgen receptor (7).

A multicenter, double-blind, randomized, placebo-controlled clinical trial assessed the effects that long-term treatment for 2 years with 0.5 mg/day of dutasteride might have on spermatogenesis in 99 healthy volunteers. Dutasteride produced a nearly complete maximal suppression of DHT levels. Compared to placebo, the 5α-reductase inhibitor increased testosterone levels by 24%, decreased semen volume by 19-24% and decreased sperm motility by 7-15%. These effects, however, were not clinically significant, and the authors concluded that dutasteride could be safely administered to men of reproductive age (8). The results of this study and those that follow are summarized in Table I.

A multicenter, double-blind clinical trial assessed the effects on the bone metabolism and lipid profile of 99 healthy male volunteers with a body mass index of 19-32 who received 0.5 mg dutasteride, 5.0 mg finasteride or placebo once daily for 52 weeks. The measurement of bone density by X-ray absorptiometry revealed no significant differences among treatments at baseline, at the end of the treatment or after follow-up for 20-24 weeks. No clinically significant changes were found in the serum levels of bone metabolism markers (*e.g.*, osteocalcin and bone alkaline phosphatase) compared to baseline. After follow-up for 24 weeks, the only significant change in the lipid profile was an increase in triglyceride levels in both placebo and dutasteride study groups. However, these changes were not considered to be clinically relevant by the authors, as triglycerides were the most variable lipid parameter (9, 10).

A total of 399 men with BPH were enrolled in a clinical trial that compared the suppression of DHT levels induced by a 24-week treatment with dutasteride (0.1-5.0 mg/day), finasteride (5 mg/day) or placebo. At the end of the treatment period, 85.4% and 100.0% of the 48 patients who received a daily dose of 0.5 mg of dutasteride showed a > 90% and > 75% reduction in baseline DHT levels, respectively. In the 45 finasteride-treated patients, the respective reductions in baseline DHT levels were 2.2% and 49% (11).

The effects of dutasteride on the intraprostatic levels of DHT were evaluated in a double-blind, randomized clinical trial in 46 patients with previously untreated prostate cancer. A daily dose of 5 mg of dutasteride administered for 17-82 days before radical prostatectomy was more effective than placebo in suppressing serum

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

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized, double-blind, multicenter	Dutasteride, 0.5 mg od x 52 wk Finasteride, 5 mg od x 52 wk Placebo	99	No clinically significant changes in bone density, bone metabolism markers or lipid profile were found in healthy male volunteers after 52 weeks of treatment with dutasteride, finasteride or placebo or after follow-up for 20-24 weeks	8-10
Benign prostatic hyperplasia	Randomized, double-blind, multicenter	Dutasteride, 0.1-5.0 mg po od x 24 wk Finasteride, 5 mg po od x 24 wk Placebo	399	Dutasteride was more effective than placebo in reducing the levels of dihydrotestosterone in patients with benign prostatic hyperplasia	11
Prostate cancer	Randomized, double-blind, multicenter	Dutasteride, 10 mg od x 7 d → 5 mg od x 10-75 d (n=24)$ Placebo (n=22)	46	Dutasteride increased the levels of testosterone in serum and was more effective than placebo in reducing the levels of dihydrotestosterone in both serum and prostate. The drug also decreased the overall androgen content in the prostate	12

and intraprostatic levels of DHT. This reduction was associated with an increase in the levels of testosterone in both serum and prostate, but whereas the median concentration of DHT in the prostate had decreased from 6.49 ng/g tissue with placebo to 0.095 ng/g with dutasteride, that of testosterone had increased from 0.107 ng/g to 2.43 ng/g. This difference suggested that dutasteride also reduced the overall androgen burden in the prostate of these patients (12).

1. *Swedish approval for dutasteride for benign prostatic hyperplasia*. DailyDrugNews.com (Daily Essentials) July 30, 2002.

2. *GSK celebrates the international launch of Avodart*. DailyDrugNews.com (Daily Essentials) March 17, 2003.

3. *Dutasteride approved for launch as first dual-acting 5α-reductase inhibitor for BPH*. DailyDrugNews.com (Daily Essentials) Oct 11, 2002.

4. *Avodart introduced in U.K.* DailyDrugNews.com (Daily Essentials) March 11, 2003.

5. *European approval for Avodart for benign prostatic hyperplasia*. DailyDrugNews.com (Daily Essentials) Dec 11, 2002.

6. *GSK launches Avodart for BPH in U.S.* DailyDrugNews.com (Daily Essentials) Jan 16, 2003.

7. Lazier, C., Thomas, L., Douglas, R., Schmidt, L., Tindall, D. *Dual 5α-reductase inhibitor, dutasteride, inhibits androgen action, cell growth/viability in prostate cancer cell lines*. Eur Urol Suppl 2003, 2(1): Abst 137.

8. Clark, R., Huffman, C., Haberer, L., Swerdloff, R., Wang, C., Matsumoto, A., Bremner, W. *Marked suppression of dihydrotestosterone (DHT) by dutasteride has no adverse effect on spermatogenesis in healthy men*. BJU Int 2002, 90(Suppl. 2): Abst P-1.2.10.

9. Clark, R., Huffman, C., Swerdloff, R., Wang, C., Matsumoto, A., Bremner, W. *Potent DHT suppression by the novel dual 5α-reductase inhibitor dutasteride does not affect bone density, bone metabolism or lipid profiles in healthy men*. Eur Urol Suppl 2003, 2(1): Abst 630.

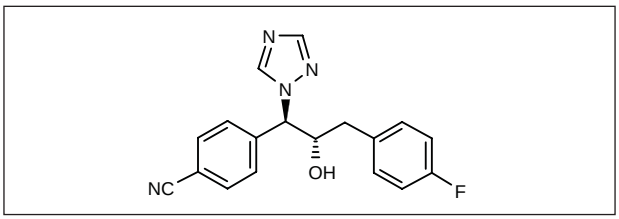
10. Clark, R.V., Matsumoto, A.M. *Bone density, bone metabolism markers and lipid profiles in healthy men are unaffected by the novel dual 5A-reductase inhibitor dutasteride*. J Urol 2003, 169(4, Suppl.): Abst 1796.

11. Roehrborn, C., Andriole, G., Schalken, J., Wilson, T., Clark, R. *Dutasteride, a novel dual 5α-reductase inhibitor, reduces serum DHT to a greater extent versus finasteride and achieves finasteride maximal reduction in a larger proportion of patients*. Eur Urol Suppl 2003, 2(1): Abst 635.

12. Andriole, G., Ray, P., Humphrey, P., Gleave, M., Rittmaster, R. *The impact of dutasteride, a novel dual 5α-reductase inhibitor, on both serum and intraprostatic androgens*. Eur Urol Suppl 2003, 2(1): Abst 332.

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

Finrozole



Finrozole (MPV-2213ad) is a nonsteroidal competitive aromatase inhibitor which is being evaluated at Hormos in phase II trials for the treatment of lower urinary tract symptoms (LUTS) associated with a reduced androgen/estrogen ratio.

Using two rodent models of infravesical obstruction, the effect of treatment with finrozole on developmentally induced alterations in urodynamics and rhabdosphincter were evaluated. In aromatase-positive mice, reduced maximal urinary flow rate was significantly increased following treatment with the drug; similarly, the relative thickness of the proximal rhabdosphincter, seminal vesicle size and mean serum testosterone concentrations were increased. Additionally, finrozole-treated estrogenized rats demonstrated increased urinary flow rates (1).

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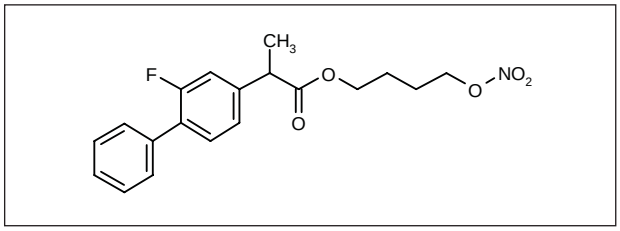
Original monograph - Drugs Fut 1998, 23(10): 1071.

