Drugs Fut 2005, 30(9): 931-980

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Annual Update 2004/2005 - Treatment of Genitourinary Disorders

Treatment of Genitourinary Disorders by Condition

Condition	Phase	Drug	Source
Benign prostatic hyperplasia	Prereg. (JP)	Silodosin[3]	Daiichi Pharmaceutical/Kissei
	III	Lonidamine[1,3]	Threshold Pharmaceuticals
	III (US)	Silodosin[3]	Watson
	II	BXL-628	BioXell
	II	Cetrorelix[1,3]	AEterna Zentaris/Solvay
	II	Dihydrotestosterone[2], gel	Ascend Therapeutics
	II	GYKI-16084	Ivax
	II	Lemuteporfin	QLT
	II	NX-1207	Nymox
	II	Ozarelix	AEterna Zentaris/Spectrum Pharmaceutical
	II-On hold	Pamirosin	Schwarz Pharma/Ranbaxy
	II (EU)	Silodosin[3]	Recordati
	II	Tadalafil[1,3]	Lilly Icos
	II	Teverelix	Ardana Bioscience/AEterna Zentaris
	I	Cetrorelix[1,3]	Shionogi/Nippon Kayaku
Erectile dysfunction	Prereg.	Udenafil	Dong-A
	II	ABT-724	Abbott
	II	Apomorphine hydrochloride[2], inhalation	Vectura
	II	Avanafil	Tanabe Seiyaku/Vivus
	II	GPI-1485	Symphony Neuro/Guilford Pharmaceuticals
	II	PT-141	Palatin Technologies/King Pharmaceuticals
	I	Apomorphine hydrochloride[2], intranasal	Britannia
	I	R-873	Roche
	I	SLx-2101	Surface Logix
	Clinical	Dasantafil	Schering-Plough
Glomerulonephritis	III	Olmesartan medoxomil[1,3]	Sankyo
	I	CR002	CuraGen
	Discontinued	TJN-598	Tsumura
Hepatorenal syndrome	III	Terlipressin[1]	ESP Pharma (Protein Design Labs)/Orphan Therapeutics
Hypoactive bladder	Discontinued	TAK-802	Takeda
Hyponatremia	Prereg.	Conivaptan hydrochloride[3]	Astellas Pharma
	III	SR-121463	Sanofi-Aventis
	III	Tolvaptan[3]	Otsuka
	II	Lixivaptan	CardioKine
Nephritis, lupus	III	Mycophenolate mofetil[1,3]	Aspreva/Roche
	III	Tacrolimus[1,3]	Astellas Pharma
Nephropathy, diabetic	III	Avosentan	Speedel
	III	Olmesartan medoxomil[1,3]	Sankyo
	III (US)	Pyridoxamine	BioStratum
	III	Sulodexide[1]	Keryx Biopharmaceuticals
	III	Telmisartan[1,3]	Astellas Pharma/Boehringer Ingelheim
	II	AVE-7688	Sanofi-Aventis

Continuation

Treatment of Genitourinary Disorders by Condition

Condition	Phase	Drug	Source
Nephropathy, diabetic	II	Candesartan cilexetil[1,3]	Takeda
	I	FG-3019	FibroGen
	I (JP)	Pyridoxamine	Kowa
Overactive bladder	L-2005	Darifenacin hydrobromide[3]	Novartis/Procter & Gamble/Bayer
	L-2004	Solifenacin succinate[3]	Astellas PharmaGlaxoSmithKline
	L-2004	Trospium chloride	Indevus/Esprit Pharma
	Prereg.	Imidafenacin	Kyorin/Ono Pharmaceutical/LG Life Sciences
	Prereg.	Temiverine hydrochoride	Nippon Shinyaku
	III	Botulinum toxin type A[1]	Allergan
	III	Fesoterodine[3]	Schwarz Pharma
	II	AZD-7371	AstraZeneca
	II	BX-628	BioXell
	II	Oxybutynin[2], gel	Antares Pharma
	II	PD-217014	Pfizer
	II	REC-0545	Recordati
	II	YM-178	Astellas Pharma
	I	DDP-200	Dynogen Pharmaceuticals
	I	KUC-7483	Kissei/Boehringer Ingelheim
	I	NS-8	Nippon Shinyaku/Apogepha
	I	Solabegron hydrochloride	GlaxoSmithKline
	I	TA-5538	Tanabe Seiyaku
	I	TD-6301	Theravance
Premature ejaculation	Prereg.	Dapoxetine hydrochloride[3]	Alza (Johnson & Johnson)
	II	LI-301 (DMI-7958)	Enhance Biotech/DMI BioSciences
	II	NM-100061	NexMed
	II	UK-390957	Pfizer
	II	UK-464273	Pfizer
Renal disorders	I	Tolvaptan[3]	Otsuka
Renal failure	II	NZ-419	Nippon Zoki
	II	SLV-320	Solvay
	I	Sevelamer carbonate	Genzyme
Urinary incontinence	II	Cizolirtine citrate[3]	Esteve
	II	FE-106483	Ferring
	II	KW-7158	Kyowa Hakko
	II	Oxybutynin[2], transvaginal ring	Barr
	II	REC-0545	Recordati
	II	SVT-40776	Salvat
	I	C-0172	Merck & Co.
	I	C-4699	Merck & Co.
	I	KUC-7483	Kissei/Boehringer Ingelheim
	I	SOU-003 (OPC-51803)	Sosei/Otsuka
Urinary incontinence, stress	L-2004	Duloxetine hydrochloride[3]	Lilly/Boehringer Ingelheim
	II	(+)-(*S*,*S*)-Reboxetine	Pfizer
	I/II	SOU-001 (AA-10020)	Sosei/Arachnova
	I	R-1484	Roche
Urinary incontinence, urge	III	Fesoterodine[3]	Schwarz Pharma
	II	SL-65.0155	Sanofi-Aventis
	I	679769	GlaxoSmithKline
Urolithiasis	I	KUL-7211	Kissei

[1]Launched for another indication. [2]New formulation. [3]Monograph previously published in Drugs of the Future.