HCT-1026



NicOx is developing the nitric oxide (NO)-donating flurbiprofen derivative HCT-1026 for a number of indications. It is in phase II clinical trials for overactive bladder and osteoporosis and phase I for Alzheimer's disease.

Promising phase I pharmacokinetic results for HCT-1026 in healthy volunteers have been reported. The study showed penetration of the blood-brain barrier and the presence of effective drug concentrations in the cerebrospinal fluid after repeated oral dosing. HCT-1026's underlying mechanism is based on NO release and the inhibition of multiple inflammatory mediators such as prostanoids, cytokines and free radicals, likely through inhibition of nuclear transcription factors. Nitric oxide is able to prevent or repair injury to the gastrointestinal tract caused by NSAIDs. In previous phase I and II trials in more than 200 subjects, HCT-1026 was well tolerated. Endoscopic analysis showed that the drug has superior gastric tolerability (1).

A double-blind, placebo-controlled clinical study conducted in healthy human volunteers compared the inhibitory activity against cyclooxygenase type 1 and 2 (COX-1 and COX-2) of flurbiprofen and HCT-1026. Thirty-two subjects were randomized to receive HCT-1026 (100 or 150 mg b.i.d.), flurbiprofen (100 mg b.i.d.) or placebo for 7 days. Endoscopic evaluations conducted at baseline and at the end of the treatment revealed that flurbiprofen was associated with a greater incidence of gastric or duodenal ulcers (62% *vs*. 12.5-25% on HCT-1026) and a higher mean endoscopic score (17.6 *vs*. 7.0-8.0). Flurbiprofen and both dose levels of HCT-1026 were effective in inhibiting COX-1 activity, as measured by inhibition of arachidonic acid-induced platelet aggregation, the generation of TxB_2 and the levels of 11-DH-TxB_2 in urine, and also COX-2 activity, as measured by inhibition of the generation of PGE_2 in response to lipopolysaccharide. Neither drug had any effect on blood pressure or heart rate. The authors estimated that the use of HCT-1026 would reduce gastrointestinal ulcers by 60-80% compared to flurbiprofen and concluded that HCT-1026 was a potent COX-1 and COX-2 inhibitor, confirming that the addition of NO is an effective way to reduce the gastrointestinal toxicity without adversely affecting the efficacy of nonsteroidal antiinflammatory drugs in humans (2).

Results from a 6-week, randomized, double-blind, placebo-controlled, crossover study involving 25 women with symptoms of urgency and frequency with or without incontinence showed that treatment with HCT-1026 (100 mg b.i.d.) significantly decreased urgency and pain as compared to placebo. No differences in cystometric or frequency volume parameters were seen between treatment and placebo groups. Only 2 serious adverse events were reported, which included 1 case of unconfirmed rectal bleeding and another of hypertension. Four patients discontinued due to adverse events. No significant differences in adverse events were seen between placebo and HCT-1026 groups. HCT-1026 may therefore be safe and effective in the treatment of overactive bladder (3).

In phase IIa trials, HCT-1026 demonstrated a statistically significant benefit compared to placebo in symptoms of urinary incontinence and pain intensity, and in the sensation of complete bladder emptying (4).

1. *HCT-1026 pharmacokinetic results in humans*. DailyDrugNews.com (Daily Essentials) May 14, 2003.

2. Fiorucci, S., Santucci, L., Sardina, M., Santus, G., Fransioni, A., Del Soldato, P., Morelli, A. *Effect of HCT1026, a nitric oxide (NO) releasing derivative of flurbiprofen, on gastrointestinal mucosa: A double blind placebo-controlled endoscopic study*. Dig Dis Week (May 17-22, Orlando) 2003, Abst T1326.

3. Rufford, J., Cardozo, L., Toozs-Hobson, P., Dixon, A. *HCT 1026 - A novel treatment for urgency?* 32nd Annu Meet Int Continence Soc (Aug 28-31, Heidelberg) 2002, Abst 225.

4. *NicOx reviews first-half clinical developments*. DailyDrugNews.com (Daily Essentials) July 29, 2002.

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

Lanthanum Carbonate

$La_2 (CO_3)_3$

Shire has developed lanthanum carbonate (Fosrenol™, formerly Foznol™), a noncalcium, nonaluminium phosphate binder for end-stage renal disease patients, under an exclusive development, manufacturing and marketing license from AnorMED. The company has received an approvable letter from the FDA requesting additional data and analysis to address several remaining questions. Shire remains on track to launch Fosrenol™ before the end of the year and is also awaiting regulatory approval in Europe and Canada (1-4).

Fourteen healthy volunteers were included in an open-label, crossover clinical trial and randomized to receive either 0.5 mg of digoxin alone or 30 min after a fourth dose of 1 g of lanthanum carbonate. The only effect of lanthanum carbonate on the pharmacokinetics of digoxin was a small increase in the latter's serum half-life (from 11.4 h to 14.7 h) that was not considered to be clinically significant, and none of the adverse events found in the study were severe or considered to be related to treatment (5, 6).

An open-label, crossover study determined the effects of lanthanum carbonate on the pharmacokinetics of warfarin. Fourteen healthy volunteers were randomized to receive either warfarin alone (10 mg) or four 1000-mg doses of lanthanum carbonate (three with meals during the first day and the fourth one with breakfast on the next day) combined with warfarin (10 mg) 30 min after the last lanthanum carbonate dose. No evidence of pharmacokinetic interaction was found between lanthanum carbonate and warfarin. No adverse events were drug-related, and no serious adverse events were reported. The authors concluded that lanthanum carbonate may be safely administered concomitantly with warfarin (7, 8).

The possible pharmacokinetic interaction between lanthanum carbonate and metoprolol was investigated in an open-label, crossover clinical trial. Healthy volunteers were randomized to receive either metoprolol alone (100 mg p.o. 30 min after breakfast) or four 1000-mg doses of lanthanum carbonate (three with meals during the first day and the fourth one with breakfast on the next day) combined with 100 mg of metoprolol administered 30 min after the last lanthanum carbonate dose. Lanthanum carbonate had no significant effects on the serum concentration-time curve, the serum half-life and the time to maximum concentration for metoprolol. However, there was a slight decrease in the maximum serum concentration of metoprolol, but this was not considered to be clinically relevant (9).

An open-label, 2-way crossover study in 36 healthy volunteers confirmed the low systemic absorption of lanthanum carbonate and found no significant differences in the safety profile of a regimen of 1 g t.i.d. for 3 days when administered either during or 30 min after eating (10). The results of this study and some that follow are summarized in Table II.

Daily doses of up to 4178 mg of lanthanum carbonate were well tolerated with food in a population of 25 healthy volunteers; no serious adverse events were reported and the most common adverse event was headache (11).

A randomized, double-blind clinical trial in 1,229 hemodialysis patients with hyperphosphatemia revealed that lanthanum carbonate for up to 2 years was as effective as a standard therapy in reducing serum phosphorus levels but showed a lower incidence of adverse events and a higher patient survival rate (12).

A randomized, placebo-controlled study in 9 healthy volunteers showed that a dose of 1 g of lanthanum carbonate t.i.d. for 5 days decreased urinary phosphorus excretion from 0.680 g/day to 0.212 g/day without inducing any adverse events. Plasma levels of lanthanum carbonate were less than 1 ng/ml throughout the study, thus indicating that the drug had minimal systemic absorption and no significant systemic accumulation (13).

Patients with end-stage renal disease showed a similar level of improvement in bone biopsy parameters measured after 50 weeks of treatment with either lanthanum carbonate (maximum dose of lanthanum 3.75 g/day) or calcium carbonate (maximum dose of calcium 9 g/day). Hypercalcemia was more frequent in patients treated with calcium carbonate, and lanthanum carbonate was not associated with any adverse effects on bone (14).