Treatment of Genitourinary Disorders by Source

Source	Condition	Drug	Phase
AEterna Zentaris	Benign prostatic hyperplasia	Cetrorelix[1,3]	II
		Ozarelix	II
		Teverelix	II
Allergan	Overactive bladder	Botulinum toxin type A[1]	III
Alza (Johnson & Johnson)	Premature ejaculation	Dapoxetine hydrochloride[3]	Prereg.
Antares Pharma	Overactive bladder	Oxybutynin[2], gel	II
Apogepha	Overactive bladder	NS-8	I
Arachnova	Urinary incontinence, stress	SOU-001 (AA-10020)	I/II
Ardana Bioscience	Benign prostatic hyperplasia	Teverelix	II
Ascend Therapeutics	Benign prostatic hyperplasia	Dihydrotestosterone[2], gel	II
Aspreva	Nephritis, lupus	Mycophenolate mofetil[1,3]	III
Astellas Pharma	Hyponatremia	Conivaptan hydrochloride[3]	Prereg.
	Nephritis, lupus	Tacrolimus[1,3]	III
	Nephropathy, diabetic	Telmisartan[1,3]	III
	Overactive bladder	Solifenacin succinate[3]	L-2004
		YM-178	II
AstraZeneca	Overactive bladder	AZD-7371	II
Barr	Urinary incontinence	Oxybutynin[2], transvaginal ring	II
Bayer	Overactive bladder	Darifenacin hydrobromide[3]	L-2005
BioStratum	Nephropathy, diabetic	Pyridoxamine	III (US)
BioXell	Benign prostatic hyperplasia	BXL-628	II
	Overactive bladder	BX-628	II
Boehringer Ingelheim	Nephropathy, diabetic	Telmisartan[1,3]	III
	Overactive bladder	KUC-7483	I
	Urinary incontinence	KUC-7483	I
	Urinary incontinence, stress	Duloxetine hydrochloride[3]	L-2004
Britannia	Erectile dysfunction	Apomorphine hydrochloride[2], intranasal	I
CardioKine	Hyponatremia	Lixivaptan	II
CuraGen	Glomerulonephritis	CR002	I
Daiichi Pharmaceutical	Benign prostatic hyperplasia	Silodosin[3]	Prereg. (JP)
DMI BioSciences	Premature ejaculation	LI-301 (DMI-7958)	II
Dong-A	Erectile dysfunction	Udenafil	Prereg.
Dynogen Pharmaceuticals	Overactive bladder	DDP-200	I
Enhance Biotech	Premature ejaculation	LI-301 (DMI-7958)	II
ESP Pharma (Protein Design Labs)	Hepatorenal syndrome	Terlipressin[1]	III
Esprit Pharma	Overactive bladder	Trospium chloride	L-2004
Esteve	Urinary incontinence	Cizolirtine citrate[3]	II
Ferring	Urinary incontinence	FE-106483	II
FibroGen	Nephropathy, diabetic	FG-3019	I
Genzyme	Renal failure	Sevelamer carbonate	I
GlaxoSmithKline	Overactive bladder	Solabegron hydrochloride	I
		Solifenacin succinate[3]	L-2004
	Urinary incontinence, urge	679769	I
Guilford Pharmaceuticals	Erectile dysfunction	GPI-1485	II
Indevus	Overactive bladder	Trospium chloride	L-2004
Ivax	Benign prostatic hyperplasia	GYKI-16084	II
Keryx Biopharmaceuticals	Nephropathy, diabetic	Sulodexide[1]	III
King Pharmaceuticals	Erectile dysfunction	PT-141	II
Kissei	Benign prostatic hyperplasia	Silodosin[3]	Prereg. (JP)
	Overactive bladder	KUC-7483	I
	Urinary incontinence	KUC-7483	I
	Urolithiasis	KUL-7211	I
Kowa	Nephropathy, diabetic	Pyridoxamine	I (JP)
Kyorin	Overactive bladder	Imidafenacin	Prereg.
Kyowa Hakko	Urinary incontinence	KW-7158	II
LG Life Sciences	Overactive bladder	Imidafenacin	Prereg.
Lilly	Urinary incontinence, stress	Duloxetine hydrochloride[3]	L-2004
Lilly Icos	Benign prostatic hyperplasia	Tadalafil[1,3]	II
Merck & Co.	Urinary incontinence	C-0172	I
		C-4699	I
NexMed	Premature ejaculation	NM-100061	II
Nippon Kayaku	Benign prostatic hyperplasia	Cetrorelix[1,3]	I