An open-label phase III clinical trial has compared the effects of long-term treatment with lanthanum carbonate and calcium carbonate on the evolution of renal osteodystrophy in dialysis patients. Ninety-eight patients who had started hemodialysis or were scheduled to do so due to chronic renal failure within the last 12 weeks before randomization received doses of lanthanum carbonate (to a maximum of 3750 mg/day) or calcium carbonate (to a maximum of 9000 mg/day) that resulted in an optimal reduction in serum phosphate levels. After 1 year of treatment, both study therapies were effective in controlling the levels of phosphorus in serum and were well tolerated; no significant differences were found in their respective safety profiles save for hypercalcemia, which was more common among patients treated with calcium carbonate (49% *vs*. 6%). Lanthanum carbonate was more effective than calcium carbonate in normalizing the bone turnover of patients who at baseline suffered from adynamic bone or osteomalacia (71% *vs*. 42%) or hyperparathyroidism (80% *vs*. 50%). This difference was also

Table II: Clinical studies of lanthanum carbonate (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Open, crossover	Lanthanum carbonate, 1 g po tid x 3 d [given while eating] Lanthanum carbonate, 1 g po tid x 3 d [given 30 min after eating]	36	Lanthanum carbonate was well tolerated and showed a good safety profile regardless of administration while eating or 30 min afterward	10
Healthy volunteers	Randomized, double-blind	Lanthanum carbonate, po od [later increased to tid] 1x/2 d → 3 g po tid x 3 d (n=10) Lanthanum carbonate, po od [later increased to tid] 1x/2 d → Placebo x 3 d (n=2) Placebo (n=2)	14	Lanthanum carbonate was well tolerated and resulted in a lower incidence of gastrointestinal adverse events when administered with food	11
Chronic renal failure	Open	Lanthanum carbonate, 375-3000 g/day po x 6 wk → Maintenance dose x 2 y (n=632) Standard therapy (n=633)	1228	Lanthanum carbonate was well tolerated and as effective as standard therapy in reducing serum phosphate levels in patients with hyperphosphatemia secondary to chronic renal failure	12
Chronic renal failure	Open	Lanthanum carbonate, 3.75 g/d x 50 wk Calcium carbonate, 9 g/d x 50 wk	98	Lanthanum carbonate was as effective as calcium carbonate in improving the osteodystrophy symptoms found in patients with end-stage renal disease, but was associated with a lower incidence of hypercalcemia	14
Hyperphosphatemia	Randomized, double-blind, multicenter	Lanthanum carbonate, 3750 [max] mg od x 1 y (n=49) Calcium carbonate, 9000 [max] mg od x 1 y (n=49)	98	Lanthanum carbonate was as well tolerated and as effective as calcium carbonate in controlling the levels of phosphorus in plasma. Lanthanum carbonate was more effective than calcium carbonate in normalizing the bone turnover of chronic renal failure patients who suffered from adynamic bone disease or osteomalacia or hyperparathyroidism at baseline. This difference was also correlated with a lower percentage of lanthanum carbonate-treated patients developing adynamic bone disease or hyperparathyroidism	15
Chronic renal failure	Open	Lanthanum carbonate, x 1 y Calcium carbonate, x 1 y	98	After 1 year of treatment, both lanthanum carbonate and calcium carbonate were effective in controlling the serum phosphate levels of hemodialysis patients. Lanthanum carbonate was associated with a lower incidence of hypercalcemia and a lower rate of progression towards adynamic bone disease (1 patient compared to 6 with calcium carbonate). Five of 7 patients with low baseline bone turnover and 4 of 5 patients with baseline hyperparathyroidism achieved a normal bone turnover after receiving lanthanum carbonate for 1 year	16
Chronic renal failure	Open	Lanthanum carbonate x 4 wk	77	Lanthanum carbonate was well tolerated and effective in controlling serum phosphate levels in patients with end-stage renal disease undergoing hemodialysis	17
Chronic renal failure	Open	Lanthanum carbonate, 1 g po od [on days 1 and 14] → 1 g po tid x 11 d [on days 17-26] → 1 g po sd [on day 28]	18	Lanthanum carbonate was well tolerated in healthy volunteers and in hemodialysis patients with chronic renal failure	19

correlated with a lower percentage of lanthanum carbonate-treated patients developing adynamic bone disease (4% *vs*. 26% with calcium carbonate) or hyperparathyroidism (7.5% *vs*. 17% with calcium carbonate). The authors concluded that treatment of hyperphosphatemia with lanthanum carbonate was associated with a better outcome compared to treatment with calcium carbonate (15, 16).

An open-label study evaluated the long-term efficacy and safety of lanthanum carbonate in 77 patients who had previously been included in double-blind or open-label clinical trials of the drug. Treatment with lanthanum carbonate for 1 year significantly reduced serum phosphate levels of the patients but had no clinically relevant effects on calcium or parathyroid hormone levels in serum. The drug was well tolerated, and the most common adverse events were nausea (26.0%), peripheral edema (23.4%) and myalgia (20.8%). No serious adverse events were reported, and the only drug-related adverse effects were constipation and dyspepsia (2 and 3 patients, respectively) (17).

Data from an extension trial show that continued long-term treatment with lanthanum carbonate maintains decreased levels of phosphate, which frequently escalate in end-stage renal disease patients. The 52-week open-label extension study evaluated the persistence of patients' improvement with chronic administration of lanthanum carbonate. Extension treatment with the drug resulted in reduced serum phosphate levels that averaged less than the target amount of 5.9 mg/dl in 53% of participants, all of whom had participated in one of two previous studies. At study end, participants averaged phosphorus levels of 5.7 ± 1.4 mg/dl. When the study began, patients showed average levels of 6.6 ± 2.0 mg/dl, likely due to the inclusion of patients in the extension study who had received placebo in one of the previous studies. By 4 weeks, average levels dropped to 5.7 ± 2.0 mg/dl, a significant change from the beginning of the study. The participants' serum calcium levels remained within the normal range specified by the study design (8.4-10.4 mg/dl). The extension study enrolled 77 patients who all received lanthanum carbonate for 52 weeks at doses established during earlier trials (18).

Hemodialysis patients reported a higher percentage of adverse events compared to healthy subjects after receiving 1 g of lanthanum carbonate t.i.d. for 11 days, but 80% of these events were related to the patients' health status and not to drug treatment (19).

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2. *AnorMED updates status of product development*. DailyDrugNews.com (Daily Essentials) Nov 18, 2002.

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13. Fiddler, G. *Low systemic absorption of lanthanum and excellent tolerability during administration of 3 g of lanthanum as Fosrenol™ for 5 days*. J Am Soc Nephrol 2002, 13(Abstracts issue): Abst PUB399.

14. De Broe, M.E. *Fosrenol™ (lanthanum carbonate) vs. calcium carbonate for the treatment of hyperphosphataemia: A comparison of the effects on bone using biopsy examination*. J Am Soc Nephrol 2002, 13(Abstracts issue): Abst PUB487.

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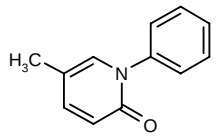
Original monograph - Drugs Fut 2003, 28(3): 224.

Pirfenidone



Pirfenidone is an orally active small molecule drug under development at InterMune that appears to inhibit collagen synthesis, downregulate the production of multiple cytokines and block fibroblast proliferation and stimulation in response to cytokines. The compound has demonstrated activity in multiple fibrotic indications and is currently in phase II clinical development for fibrotic diseases of the lung, kidney and liver.

Pirfenidone was found to improve kidney fibrosis induced in rats by administration of vanadate 1 mg/kg/day. Kidney weight and RNA content, both increased by vanadate, were reduced in animals given a diet containing 0.6% pirfenidone. Pirfenidone also decreased the vanadate-induced increase in hydroxyproline content in the kidney, and reduced the histological severity of lesions from moderate to severe to mild (1).

The efficacy of pirfenidone was assessed in a phase I/II clinical trial in 15 patients with idiopathic focal segmental glomerulosclerosis. Administration of 800 mg t.i.d. of pirfenidone combined with an angiotensin antagonist resulted in gastrointestinal symptoms that prompted adjustment of the pirfenidone dosing schedule in accordance to the patients' weight and glomerular filtration rate. The preliminary results from 12 patients who received pirfenidone for at least 4 months suggested that the drug was well tolerated and slowed down renal functional decline in patients receiving angiotensin antagonist therapy (2).

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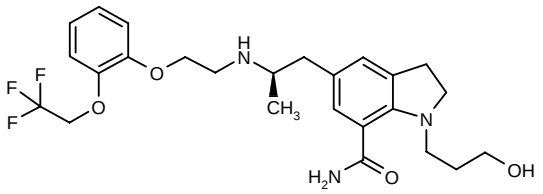
Silodosin



Silodosin (KMD-3213, KAD-3213) is an α_1-adrenoceptor antagonist which is undergoing phase II trials for the treatment of urinary disturbances associated with benign prostatic hyperplasia (BPH). The compound is being developed under an agreement between originator Kissei and Daiichi Pharmaceutical, whereby the companies will comarket the product in Japan; Kissei retains overseas development and marketing rights.

The effects of inverse agonists and neutral antagonists on α_1-adrenoceptors were investigated *in vitro* in CHO cells expressing α_1-adrenoceptor mutants and *in vivo* in rats. Inverse agonists such as prazosin lowered basal IP_3 levels and raised the receptor density, while silodosin had no effect on either but inhibited the prazosin-induced upregulation. Likewise, chronic administration of prazosin in rat heart and spleen upregulated α_1-adrenoceptors and the supersensitivity to phenylephrine in the contractile responses of thoracic aorta. Silodosin had no such effect. The response of constitutively activated receptors to inverse agonists and not to neutral antagonists may be linked with the development of tolerance (1).

Doses of up to 75 μg/kg of silodosin had no effect on tilt-induced blood pressure responses, unlike prazosin or tamsulosin, which blocked the responses and induced significant orthostatic hypotension at doses over 3 μg/kg i.v. Additionally, silodosin demonstrated the most specific uroselectivity among the three agents (2).

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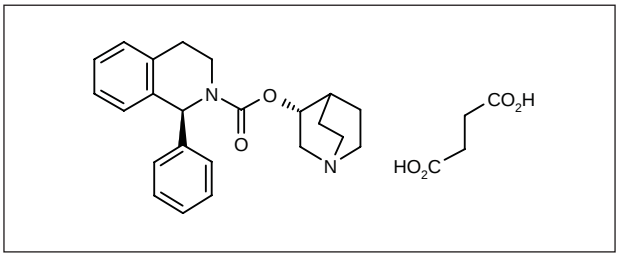
Original monograph - Drugs Fut 2001, 26(6): 553.

Solifenacin Succinate



Solifenacin succinate (YM-905, Vesicare®) is an investigational muscarinic antagonist that acts on the receptors in the smooth muscle of the bladder. It relaxes urinary bladder smooth muscle, thereby relieving symptoms such as urinary frequency, urinary incontinence or urgency associated with overactive bladder, and normalizing the voiding pattern. Yamanouchi's U.S. and European subsidiaries have submitted regulatory filings for solifenacin for the relief of symptoms of urinary frequency, urinary incontinence or urgency associated with overactive bladder. Negotiations are under way with potential candidates for copromotion of solifenacin in the U.S. The product is currently in phase III trials in Japan (1, 2).

In vitro studies using rat bladder smooth muscle and submandibular gland cells demonstrated that solifenacin inhibited the carbachol-induced elevation in intracellular Ca^{2+} with respective pK_i values of 8.12 and 7.57, showing greater bladder selectivity compared to oxybutynin, tolterodine and darifenacin. *In vivo* in anesthetized rats, solifenacin inhibited the carbachol-induced increase in intravesical pressure with an ID_{30} of 0.023 mg/kg i.v., compared to an ID_{30} of 0.15 mg/kg i.v. for inhibition of carbachol-induced salivary secretion, again showing higher bladder selectivity compared to the reference compounds. Solifenacin is therefore expected to have fewer unwanted adverse effects, *e.g.*, dry mouth, compared to currently available antimuscarinic agents (3-5).

The affinities of solifenacin and oxybutynin for M_1, M_2 and M_3 muscarinic receptors were compared in radioligand binding studies, which revealed both agents to be more selective for M_1 and M_3 than M_2 receptors (respective pK_i values: M_1 = 7.6 and 8.6; M_2 = 6.9 and 7.7; M_3 = 8.0 and 8.9). Both agents similarly antagonized carbachol-induced smooth muscle contraction and calcium mobilization in guinea pig detrusor cells, but oxybutynin was more potent in mouse submandibular gland cells. In anesthetized rats, carbachol-induced increases in bladder pressure were dose-dependently antagonized by solifenacin at doses significantly lower than those required for inhibition of salivation and bradycardia. The results demonstrate the selectivity of solifenacin for the M_3 over the M_2 muscarinic receptor and tissue preference for the bladder over the salivary gland (6).

The absolute bioavailability of solifenacin (10 mg p.o. or 5 mg i.v.) was investigated in a randomized, 2-way crossover study in 12 healthy male volunteers. Adverse events were reported by 83% of subjects, although they were generally mild to moderate in severity. There were 3 serious adverse events, but none were considered related to the study drug. Solifenacin demonstrated extensive distribution with low clearance and a long elimination half-life. The absolute bioavailability of solifenacin was calculated to be 88%. It was concluded that solifenacin would be suitable for daily dosing (7).

The effect of food on the pharmacokinetics of solifenacin (10 mg) was evaluated in 24 healthy volunteers. The study drug was well tolerated, with only 17% of subjects reporting adverse events that were possibly or probably related to drug; no serious adverse events were reported. No clinically relevant effects on the pharmacokinetics of solifenacin were observed between the fed and fasted groups. It was concluded that solifenacin may be administered in the fed or fasted state (8).

The safety and pharmacokinetics of solifenacin were investigated in 33 elderly healthy subjects using a double-blind, placebo-controlled study design. Subjects were administered solifenacin (10 and 20 mg) as a single dose on day 1 and then single daily doses on days 5-19. A proportional rise in C_{max} and AUC was observed in male subjects, but a less than proportional rise for these parameters was observed in women, possibly due to the small study population. Between 5% and 10% of the administered dose was excreted as unchanged drug in the urine. Solifenacin was generally well tolerated, with most adverse effects reported mild to moderate in severity. The most common side effects possibly or probably related to drug included dry mouth and constipation. It was concluded that solifenacin might be useful for the treatment of overactive bladder (9).

The pharmacokinetics of solifenacin (5-100 mg) were evaluated in a double-blind, placebo-controlled, randomized study in 68 healthy male subjects. Adverse events were reported by 93% of subjects administered solifenacin in the first 3 days, the most frequent of which were dry mouth, blurred vision, headache, and at the two highest doses, drowsiness. The frequency and duration of dry mouth and blurred vision increased with dose, and multiple dosing with 100 mg appears inappropriate due to the frequency of adverse events. Peak plasma levels increased linearly with dose and the $t_{1/2}$ was estimated to be around 50 h. The authors recommended longer sampling periods in future studies in order to obtain more accurate measures for $t_{1/2}$ and AUC (10).

The safety and tolerability of solifenacin (5, 10, 20 or 30 mg) were evaluated in heathy male volunteers in a placebo-controlled, double-blind, randomized trial. Solifenacin or placebo was administered as a single dose

followed by a 3-day washout period and then once daily for 21 days. All subjects withdrew from the 30-mg group due to adverse events. The frequency and severity of dry mouth and blurred vision appeared to increase with dose. The t_{max} and $t_{1/2}$ (50 h) for solifenacin were dose-independent; conversely, C_{max} and AUC appeared to increase linearly with dose. The maximum tolerated dose was 20 mg. The authors recommended treatment periods of at least 2 weeks in future studies to ensure attainment of steady state (11).

The effect of ketoconazole on the pharmacokinetics, safety and tolerability of solifenacin was evaluated in 17 healthy subjects. Subjects were administered a single 10-mg oral dose of solifenacin followed by a 14-day washout period. Subjects were then administered ketoconazole (200 mg) once daily for 21 days with a single dose of solifenacin on day 7. Coadministration increased solifenacin C_{max} by approximately 40%, AUC_{last} and $AUC_{0\text{-}inf}$ by about 100% and $t_{1/2}$ by approximately 55%; t_{max} was unchanged. These changes in the pharmacokinetics for solifenacin were suggested to be due to ketoconazole-induced inhibition of first-pass metabolism of solifenacin by CYP3A4. Coadministration of both drugs was generally well tolerated (12).