Continuation

Treatment of Genitourinary Disorders by Source

Source	Condition	Drug	
Nippon Shinyaku	Overactive bladder	NS-8	I
		Temiverine hydrochoride	Prereg.
Nippon Zoki	Renal failure	NZ-419	II
Novartis	Overactive bladder	Darifenacin hydrobromide[3]	L-2005
Nymox	Benign prostatic hyperplasia	NX-1207	II
Ono Pharmaceutical	Overactive bladder	Imidafenacin	Prereg.
Orphan Therapeutics	Hepatorenal syndrome	Terlipressin[1]	III
Otsuka	Hyponatremia	Tolvaptan[3]	III
	Renal disorders	Tolvaptan[3]	I
	Urinary incontinence	SOU-003 (OPC-51803)	I
Palatin Technologies	Erectile dysfunction	PT-141	II
Pfizer	Overactive bladder	PD-217014	II
	Premature ejaculation	UK-390957	II
		UK-464273	II
	Urinary incontinence, stress	(+)-(*S,S*)-Reboxetine	II
Procter & Gamble	Overactive bladder	Darifenacin hydrobromide[3]	L-2005
QLT	Benign prostatic hyperplasia	Lemuteporfin	II
Ranbaxy	Benign prostatic hyperplasia	Pamirosin	II-On hold
Recordati	Benign prostatic hyperplasia	Silodosin[3]	II (EU)
	Overactive bladder	REC-0545	II
	Urinary incontinence	REC-0545	II
Roche	Erectile dysfunction	R-873	I
	Nephritis, lupus	Mycophenolate mofetil[1,3]	III
	Urinary incontinence, stress	R-1484	I
Salvat	Urinary incontinence	SVT-40776	II
Sankyo	Glomerulonephritis	Olmesartan medoxomil[1,3]	III
	Nephropathy, diabetic	Olmesartan medoxomil[1,3]	III
Sanofi-Aventis	Hyponatremia	SR-121463	III
	Nephropathy, diabetic	AVE-7688	II
	Urinary incontinence, urge	SL-65.0155	II
Schering-Plough	Erectile dysfunction	Dasantafil	Clinical
Schwarz Pharma	Benign prostatic hyperplasia	Pamirosin	II-On hold
	Overactive bladder	Fesoterodine[3]	III
	Urinary incontinence, urge	Fesoterodine[3]	III
Shionogi	Benign prostatic hyperplasia	Cetrorelix[1,3]	I
Solvay	Benign prostatic hyperplasia	Cetrorelix[1,3]	II
	Renal failure	SLV-320	II
Sosei	Urinary incontinence	SOU-003 (OPC-51803)	I
	Urinary incontinence, stress	SOU-001 (AA-10020)	I/II
Spectrum Pharmaceuticals	Benign prostatic hyperplasia	Ozarelix	II
Speedel	Nephropathy, diabetic	Avosentan	III
Surface Logix	Erectile dysfunction	SLx-2101	I
Symphony Neuro	Erectile dysfunction	GPI-1485	II
Takeda	Hypoactive bladder	TAK-802	Discontinued
	Nephropathy, diabetic	Candesartan cilexetil[1,3]	II
Tanabe Seiyaku	Erectile dysfunction	Avanafil	II
	Overactive bladder	TA-5538	I
Theravance	Overactive bladder	TD-6301	I
Threshold Pharmaceuticals	Benign prostatic hyperplasia	Lonidamine[1,3]	III
Tsumura	Glomerulonephritis	TJN-598	Discontinued
Vectura	Erectile dysfunction	Apomorphine hydrochloride[2], inhalation	II
Vivus	Erectile dysfunction	Avanafil	II
Watson	Benign prostatic hyperplasia	Silodosin[3]	III (US)

[1]Launched for another indication. [2]New formulation. [3]Monograph previously published in Drugs of the Future.

Treatment of Genitourinary Disorders

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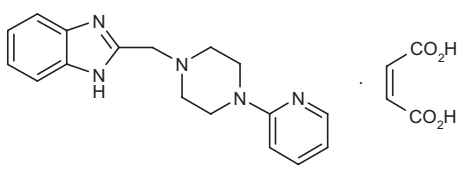
679769

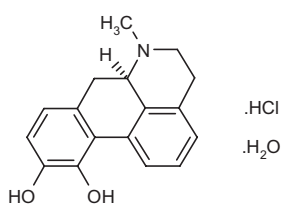
Compound 679769, a tachykinin NK_1 receptor antagonist, is in phase I clinical development at GlaxoSmithKline for the treatment of urinary incontinence, as well as phase II development for the treatment of depression, anxiety and for the prophylaxis of nausea and vomiting induced by chemotherapy or surgery.

ABT-724



ABT-724 is a selective dopamine D4 receptor agonist last reported to be in phase II clinical testing at Abbott for the treatment of erectile dysfunction.

Apomorphine Hydrochloride, Inhalation



New formulations of apomorphine, currently available in the form of a sublingual tablet, are under development for the treatment of erectile dysfunction, specifically a nasal powder formulation in phase I at Britannia and an inhalable formulation in phase II at Vectura (VR-004). Britannia's product, formulated using its proprietary Lyonase technology, is available for licensing worldwide; a higher dose formulation is also in phase III development for Parkinson's disease. VR-004 consists of Vectura's proprietary apomorphine formulation and the company's high-efficiency Aspirair® inhaler delivery device.

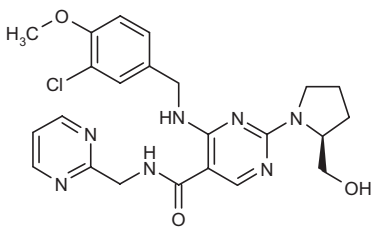
The preparation of powdered formulations that facilitate the nasal delivery of therapeutics such as the dopamine D2 agonist apomorphine or the $5\text{-}HT_{1B/1D}$ receptor agonist dihydroergotamine has been claimed for the treatment of migraine, Parkinson's disease and/or sexual dysfunction (1).

1. Merkus, F.W.H. et al. (Britannia Pharmaceuticals, Ltd.) *Pharmaceutical compositions for nasal delivery*. WO 2004075824.

Additional References

Brandt, G.C. et al. *Intranasal apomorphine for erectile dysfunction: Multiple dose safety study*. J Sex Med 2004, 1(Suppl. 1): Abst O57.

Avanafil



Vivus has completed enrollment (298 patients) in its multicenter, double-blind, randomized, placebo-con-

trolled, parallel-design phase II study of avanafil, a highly selective, orally administered phosphodiesterase type 5 (PDE5) inhibitor being developed to treat erectile dysfunction under license from Tanabe Seiyaku (TA-1790). The trial aims to evaluate the safety and efficacy of a number of different doses of avanafil with the goal of selecting the appropriate doses for phase III trials. Previous studies with avanafil have demonstrated a rapid onset of action and a half-life of 60-90 min. Results are expected at the completion of the trial, anticipated for late 2005 (1, 2).

Previous studies have found that coadministration of nitrates (commonly used to treat angina pectoris) and PDE5 inhibitors may sometimes induce a life-threatening decrease in blood pressure. A total of 101 healthy male volunteers participated in a double-blind, randomized, crossover clinical trial that compared the response to a sublingual dose of 0.4 mg of glyceryl trinitrate when administered between 30 min and 12 h after single oral doses of placebo, 100 mg of sildenafil citrate or 200 mg of avanafil. The average maximal decrease in standing systolic blood pressure after glyceryl trinitrate administration was greater with sildenafil (25.5 mmHg) compared to avanafil (20.6 mmHg) or placebo (21.5 mmHg). Sildenafil also resulted in a greater average maximal increase in heart rate (22.9 beats/min *vs.* 17.6 beats/min with avanafil and 18.8 beats/min with placebo), and was associated with a greater number of patients developing clinically significant orthostatic hypotension. Additional studies are needed to better define the clinical relevance of these differences (3).