The pharmacokinetics and safety of solifenacin were assessed in a double-blind, dose-escalating clinical trial that included 33 healthy men and women aged 65-80 years old. Single doses of 10 or 20 mg of the drug or placebo were given to the subjects on day 1 and then once daily on days 5-19 of the study. The authors reported dose-dependent increases in the peak plasma concentration and the area under the curve for solifenacin in male volunteers, whereas no clear dose-effect was found in female volunteers. The incidence of adverse events was 68% with solifenacin and 62% with placebo; the most common adverse events were dry mouth and constipation, and no clinically significant effects were detected in the laboratory values, vital signs or ECGs of the subjects. The results suggested that solifenacin was safe when administered to elderly patients with overactive bladder (13). The results of this study and those that follow are summarized in Table III.

In a phase II study in patients with overactive bladder, 265 patients were randomized to solifenacin 2.5, 5, 10 or 20 mg or placebo once daily. The number of micturitions per 24 h was significantly reduced in patients given solifenacin 10 and 20 mg compared with placebo. Fewer anticholinergic side effects, including dry mouth, were seen with the 5- and 10-mg doses of solifenacin than with the 20-mg dose (14).

A multicenter, double-blind, randomized, placebo-controlled phase III study evaluated solifenacin (5 or 10 mg once daily) *versus* placebo for 12 weeks in 907 patients with symptomatic overactive bladder. Solifenacin was significantly more effective than placebo in improving all symptoms, including the primary endpoint of micturitions per 24 h. The most frequent adverse events were dry mouth, constipation and blurred vision, and a lower incidence was seen on the 5-mg dose of solifenacin. The rate of discontinuation due to these adverse events was very low (0.3% on solifenacin 5 mg and 2.0% on solifenacin 10 mg). Overall, the lower dose of solifenacin appeared to have the best risk/benefit profile (15-17).

A multicenter, randomized, double-blind study compared the effects of solifenacin and tolterodine in 1,077 patients with overactive bladder. The patients were randomized to receive placebo, tolterodine (2 mg b.i.d.) or solifenacin (5 or 10 mg once daily) for 12 weeks. Both muscarinic antagonists were more effective than placebo in reducing the daily number of micturitions reported by the patients, but only solifenacin significantly improved all the overactive bladder symptoms. The good safety profile of solifenacin was confirmed, especially at a daily dose of 5 mg. The most common adverse events in all study drug groups were dry mouth, constipation and blurred vision, and few patients discontinued the study due to adverse events (0.4% with placebo, 0.0% with solifenacin 5 mg, 0.7% with solifenacin 10 mg and 0.8% with tolterodine) (18).

The results of 2 double-blind, randomized, placebo-controlled phase III clinical trials established that a daily dose of 10 mg of solifenacin given for 12 weeks increased the level of urinary continence among patients with overactive bladder. Of the 1,306 patients enrolled in these studies, 53% of solifenacin-treated patients and 31% of placebo-treated patients who were incontinent at baseline became continent by the end of the 12-week therapy. The drug was also more effective than placebo in reducing the level of incontinence, with a reduction of at least 25% in incontinence being reported by 88% and 66% of the patients treated with the drug or placebo, respectively (19).

Two randomized, double-blind, placebo-controlled clinical trials assessed the safety and efficacy of solifenacin in a population of 1,208 patients with overactive bladder. After 12 weeks of treatment, a dose of 10 mg given once daily was significantly better than placebo in increasing the percentage of patients who became continent (53% *vs*. 31%) or who experienced a reduction in incontinence of > 50% (82% *vs*. 57%) or > 25% (88% *vs*. 66%). The volume voided in each micturition increased by 46.8 ml with solifenacin compared to 7.7 ml with placebo. Solifenacin was well tolerated, and the most common adverse events associated with its administration were dry mouth and constipation (20, 21).

Solifenacin 2.5, 5, 10 or 20 mg once daily or tolterodine 2 mg b.i.d. was assigned to 225 patients with idiopathic detrusor overactivity in a 4-week, multicenter, double-blind phase II trial. Solifenacin had a dose-related effect on the frequency of micturition per 24 h and on dry mouth, which was the most common adverse effect. On the basis of efficacy and the occurrence of dry mouth, the 5- and 10-mg doses of solifenacin were chosen for study in phase III trials (22).

Table III: Clinical studies of solifenacin (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Double-blind	Solifenancin, 10 mg od on d 1 & 5-19 (n=13) Solifenancin, 20 mg od on d 1 & 5-19 (n=12) Placebo (n=8)	33	Solifenancin was well tolerated by elderly male and female healthy subjects. Most adverse events were mild, and the most frequent were dry mouth and constipation	13
Urinary incontinence, overactive bladder	Randomized, double-blind	Solifenacin, 2.5 mg od x 4 wk Solifenacin, 5 mg od x 4 wk Solifenacin, 10 mg od x 4 wk Solifenacin, 20 mg od x 4 wk Placebo	265	All but the lowest dose of solifenacin were safe and effective in treating overactive bladder	14
Urinary incontinence, overactive bladder	Randomized, double-blind, multicenter	Solifenancin, 5 mg od x 12 wk (n=301) Solifenancin, 10 mg od x 12 wk (n=299) Placebo (n=307)	907	Solifenancin was more effective than placebo in improving the symptoms of frequency of micturition, urgency and urge incontinence in patients with overactive bladder. The drug was also well tolerated, although a better safety profile was found with a daily dose of 5 mg	15-17
Urinary incontinence, overactive bladder	Randomized, double-blind, multicenter	Solifenacin, 5 mg od x 12 wk (n=279) Solifenacin, 10 mg od x 12 wk (n=268) Tolterodine x 12 wk (n=263) Placebo (n=267)	1077	Solifenacin was more effective than tolterodine or placebo in improving the symptoms associated with overactive bladder, including frequency, urgency and urge incontinence. All study treatments were well tolerated, and the adverse events most commonly associated with the active drugs were dry mouth, constipation and blurred vision	18
Urinary incontinence, overactive bladder	Randomized, double-blind, multicenter, pooled/meta-analysis	Solifenacin, 10 mg od x 12 wk (n=604) Placebo (n=604)	1306	Solifenacin markedly increased the percentage of overactive bladder patients who became continent by the end of the 12-week therapy over placebo. The drug was also more effective than placebo in reducing the level of incontinence, with a 25% or greater reduction in incontinence	19
Urinary incontinence, overactive bladder	Randomized, double-blind, pooled/meta-analysis	Solifenacin, 10 mg od x 12 wk (n=604) Placebo (n=604)	1208	Compared with placebo, solifenacin was more effective in reducing the daily number of micturitions, incontinence episodes and urgency episodes. The drug also increased the volume voided per micturition	20, 21
Detrusor hyperreflexia, urinary incontinence	Randomized, double-blind, multicenter	Solifenacin, 2.5 mg od x 4 wk Solifenacin, 5 mg od x 4 wk Solifenacin, 10 mg od x 4 wk Solifenacin, 20 mg od x 4 wk Tolterodine, 2 mg bid x 4 wk Placebo	225	On the basis of the drug's effect on micturition frequency and dry mouth, the 5 and 10 mg doses of solifenacin were chosen for study in phase III trials	22

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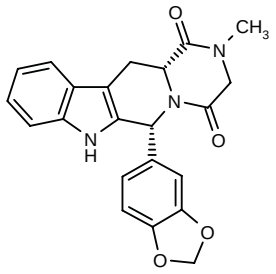
Tadalafil



The oral phosphodiesterase type 5 (PDE5) inhibitor tadalafil (Cialis™) was introduced by Lilly Icos earlier this year in a number of European countries, including the U.K., Germany, Denmark, Finland and Sweden, New Zealand and Australia, Brazil and Singapore, for the treatment of erectile dysfunction (ED). Following the receipt of an approvable letter from the FDA in April 2002, the company continues to anticipate U.S. approval in the second half of 2003. The compound is also under clinical evaluation for use in diabetic gastroparesis (1-7).

Two 3-month studies (up to 800 mg/kg /day) and a 2-year carcinogenicity study (up to 400 mg/kg/day) in mice and 1-, 6- and 24-month studies (all up to 400 mg/kg) in rats were undertaken in order to assess the effects of tadalafil. The drug had no effect on the testes of either rats or mice at respective plasma levels up to 18- and 25-fold greater than those achieved with a single 20-mg dose in man (8).

A placebo-controlled, crossover study evaluated the potential effect of alcohol on the tolerability and pharmacodynamics of tadalafil in 48 healthy male volunteers aged 16-60 years. Subjects received a single dose of alcohol (0.6 g/kg) 2 h after a single dose of tadalafil (20 mg). The treatment regimen was well tolerated and no adverse events were reported. No differences in maximum standing or supine blood pressure were observed between the treatment groups (9).

Possible pharmacodynamic interactions between tadalafil and nitrates were evaluated in 2 randomized, double-blind, 3-way crossover studies. In the first study, participants received sublingual nitroglycerin 2 h after tadalafil (5 or 10 mg). In the second study, tadalafil (5 or 10 mg) was administered during long-acting daily nitroglycerin therapy. No significant differences were observed between the active treatment groups and placebo in the mean maximal standing systolic blood pressure;

however, in the active treatment groups, there was a high frequency of outliers. It was concluded that tadalafil should not be coadministered with nitrates (10).

The hypothesis that tadalafil might increase the risk of cardiovascular side effects due to relaxation of vascular smooth muscle was assessed using data from clinical pharmacology and large-scale clinical trials. No significant changes in standing systolic and diastolic blood pressure were found in healthy subjects after administration of 20 mg tadalafil. Patients with stable cardiovascular conditions who had been included in phase III clinical trials showed no significant differences in the incidence of cardiovascular events (*e.g.*, flushing, dizziness, hypertension or syncope) after being randomized to receive tadalafil or placebo. The authors concluded that tadalafil was not associated with an increased incidence of cardiovascular events (11). The results of this study and some that follow are summarized in Table IV.

The potential effects of tadalafil on semen characteristics were evaluated in a double-blind study. Healthy men or those with mild ED were randomized to receive 20 mg tadalafil or placebo daily for 6 months. Analysis of the results revealed no significant differences between the groups in the mean sperm concentration, mean sperm count per ejaculate, mean percentage of sperm with normal morphology, serum testosterone, luteinizing hormone or follicle-stimulating hormone. Sperm motility, however, was found to deteriorate in the placebo *versus* the tadalafil group (12).

According to a recent study, a single dose of tadalafil 20 mg allows men with mild to severe ED to achieve successful intercourse up to 36 h after administration. The double-blind, randomized, placebo-controlled study enrolled 348 men with ED to treatment with tadalafil or placebo, who then attempted intercourse twice about 24 h later and twice about 36 h after the dose. Significantly more patients on tadalafil had successful intercourse at both 24 h (57.3% *vs*. 31.3% on placebo) and 36 h (60.4% *vs*. 29.9%). Tadalafil was well tolerated, mostly mild to moderate dyspepsia and headache being the most frequent adverse events (13).

A meta-analysis of 5 randomized, double-blind, placebo-controlled, parallel studies has provided new data on the efficacy and safety of tadalafil in the treatment of ED. A total of 1,112 men with mild to severe ED were randomized to receive either placebo or tadalafil at daily doses of 2.5-20 mg for 12 weeks. Patients treated with the drug showed improvement in all the scales used to evaluate ED, *i.e.*, the International Index of Erectile Dysfunction (IIEF), the Sexual Encounter Profile (SEP) and the Global Assessment Question (GAQ). The drug also increased the percentage of men with successful intercourse attempts (from 32% with placebo to 75% at 20 mg) and the percentage of patients with normal erectile function at endpoint (from 11% with placebo to 59% at 20 mg), regardless of the severity of etiology of ED. Tadalafil was well tolerated at all the tested doses; most adverse events were mild or moderate and the discontinuation rate was very similar with tadalafil (2.1%) and control (1.3%). Tadalafil was also safe in patients aged over 65 years, diabetics and patients with hypertension (14-16).

A study involving 23 patients with coronary artery disease who demonstrated ischemia during a screening exercise test were randomized to receive 10 mg tadalafil or placebo 2-2.5 h prior to an exercise test (comparable to that during sexual activity) in order to evaluate the effects of tadalafil on time to ischemia. No differences in exercise time/time to ischemia, blood pressure or heart rate were observed between the groups. Tadalafil was well tolerated, with all treatment-related adverse events characterized as mild to moderate (17).

Tadalafil (10 or 20 mg) administered to Taiwanese men with ED in a randomized, double-blind, placebo-controlled trial was found to be well tolerated. Compared to placebo, tadalafil treatment significantly improved penile erection and the percentage of intercourse attempts. No serious adverse events were reported. These results suggest that tadalafil treatment “on demand” may be an effective treatment for erectile dysfunction (18).

A multicenter, double-blind, placebo-controlled clinical trial determined the efficacy and safety of tadalafil in 207 men from the U.S. and Puerto Rico with mild to severe ED. The drug was administered at a dose of 20 mg as required before sexual activity, once daily at the most, for 12 weeks. Men receiving tadalafil reported significant improvements in their IIEF Erectile Function domain score, together with higher percentages of successful penetration and intercourse attempts. The percentage of patients with improved erections was 79% with tadalafil versus 19% with placebo, as determined using the GAQ. Tadalafil also showed a good safety profile, the adverse events most commonly related to the drug being headache, back pain and dyspepsia, and the percentage of patients who discontinued the treatment due to adverse events was low (5% with tadalafil and 2% with placebo) (19).

Two separate clinical trials revealed that the administration of tadalafil at daily doses of 10 or 20 mg had no adverse effects on spermatogenesis in 421 healthy men or men with mild ED. The percentage of patients who reported at least a 50% reduction in sperm concentration after receiving tadalafil or placebo for 6 months was not significantly different. The drug was well tolerated and induced no adverse effects on sperm count and motility or on the serum levels of reproductive hormones (20).

The long-term safety of tadalafil was assessed in 1,173 patients with ED who had previously been included in placebo-controlled studies on this drug. In this ongoing multicenter clinical trial, the patients were treated with an initial daily dose of 10 mg of tadalafil, which was later increased to 20 mg/day or decreased to 5 mg/day depending on the therapy’s efficacy or safety profile. After 18 months of treatment, the most common adverse events reported were headache (15%), dyspepsia (11%), infection (10%), back pain (7%), rhinitis (6%), flu syndrome (6%), pain (6%) and surgical procedures (6%). Overall, tadalafil showed a good safety and tolerability

Table IV: Clinical studies of tadalafil (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Erectile dysfunction	Pooled/meta-analysis	Tadalafil (n=949) Placebo (n=179)	1128	Compared with placebo, tadalafil was not associated with an increased incidence of cardiovascular adverse events in patients with erectile dysfunction	11
Erectile dysfunction	Randomized, double-blind	Tadalafil, 20 mg/d x 6 mo (n=87) Placebo (n=89)	176	Tadalafil did not alter sperm concentrations or morphology in healthy males and men with erectile dysfunction	12
Erectile dysfunction	Randomized, double-blind, multicenter, pooled/meta-analysis	Tadalafil, 2.5-20 mg/d Placebo	1112	Tadalafil was well tolerated and increased the percentage of successful intercourse attempts in patients with erectile dysfunction	14-16
Erectile dysfunction	Randomized, double-blind, crossover	Tadalafil, 10 mg Placebo	23	Tadalafil did not reduce the time to exercise-induced ischemia in coronary artery disease patients exercising at a level similar to that of sexual activity	17
Erectile dysfunction	Randomized, double-blind	Tadalafil, 10 mg po od PRN x 12 wk Tadalafil, 20 mg po od PRN x 12 wk Placebo	196	On-demand tadalafil was effective and well tolerated in patients with erectile dysfunction	18
Erectile dysfunction	Randomized, double-blind, multicenter	Tadalafil, 20 mg od [before sexual intercourse] x 12 wk Placebo	207	Tadalafil was more effective than placebo in improving erectile function in patients with erectile dysfunction, as measured using the IIEF Erectile Function domain and Sexual Encounter Profile diary questions. The active drug also showed a good safety profile	19
Erectile dysfunction	Double-blind, pooled/meta-analysis	Tadalafil, 10 mg x 6 mo (n=103) Tadalafil, 20 mg x 6 mo (n=111) Placebo (n=207)	421	Tadalafil was well tolerated and had no adverse effects on sperm count per ejaculate, percent normal sperm motility or morphology, or serum levels of reproductive hormones in healthy volunteers and patients with erectile dysfunction	20
Erectile dysfunction	Open, multicenter	Tadalafil, 10 [5-20 PRN] mg od x 18 mo	1173	Tadalafil administered at daily doses up to 20 mg for 18 months was safe and well tolerated in the treatment of erectile dysfunction	22
Healthy volunteers	Randomized, double-blind, crossover	Sildenafil, 50 mg Tadalafil, 10 mg Placebo	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	23
Erectile dysfunction	Randomized, double-blind, multicenter	Tadalafil, 5 mg/d x 12 wk Tadalafil, 10 mg/d x 12 wk Placebo	268	Tadalafil was well tolerated and effective in patients with erectile dysfunction	24