Vivus has announced encouraging results from a clinical trial designed to evaluate the feasibility of twice-a-day dosing with avanafil. This open-label pharmacokinetic study compared blood levels of avanafil in healthy volunteer subjects after taking a single dose of avanafil with blood levels after taking avanafil twice daily (every 12 h) for 7 days. Results revealed no significant plasma accumulation of avanafil after the twice-a-day treatment regimen when compared to the single dose, indicating the drug was quickly removed from the bloodstream. A total of 15 subjects were enrolled in the study, with 13 subjects included in the final evaluation. These results support the company's development strategy that avanafil may have a different profile than existing PDE5 inhibitors. The study also corroborates earlier studies that demonstrated a short plasma half-life of avanafil of 60-90 min (4).

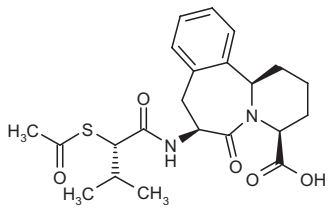
1. *Enrollment completed in phase II study of avanafil.* DailyDrugNews.com (Daily Essentials) Feb 22, 2005.

2. *Tanabe Seiyaku reports Q1 R&D highlights*. Tanabe Seiyaku Co., Ltd. Press Release 2005, May 12.

3. *Good cardiovascular profile reported for avanafil in male volunteers.* DailyDrugNews.com (Daily Essentials) April 28, 2005.

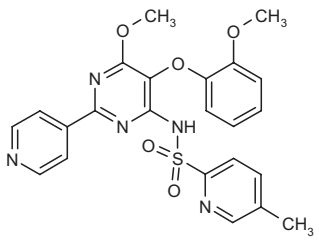
4. *Encouraging results with twice-daily avanafil.* DailyDrugNews.com (Daily Essentials) May 9, 2005.

AVE-7688



AVE-7688 is a dual angiotensin I-converting enzyme (ACE) and neutral endopeptidase (NEP) inhibitor in phase II clnical testing at Sanofi-Aventis for the treatment of hypertension and diabetic nephropathy.

Avosentan



Two recently completed phase II clinical trials have provided new evidence confirming the benefits of Speedel's oral, once-daily, second-generation endothelin A (ET_A) receptor antagonist avosentan (SPP-301) in the management of diabetic nephropathy. A phase IIa study revealed that administration of avosentan for 4 weeks significantly reduced 24-h proteinuria in patients who were under treatment with high doses of angiotensin receptor blockers (ARBs). A double-blind phase IIb clinical trial randomized 286 patients with diabetic nephropathy to receive placebo or avosantan (5, 10, 25 or 50 mg p.o.) once daily together with standard treatment (ARBs or angiotensin-converting enzyme [ACE] inhibitors) for 12 weeks. Avosentan was more effective than placebo in decreasing the patients' urinary albumin excretion rate, with greater reductions obtained with daily doses of 25 and 50 mg. Overall, proteinuria decreased by at least 30% in 55% of patients treated with avosentan. The compound was also well tolerated and was associated with minimal liver toxicity. Speedel subsequently commenced the pivotal randomized, placebo-controlled phase III ASCEND clinical trial with avosentan in diabetic nephropathy. This study is being conducted in Europe, the U.S. and other countries in more than 2,000 patients with type 2 diabetes and nephropathy and is designed to assess time to doubling of serum creatinine, end-stage renal disease or death. Patients will be given either 25 or 50 mg of avosentan once daily on top of standard therapy, or will receive standard therapy alone. The study, which has been discussed and agreed upon with the FDA and the European Medicines Agency (EMEA), will be

conducted at about 260 sites in Europe, the U.S. and other countries. This is an event-driven study, and the current best estimate is that it will take approximately 3.5 years for enough events to occur in the composite endpoint to demonstrate statistically significant efficacy. Clinical results obtained to date are encouraging and suggest that avosentan could impact morbidity and mortality in patients suffering from diabetic nephropathy. Avosentan, a second-generation endothelin receptor antagonist specifically optimized for improved liver safety, was licensed by Speedel from Roche in October 2000 when it was in regulatory toxicology studies. Speedel has exclusive worldwide development and commercialization rights under the licensing agreement with Roche. The company has been granted fast track designation for avosentan by the FDA (1-3).

1. *Phase II data support the use of SPP-301 in diabetic nephropathy*. DailyDrugNews.com (Daily Essentials) March 4, 2005.

2. *SPP-301 begins phase III for diabetic nephropathy*. DailyDrugNews.com (Daily Essentials) July 11, 2005.

3. *Speedel boosts pipeline development with private funding round*. DailyDrugNews.com (Daily Essentials) Aug 11, 2005.

Additional References

Dieterle, W. et al. *Multiple-dose pharmacokinetics, pharmacodynamics and tolerability of the oral ETA endothelin-receptor antagonist SPP301 in man*. Int J Clin Pharmacol Ther 2005, 43(4): 178.

AZD-7371

A serotonin modulator, AZD-7371 is currently in phase II development at AstraZeneca for the treatment of overactive bladder (OAB). Development of AZD-7371 for the treatment of irritable bowel syndrome was discontinued earlier this year after the product failed to fulfill the expected product profile.

Botulinum Toxin Type A, New Indication

Earlier this year, Allergan met with the FDA and reached agreement to enter phase III trials for botulinum toxin type A (Botox®) to treat neurogenic OAB and phase II trials to treat idiopathic OAB (1, 2).

Botulinum toxin type A is a presynaptic neuromuscular blocking agent that induces selective and reversible muscle weakness for up to several months when injected intramuscularly in minute quantities. Different medical disciplines have applied the toxin to treat mainly muscular hypercontraction. For neurourologically impaired patients, the reported successful treatment of neurogenic detrusor overactivity and detrusor sphincter dyssynergia with botulinum toxin is a promising alternative option to conservative medication or surgery. A review of the literature presents current indications, techniques for and results of the use of botulinum toxin in neurourologically impaired patients and aims to provide insight into this new therapeutic option (3).

The analysis of flexible cytoscopic bladder biopsy samples from 38 patients with neurogenic or idiopathic detrusor overactivity and 13 healthy volunteers suggested that botulinum toxin type A improved detrusor overactivity by interacting with afferent bladder nerves. Detrusor overactivity at baseline was associated with increases in the number of subepithelial fibers expressing afferent markers. Administration of a single injection of botulinum toxin type A reduced the expression of these markers but was not associated with suburothelial neuronal or cholinergic fiber degeneration (4).

1. *Allergan reports Q1 R&D highlights*. Allergan Press Release 2005, April 27.

2. *Allergan reports Q2 R&D highlights*. Allergan Press Release 2005, July 27.

3. *Schurch, B. The role of botulinum toxin in neurourology*. Drugs Today 2004, 40(3): 205.

4. Apostolidis, A., Popat, R., Yiangou, Y., Dasgupta, P., Anand, P., Fowler, C.J. *A possible explanation for the exceptional efficacy of botulinum toxin treatment for detrusor overactivity*. 34th Annu Meet Int Continence Soc (Aug 23-27, Paris) 2004, Abst 150.

5. Chartier-Kastler, E., Schurch, B., De Seze, M., Denys, P., Haab, F., Everaert, K., Plante, P., Perrouin-Verbe, B. *Focal administration of botulinum toxin A in patients with neurogenic detrusor overactivity produces bladder function improvements without drug-related adverse events*. Eur Urol Suppl 2005, 4(3): Abst 414 (Table I).

6. Denys, P., Schurch, B., De Seze, M., Chartier-Kastler, E., Haab, F., Everaert, K., Plante, P., Perrouin-Verbe, B. *Significant improvements in incontinence quality of life instrument scores following botulinum toxin A treatment in patients with neurogenic urinary incontinence*. Eur Urol Suppl 2005, 4(3): Abst 645 (Table I).

7. Giannantoni, A., Di Stasi, S.M., Nardicchi, V., Macchioni, L., Guercini, F., Goracci, G., Porena, M. *Botulinum A toxin intravesical treatment induces a reduction of nerve growth factor bladder tissue levels in patients with neurogenic detrusor overactivity*. J Urol 2005, 173(4, Suppl.): Abst 1217 (Table I).

8. Giannantoni, A., Nardicchi, V., Macchioni, L., Di Stasi, S.M., Storti, L., Costantini, E., Bini, V., Goracci, G., Porena, M. *Nerve growth factor bladder tissue levels in patients with neurogenic detrusor overactivity before and after botulinum-A toxin injections into the detrusor muscle*. 34th Annu Meet Int Continence Soc (Aug 23-27, Paris) 2004, Abst 219 (Table I).

9. Gousse, A., Tunuguntla, H., Leboeuf, L., Bateman, D., Velazquez, D. *Intravesical botulinum-A toxin therapy for refractory overactive bladder: Early results*. 27th Congr Soc Int Urol (Oct 3-7, Honolulu) 2004, Abst MP-19.01 (Table I).

Table I: Clinical studies of botulinum toxin type A (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Incontinence, urinary	Randomized Double-blind	Botulinum toxin type A, 200 U (n=19) Botulinum toxin type A, 300 U (n=19)	57	Botulinum toxin type A significantly improved incontinence quality-of-life scores in patients with neurogenic urinary incontinence	5,6
Detrusor hyperreflexia, Injury, spinal cord	Open	Botulinum toxin type A, i.ves.	23	Botulinum toxin type A treatment demonstrated significant reduction in nerve growth factor bladder tissue levels in patients with neurogenic detrusor overactivity	7
Detrusor hyperreflexia	Open	Botulinum toxin type A, i. detrusor	12	Botulinum toxin type A injection into the detrusor muscle was safe and effective in patients with neurogenic detrusor overactivity	8
Overactive bladder, Pain, pelvic	Open	Botulinum toxin type A, 100-150 U i.ves. x 4	6	Botulinum toxin type A was safe and effectively improved urine frequency, voided volume, nocturia, pelvic pain and residual volume in patients with overactive bladder-associated pelvic pain	9
Overactive bladder	Randomized Open	Botulinum toxin type A, 100 U i.ves. inst. 1x/6 mo (n=10) Botulinum toxin type A, 150 U i.ves. inst. 1x/6 mo (n=10)	20	Botulinum toxin type A was effective in patients with refractory non-neurogenic overactive bladder	10
Overactive bladder	Open	Botulinum toxin type A [depot], 200-300 i. detrusor	42	Botulinum toxin type A detrusor injections reduced voiding frequency and increased cystometric parameters in patients with non-neurogenic bladder hyperactivity	11
Detrusor hyperreflexia	Open	Botulinum toxin type A, 300 U i. detrusor	22	Botulinum toxin type A was effective and demonstrated a short-term partial effect in patients with both idiopathic and neurogenic detrusor hyperreflexia resistant to anticholinergic treatment	12
Detrusor hyperreflexia	Open	Botulinum toxin type A, 200 U [suburothelial injection]	20	Suburothelial injection of botulinum toxin type A impaired bladder sensation and voiding efficiency, but was effective in patients with non-neurogenic detrusor overactivity refractory to anticholinergics	13
Detrusor hyperreflexia		Botulinum toxin type A, 200 U i.m. [at 20 bladder sites] (n=21) Botulinum toxin type A, 300 U i.m. [at 30 bladder sites] (n=39)	60	Botulinum toxin administration resulted in substantial improvement in lower urinary tract symptoms and urodynamic parameters in patients with both neurogenic and idiopathic detrusor hyperreflexia	14
Incontinence, urinary, Incontinence, urinary urge, Overactive bladder, Urinary frequency	Open	Botulinum toxin type A, 300 U [transurethral] + Antibiotics [perioperatively]	35	Transurethral botulinum toxin type A was well tolerated and without major adverse events in patients with refractory overactive bladder symptoms	15
Overactive bladder	Open	Botulinum toxin type A, 100 U i. detrusor	100	Botulinum toxin type A injections into the detrusor muscle were safe and effective in patients with overactive bladder refractory to anticholinergic drugs and physiotherapy	16, 17
Detrusor hyperreflexia, Incontinence, urinary	Randomized Double-blind Multicenter	Botulinum toxin type A, 200 U i.m. Botulinum toxin type A, 300 U i.m. Placebo	59	Botulinum toxin type A was well tolerated and considerably decreased urinary incontinence episodes in patients with detrusor hyperreflexia refractory to oral anticholinergics. Disease severity and voiding pattern, but not age and gender, were predictors of response to botulinum toxin type A	18

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13. Kuo, H.-C. *Clinical effects of suburothelial injection of botulinum A toxin on patients with nonneurogenic detrusor overactivity refractory to anticholinergics*. Urology 2005, 66(1): 94 (Table I).