profile, as only 5% of the patients discontinued the study due to adverse events (21, 22).

A double-blind, crossover study conducted in 49 healthy volunteers established that a 50-mg dose of sildenafil, but not a 10-mg dose of tadalafil, significantly enhanced the reduction in mean blood pressure induced by sublingual administration of nitroglycerin. The incidence of blood pressure changes that were potentially significant from a clinical point of view was higher with tadalafil or sildenafil than with placebo, suggesting that neither sildenafil nor tadalafil should be combined with nitrates in patients with erectile dysfunction (23).

The safety and efficacy of once-daily tadalafil (5 and 10 mg) for ED were evaluated in 268 men. Erectile

function was significantly improved in both active treatment groups as compared to placebo and the treatment was well tolerated. The most commonly reported adverse events were dyspepsia, headache, back pain, upper abdominal pain and myalgia (24).

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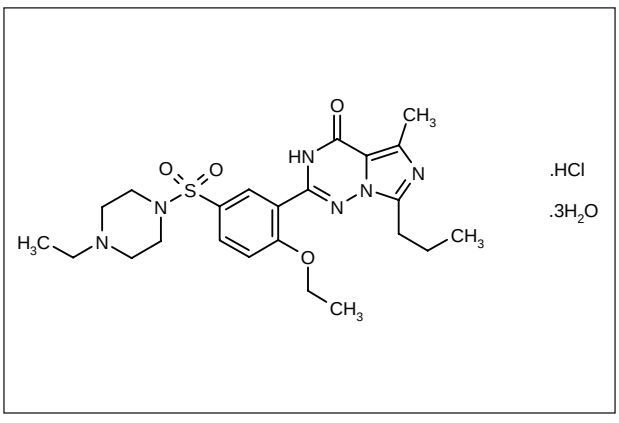
Original monograph - Drugs Fut 2001, 26(6): 15.

Vardenafil Hydrochloride Hydrate



Vardenafil hydrochloride hydrate (Bay-38-9456), an oral phosphodiesterase type 5 (PDE5) inhibitor, is now being marketed by Bayer and GlaxoSmithKline under a worldwide codevelopment and copromotion agreement as Levitra™ for the treatment of ED, with Germany being the first market. The launch came just days after the European Commision approved the drug. The companies have received an approvable letter from the FDA with a request for additional clinical pharmacology studies before final approval is granted. Vardenafil has also been approval in several Latin American countries and has been submitted for approval in all major markets (1-5).

The effect of vardenafil was evaluated on blood flow changes induced by pelvic nerve electrical stimulation (PNES; 5 and 10 Hz) of the vagina and clitoris in anesthetized female dogs. A significant potentiation of the blood flow in response to PNES was observed in the vagina and clitoris 20 min after vardenafil administration (1

mg/kg i.v.), which was sustained up to 80 min postdose. The results provide a rationale for evaluating the efficacy of vardenafil as a potential new therapy in certain forms of female sexual dysfunction (6, 7).

In a rat model of selective serotonin reuptake inhibitor-induced impotence, administration of paroxetine 10 mg/kg significantly reduced intracavernosal pressure increases induced by electrical stimulation of the cavernosal nerve. Vardenafil 0.3 mg/kg reversed this effect, allowing responses similar to those seen in controls (8).

The pharmacokinetics of vardenafil at a dose of 3 mg/kg and the efficacy of the agent at a dose of 1 mg/kg followed by an i.v. dose of sodium nitroprusside (SNP) 0.5-7 h later, were evaluated in a conscious rabbit model. Sodium nitroprusside-induced erections were significantly enhanced at all time points evaluated even when SNP was administered 7 h after vardenafil, when plasma levels had decreased to 2.5%. Vardenafil elimination from plasma was more rapid in rabbits than in humans ($t_{1/2}$ = 1.2 h *vs.* 4-5 h) and the t_{max} was 0.9 h. The results suggest that vardenafil may be effective in humans for longer than its plasma half-life (9-11).

A study in New Zealand white rabbits confirmed that the intracavernosal administration of PDE5 inhibitors induced penile erection in the absence of sexual stimulation. The anesthetized male rabbits were randomized to receive zaprinast 30-1000 μg/kg, sildenafil 1-30 mcg/kg or vardenafil 1-30 μg/kg given either intravenously with penile nerve stimulation or intracavernosally with no stimulation. All drugs dose-dependently increased penile intracavernosal pressure and duration of response, with similar effects after intracavernosal dosing without stimulation and i.v. administration with stimulation (12).

The effect of a high-fat breakfast or moderately fat meal on the pharmacokinetics of vardenafil was evaluated in healthy volunteers. Following an overnight fast and after a high-fat breakfast, respective C_{max} values were 17.14 and 14.0 μg/l, AUC values were 66.78 and 67.09 μg·h/ml, and t_{max} values were 1 and 2 h. Administration of the agent on an empty stomach and after a moderately fat meal resulted in respective C_{max} values of 14.22 and 13.04 μg/l, AUC values of 51.97 and 59.12 μg·h/ml and a t_{max} value of 1 h. It was concluded that a high-fat meal may alter C_{max} and slightly delay absorption, although changes in dose should not be needed (13).

Two randomized, crossover clinical studies evaluated the effects of ethanol, a high-fat breakfast and a moderate-fat evening meal on the pharmacokinetics of vardenafil in healthy male volunteers. Neither alcohol consumption nor the meals had any significant effects on the maximum plasma concentration or half-life of vardenafil in healthy volunteers. Absorption was not affected by either alcohol or the moderate-fat meal, although it was delayed by 1 h with the high-fat meal. No significant differences were found in the safety profile of the treatments, and the most common adverse events reported were flushing and rhinitis with ethanol, and headache with the meals (14).

The effect of alcohol on the pharmacokinetics and hemodynamic profile of vardenafil was evaluated in 12 male subjects in a double-blind, crossover study. Subjects were randomized to receive vardenafil (20 mg) or placebo with alcohol (0.5 g/kg in orange juice) or placebo. The combination was generally well tolerated, with no significant differences observed on the pharmacokinetic or hemodynamic profiles of vardenafil. Changes in heart rate were considered primarily due to alcohol (15).

The perception of patients with ED concerning erection quality and sexual satisfaction after treatment with vardenafil was assessed in a multicenter, double-blind phase III clinical trial. A total of 805 men with ED lasting for > 6 months before enrollment were randomized to receive either placebo or vardenafil 5, 10 or 20 mg for 26 weeks. The drug significantly improved the patients' satisfaction with erection hardness, sexual experience and orgasmic function. Most men with mild ED and many with severe ED regained normal erectile function following treatment with vardenafil. The percentage of patients who withdrew from the study due to adverse events was low (2% with placebo and 3.4-7.6% for vardenafil) and the most common adverse events were mild to moderate headache, flushing and rhinitis (16-19). The results of these studies and some that follow are summarized in Table V.