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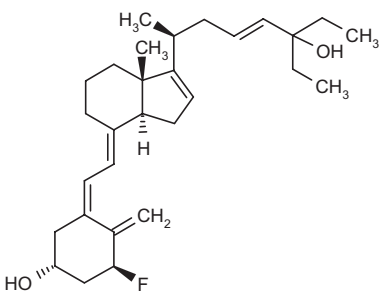
BXL-628



BioXell has purchased additional indications from Roche for its lead compound BXL-628 (formerly Ro-26-9228), a vitamin D analogue originally licensed to BioXell for BPH, secondary hyperparathyroidism, transplant rejection and type 1 diabetes. Under the new agreement, Roche has granted BioXell exclusive worldwide development rights to BXL-628 for all nontopical and nondermatological applications. BioXell is developing the product for benign prostatic hyperplasia, overactive bladder, chronic prostatitis and interstitial cystitis. A phase IIa trial of BXL-628 in patients with BPH met the primary endpoint of prostate volume reduction with a high degree of significance. In the 12-week double-blind, randomized, placebo-controlled study in 120 patients, BXL-628 (50 μg p.o.) showed a reduction of 7.2% in prostate volume *versus* patients on placebo. In a separate predefined responder analysis, 92% of patients on BXL-628 did not experience a clinically significant growth in prostatic volume compared to 48% of those on placebo. BXL-628 was well tolerated and induced no significant effects on urinary flow rate, serum prostate-specific antigen (PSA) levels or androgen levels. BioXell subsequently initiated a phase IIb trial evaluating the efficacy of BXL-628 in BPH. Coordinated by the Division of Urology at the San Raffaele Hospital in Milan, the study will enroll more than 500 patients at 60 Italian urology centers. The primary objective of the double-blind, randomized, placebo-controlled, parallel-group study is to confirm the ability of BXL-628 monotherapy to reduce prostate volume after 24 weeks of treatment. Secondary endpoints are severity of symptoms, urinary flow rate, sexual function and quality of life. In addition, the study will evaluate the effectiveness of a fixed combination of BXL-628 and tamsulosin, currently the gold standard alpha-blocker therapy for BPH. In addition to an ongoing phase IIa trial in overactive bladder, BioXell also plans to evaluate BXL-628 in nonbacterial chronic prostatitis and interstitial cystitis. Because of its novel mechanism of action, BXL-628 does not affect testosterone levels, potentially avoiding the negative sexual side effects seen with existing treatments. BioXell is now looking for a potential commercialization partner (1-6).

1. *BioXell acquires from Roche rights to new indications for BXL-628*. DailyDrugNews.com (Daily Essentials) July 6, 2004.

2. *Phase IIa study of BXL-628 for BPH meets primary endpoint*. DailyDrugNews.com (Daily Essentials) Sept 29, 2004.

3. *R&D highlights from the 4th Annual Biotech In Europe Investor Forum: BioXell*. DailyDrugNews.com (Daily Essentials) Oct 18, 2004.

4. *Phase IIb study evaluates BXL-628 for benign prostatic hyperplasia*. DailyDrugNews.com (Daily Essentials) July 13, 2005.

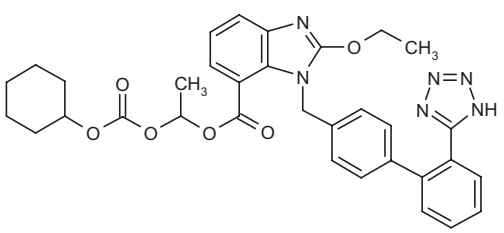
5. *BioXell to commence phase IIa trial of its lead compound BXL-628 in overactive bladder*. BioXell Press Release 2004, Nov 29.

6. Rigatti, P. et al. *BXL628 in the treatment of BPH: A multicentre, randomized, placebo-controlled clinical trial*. Eur Urol Suppl 2005, 4(3): Abst 836.

C-0172/C-4699

C-0172 and C-4699 are in early clinical development at Merck & Co. for the treatment of urinary incontinence.

Candesartan Cilexetil, New Indication



Candesartan cilexetil (Atacand, Blopress, Amias, Kenzen), an angiotensin AT_1 receptor blocker, was previ-

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

Indication	Design	Treatments	n	Conclusions	Ref.
Prostatic hyperplasia, benign	Randomized Multicenter	Cetrorelix, 20 mg s.c. 1x/7 d (n=35) Cetrorelix, 40 mg s.c. 1x/7 d (n=35) Cetrorelix, 20 mg s.c. 1x/14 d (n=35) Cetrorelix, 60 mg i.m. 1x/14 d (n=30) Cetrorelix, 90 mg i.m. 1x/14 d (n=30) Cetrorelix, 60 mg i.m. 1x/14 d → 30 mg i.m. (n=30) Cetrorelix, 60 mg i.m. 1x/14 d → 120 mg i.m. (n=30) Placebo (n=65)	290	Cetrorelix reduced prostate size in a dose-dependent manner and was well tolerated at all doses without castration-like withdrawal symptoms in patients with symptomatic benign prostatic hyperplasia	7

ously introduced by Takeda and partner AstraZeneca for the treatment of hypertension and in certain markets for chronic heart failure. Takeda is currently conducting phase II trials in Japan evaluating its potential in the treatment of diabetic nephropathy and AstraZeneca is also conducing phase II clinical trials in diabetic retinopathy.

Original monograph – Drugs Fut 1993, 18(7): 609.

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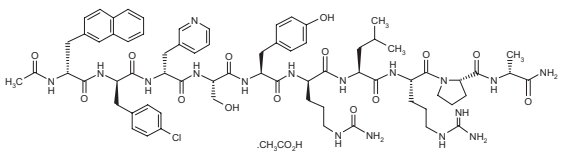
Cetrorelix, New Indication



Solvay has decided to undertake full phase III development of cetrorelix, a luteinizing hormone-releasing hormone (LHRH) antagonist licensed from AEterna Zentaris, for the treatment of endometriosis as a primary indication. The decision follows successful completion of a broad program of 7 phase II trials of cetrorelix in endometriosis, benign prostatic hyperplasia (BPH) and uterine myoma. An improved side effect profile, absence of hormonal castration, convenience of dosing, suitability for long-term use as an intermittent treatment and speed of onset of action are among key benefits that could favorably position cetrorelix. Following development, registration submissions are expected to be made in 2008, with first launches from 2009. Solvay is AEterna Zentaris's exclusive worldwide development and marketing partner for cetrorelix, excluding Japan where Shionogi and Nippon Kayaku are the company's partners. Shionogi and Nippon Kayaku have decided to advance the development of cetrorelix pamoate (NS-75A) to phase II for the BPH indication. The first phase IIa trial in Japan will be designed to evaluate safety and to explore efficacy, including effects on BPH-related parameters such as the International Prostate Symptom Score (I-PSS). The multicenter, placebo-controlled, randomized trial using cetrorelix pamoate will comprise both single- and multiple-dose groups. Data generated in this trial will serve as verification for the applicability of the results from European studies on cetrorelix in BPH to Japanese patients (1-5). Cetrorelix (Cetrotide®) was first launched in 1999 in Europe by the former Asta Medica, and subsequently in the U.S. by licensee Serono, for the prevention of premature ovulation in controlled ovarian stimulation and assisted reproductive techniques.

Statistically significant positive results were reported from a randomized, double-blind, placebo-controlled phase II trial evaluating different dose regimens of a

depot formulation of cetrorelix in 250 patients with symptomatic BPH. The trial enrolled patients with symptomatic and objectively defined BPH (decreased urine flow) and was conducted in Europe. All eligible patients received 2 intramuscular injections of placebo, 2 weeks apart, during a run-in period. After the initial 4-week run-in period, 250 patients with symptomatic BPH were randomized to 5 groups receiving either placebo injections or 4 different dose regimens from 60 to 120 mg in 2 or 3 injections of a depot formulation of cetrorelix over the course of 4 weeks. Patients were followed for up to 26 weeks after the last injection for efficacy and safety assessments, as well as for assessment of testosterone levels, quality of life and sexual function. As early as 1 month following the initiation of therapy, the use of cetrorelix was associated with a dose-dependent, statistically significant improvement in clinical signs and symptoms, including I-PSS and maximum uroflow, compared to placebo. The dose-dependent, durable and statistically significant improvement of clinical symptoms was seen at all doses except the lowest. For all dose regimens, the therapeutic response lasted until the last observation point (6).

1. *AEterna reports Q1 R&D highlights*. AEterna Laboratories Press Release 2004, May 4.

2. *AEterna Zentaris reports Q2 R&D highlights*. AEterna Zentaris Press Release 2004, Aug 11.

3. *Cetrorelix enters development for endometriosis and BPH*. DailyDrugNews.com (Daily Essentials) March 22, 2005.

4. *AEterna Zentaris reports Q1 R&D highlights*. AEterna Zentaris Press Release 2005, May 4.

5. *AEterna Zentaris reports Q2 R&D highlights*. AEterna Zentaris Press Release 2005, Aug 3.

6. *Positive phase II results for cetrorelix in BPH*. DailyDrugNews.com (Daily Essentials) Oct 14, 2004.

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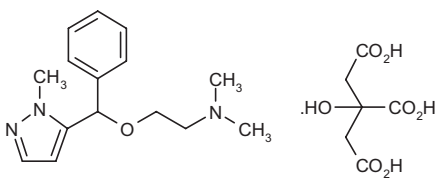
Original monograph – Drugs Fut 1994, 19(3): 228.

Cizolirtine Citrate

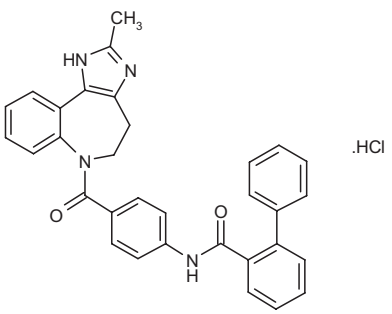


Esteve has initiated a phase II clinical program with cizolirtine citrate in stress urinary incontinence. The compound, a substance P and calcitonin gene-related peptide (CGRP) modulator, was previously studied for the treatment of urge urinary incontinence. Recent experimental results indicate that cizolirtine has a unique and novel mechanism of action in that it increases serotonin and noradrenaline release in different areas of the brain. It is known that the regulation of the noradrenergic pathway induces a decrease in the release of substance P and CGRP in the spinal cord, and all of these neurotransmitters are involved in the pathogenesis of urinary incontinence. The objective of the phase II study is to assess the efficacy and tolerability of cizolirtine in patients with stress urinary incontinence. The dose-escalation clinical study is a multicenter trial to be carried out in leading clinical centers across Europe. Subsequent phase III programs in urge and stress urinary incontinence will be carried out with a modified-release formulation of cizolirtine, which is being developed by Esteve (1).

1. *Cizolirtine enters phase II for stress urinary incontinence*. DailyDrugNews.com (Daily Essentials) Feb 25, 2005.

Original monograph – Drugs Fut 2002, 27(8): 721.

Conivaptan Hydrochloride



Astellas received an approvable letter in late 2004 from the FDA for conivaptan hydrochloride (YM-087), an investigational drug to treat hyponatremia. Conditions for marketing approval include submission of additional safety data. Conivaptan is an injectable dual vasopressin V_{1a}/V_2 receptor antagonist that increases blood sodium levels in patients with euvolemic and hypervolemic hyponatremia by increasing excretion of free water without increasing sodium output. Conivaptan is expected to become the world's first drug for hyponatremia (1). The development of the drug for acutely decompensated chronic heart failure, an indication for which it had reached phase II trials in Europe and the U.S., was discontinued.