A 6-month, multicenter, open-label study evaluated the sustained efficacy of vardenafil (20 mg as needed, no more than once daily) in men with ED. Analysis of the results from 494 of 574 patients who completed the study found that vardenafil was effective and well tolerated in this patient population. Success rate per patient to maintain erections sufficient to complete intercourse rose from 15.4% at baseline to 74.9%, 80.7% and 83.3% at 1, 3 and 6 months, respectively. The most common adverse events reported were headache, flushing and dyspepsia (20, 21).

The efficacy of vardenafil (10 or 20 mg) on ED following radical prostatectomy was evaluated in a double-blind study. At baseline, ED was generally severe, but following 12 weeks of active treatment, ED and depressive symptoms had significantly improved. Drug-related adverse events reported were mild to moderate in severity, the most frequent being headache, cutaneous flushing and rhinitis (22).

The long-term safety, tolerability and efficacy of vardenafil (10-20 mg) in the treatment of ED were evaluated in a 52-week, multicenter, randomized, placebo-controlled, double-blind, fixed-dose study. Analysis of the data from 1,000 patients revealed significant long-term improvement in ED with an average success rate of maintaining erections of 82.0% and 85.6% in the 10- and 20-mg groups, respectively, at week 52. Vardenafil was generally well tolerated, with no cardiovascular-related adverse events reported (23, 24).

A total of 323 male patients with mild to severe ED were randomized to receive either placebo or vardenafil 10 mg as needed, with the possibility of later increasing the daily dose to 20 mg (to increase efficacy) or reducing it to 5 mg (due to adverse events). Vardenafil was better than placebo in improving the erectile function of these

Table V: Clinical studies of vadenafil (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Erectile dysfunction	Randomized, double-blind, multicenter	Vardenafil, 5 mg (n=205) Vardenafil, 10 mg (n=206) Vardenafil 20 mg (n=197) Placebo (n=197)	805	Vardenafil administered for 26 weeks was well tolerated and significantly improved satisfaction, erection hardness, sexual experience and ejaculation in men with erectile dysfunction	16-19
Erectile dysfunction	Open, multicenter	Vardenafil, 20 mg od PRN x 6 mo	574	Vardenafil was effective and well tolerated in patients with erectile dysfunction	21
Erectile dysfunction	Randomized, double-blind	Vardenafil, 10 mg x 12 wk (n=146) Vardenafil, 20 mg x 12 wk (n=149) Placebo (n=145)	439	Vardenafil was more effective than placebo in improving erectile hardness, patient satisfaction, orgasmic function and sexual experience of patients with erectile dysfunction after nerve-sparing radical prostatectomy. The drug was safe and well tolerated, and most adverse events were mild or moderate and transient	22, 31
Erectile dysfunction	Randomized, double-blind, multicenter	Vardenafil, 10 mg od PRN x 1 y Vardenafil, 20 mg od PRN x 1 y	1020	Vardenafil was well tolerated and provided marked, long-term efficacy to patients with erectile dysfunction	23
Erectile dysfunction	Randomized, Double-blind	Vardenafil, 10 [increased to 20 or decreased to 5] mg od x 12 wk Placebo	323	The mean IIEF-Erectile Function Domain score measured at 12 weeks was significantly higher in vardenafil than in placebo-treated patients. Vardenafil was also associated with a higher percentage of patients reporting improved erections. At the end of the treatment, most patients were taking a daily vardenafil dose of 20 mg	25, 26
Erectile dysfunction	Open, multicenter	Vardenafil, 10 mg od x 10 wk Vardenafil, 10 mg od x 6 wk → 20 mg od x 4 wk Vardenafil, 10 mg od x 2 wk → 20 mg od x 8 wk	390	A flexible dose regimen of vardenafil administered at doses of 10-20 mg once daily for up to 10 weeks was well tolerated and improved the erection rate, penetration success rate and erection maintenance success rate of patients with erectile dysfunction. Most adverse events were mild or moderate	27, 28
Erectile dysfunction	Pooled/meta-analysis	Vardenafil, 5 mg od PRN x 12 wk Vardenafil, 10 mg od PRN x 12 wk Vardenafil, 20 mg od PRN x 12 wk Placebo	2718	Vardenafil did not increase the cardiovascular event risk in patients with erectile dysfunction	29
Erectile dysfunction	Randomized, double-blind, pooled/meta-analysis	Vardenafil, 5 mg x 12 wk Vardenafil, 10 mg x 12 wk Vardenafil, 20 mg x 12 wk Placebo	1479	Vardenafil at doses of 10 or 20 mg was significantly more effective than placebo in improving several erectile function parameters in all age groups of patients with erectile dysfunction, including erection hardness, sexual experience, ejaculation and intercourse satisfaction	30

patients after 12 weeks of treatment. At the end of the treatment, most patients (68%) were taking a daily dose of 20 mg of the drug, whereas the percentages of patients taking doses of 5 and 10 mg were, respectively, 3% and 28%. The mean IIEF-Erectile Function Domain score measured at 12 weeks was significantly higher in vardenafil-treated patients than in placebo-treated patients (24.2 *vs.* 15.6). The active drug was also associated with a higher percentage of patients reporting improved erections (86% *vs.* 36% with placebo). At the end of the treatment, most patients (72%) were taking a daily vardenafil dose of 20 mg (3% taking 5 mg and 25% taking 10 mg).

All treatments were well tolerated, and the most common adverse events reported with vardenafil were headache (11%), flushing (12%) and rhinitis (6%) (25, 26).

The safety, tolerability and efficacy of flexible dosing of vardenafil were evaluated in a multicenter, open-label clinical trial in 390 patients with ED. A flexible dose of 5-20 mg of vardenafil administered for 10 weeks improved erection in 91.8% of these patients, as assessed using the IIEF Erectile Function domain score, the Global Assessment Question and questions to the patients concerning penetration and erection maintenance. The good safety profile of vardenafil was confirmed by the finding that most drug-related adverse events were mild or moderate and transient (27, 28).

The cardiovascular safety of vardenafil administered to patients with ED was evaluated in a study that analyzed data pooled from 5 randomized, double-blind, placebo-controlled phase II trials. Analysis of data from 2,718 men with ED who received vardenafil (5-20 mg) for more than 5 months but no more than once daily for 12 weeks revealed a favorable cardiovascular safety profile with the incidence of cardiovascular-related adverse events similar in the vardenafil and placebo groups (29).

A retrospective analysis of the data obtained from 2 double-blind phase III clinical trials revealed that the beneficial effects induced by vardenafil on the erectile function of male patients were not age-dependent. A total of 1,479 men with ED for more than 6 months were randomized to receive either placebo or vardenafil (5, 10 or 20 mg) for 12 weeks. Compared to placebo, vardenafil at doses of 10 or 20 mg was significantly more effective in improving several erectile function parameters in all age groups, including erection hardness, sexual experience, ejaculation and intercourse satisfaction (30).

A multicenter, double-blind phase III trial evaluated the efficacy and safety of vardenafil in patients with ED after nerve-sparing radical prostatectomy, a condition potentially harder to treat with oral therapy. A total of 440 patients were randomized to receive either placebo or vardenafil (10 or 20 mg) for 12 weeks. Important aspects of the quality of life of the patients, including overall satisfaction and orgasmic function, increased significantly with vardenafil compared to placebo. The drug was also well tolerated in this population of patients, showing a safety profile similar to that found in other clinical trials (31).

A multicenter, double-blind, placebo-controlled, crossover trial assessed the effects of a single dose of 20 mg of vardenafil on cardiac ischemia induced by exercise in 39 male patients with stable angina pectoris. A symptom-limited exercise treadmill test conducted 1 h after administration showed similar mean values in several test parameters, including the treadmill exercise time (414 and 411 s), the time to angina pectoris first awareness (354 and 347 s) and the time to S-T segment depression of 1 mm or more (364 and 366 s) for vardenafil and placebo, respectively. Facial flushing and headache were the most commonly reported adverse events with vardenafil, but these were transient and mild to moderate. The results suggested that the drug had no effect on the ischemic threshold or the exercise tolerance of patients with stable cardiovascular disease (32).

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