Oral doses of placebo or conivaptan 40 or 80 mg/day were given for 5 days to 83 patients with euvolemic or hypervolemic hyponatremia in a multicenter, randomized, double-blind study. Compared to placebo, both doses of conivaptan significantly increased serum sodium concentrations (mean change on day 5: 1, 6.8 and 8.8 mEq/l, respectively). Conivaptan was also associated with increases in effective water clearance, a parameter that

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

Indication	Design	Treatments	n	Conclusions	Ref.
Hyponatremia	Randomized Double-blind Multicenter	Conivaptan, 20 mg p.o. b.i.d. x 5 d (n=27) Conivaptan, 40 mg p.o. b.i.d. x 5 d (n=26) Placebo (n=30)	83	Conivaptan was well tolerated and effective in increasing serum sodium levels in patients with hyponatremia	3, 5
Hyponatremia	Randomized Double-blind Pooled/meta-analysis	Conivaptan, 20 mg i.v. → 40 mg/d i.v. over 4 d (n=29) Conivaptan, 20 mg i.v. → 80 mg/d i.v. over 4 d (n=26) Conivaptan, 20 mg p.o. b.i.d. x 5 d (n=51) Conivaptan, 40 mg p.o. b.i.d. x 5 d (n=53) Placebo (n=82)	241	Compared to placebo, intravenous and oral conivaptan significantly increased serum sodium levels in patients with hyponatremia after only 2 days of treatment. Additional days of treatment resulted in greater sodium elevations	4
Hyponatremia	Randomized Double-blind Multicenter	Conivaptan, 20 mg p.o. b.i.d. x 5 d (n=24) Conivaptan, 40 mg p.o. b.i.d. x 5 d (n=27) Placebo (n=23)	74	Oral conivaptan was well tolerated and dose-dependently increased serum sodium levels and effective water clearance in patients with euvolemic or hypovolemic hyponatremia	7
Hyponatremia	Randomized	Conivaptan, 20 mg i.v. bolus → 40 mg/d i.v. infusion over x 4 d (n=29) Conivaptan, 20 mg i.v. bolus → 80 mg/d i.v. infusion over x 4 d (n=26) Placebo (n=29)	84	Intravenous conivaptan showed a good safety profile and was significantly more effective than placebo in increasing serum sodium levels in patients with hyponatremia	9

measures excretion of electrolyte-free water. Despite a higher incidence of treatment-emergent adverse events (56% with 40 mg/day, 42% with 80 mg/day, 40% with placebo), the study drug was well tolerated and most patients (87%) completed the trial (2-5) (see Table III).

In a randomized, double-blind study in 74 patients with euvolemic or hypervolemic hyponatremia, serum sodium increased by a mean of 3.9, 6.4 and 7.9 mEq/l on day 5 in the placebo, conivaptan 40 and conivaptan 80 mg/day treatment groups, respectively. Effective water clearance on day 1 was also superior with conivaptan compared to placebo and the treatment was well tolerated (4, 6, 7) (see Table III).

Another randomized, double-blind trial was conducted in patients with euvolemic or hypervolemic hyponatremia (n=84) who were given placebo or conivaptan as a 20-mg bolus dose followed by infusion of 40 or 80 mg/day for 4 days. Administration by this route was well tolerated. Significant differences in sodium concentrations were seen with both conivaptan doses compared to placebo, with mean changes at day 4 of 2, 6.8 and 9 mEq/l for placebo, conivaptan 40 mg/day and conivaptan 80 mg/day. Secondary measures of sodium levels and effective water clearance were also significantly superior with both doses of conivaptan (4, 8, 9) (see Table III).

1. *Approvable letter for hyponatremia drug YM-087*. DailyDrugNews.com (Daily Essentials) Dec 3, 2004.

2. Gross, P., Bisaha, J.G., Smith, N. *Conivaptan, a novel V1a/V2 antagonist, increases serum sodium and effective water clearance in hyponatremia*. J Am Soc Nephrol 2004, 15: Abst SA-PO243.

3. Gross, P., Smith, N. *Conivaptan, a novel V1a/V2 antagonist, increased serum sodium and effective water clearance in hyponatremia clinical trials*. Crit Care Med 2004, 32(12, Suppl.): Abst 590.

4. Verbalis, J.G. et al. *Vasopressin V1a and V2 antagonist conivaptan increased serum sodium concentration and effective water clearance in euvolemic and hypervolemic hyponatremia: Summary of three phase 3 clinical trials*. 87th Annu Meet Endocr Soc (June 4-7, San Diego) 2005, Abst P3-183.

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7. Ghali, J.K., Bisaha, J.G., Smith, N. *Efficacy of the vasopressin V1A/V2 antagonist conivaptan in patients with euvolemic or hypervolemic hyponatremia*. Circulation 2004, 110(17, Suppl. 3): Abst 3347.

8. Verbalis, J.G., Bisaha, J.G., Smith, N. *Novel vasopressin V1a and V2 antagonist conivaptan increases serum sodium concentration and effective water clearance in hyponatremia*. J Am Soc Nephrol 2004, 15: Abst SA-PO254.

9. Verbalis, J.G., Bisaha, J.G., Smith, N. *Novel vasopressin V1A and V2 antagonist (conivaptan) increases serum sodium concentration and effective water clearance in patients with hyponatremia*. Circulation 2004, 110(17, Suppl. 3): Abst 3346.

Original monograph – Drugs Fut 2000, 25(11): 1121.

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Verbalis, J.G. et al. *Conivaptan, a novel vasopressin V1a and V2 antagonist, increased serum sodium 2 days and 4 or 5 days after administration in patients with hyponatremia*. 87th Annu Meet Endocr Soc (June 4-7, San Diego) 2005, Abst P3-184.

CR002

CuraGen's CR002 is a fully human monoclonal antibody that targets platelet-derived growth factor-D (PDGF-D) and is being developed for the treatment of kidney inflammation such as that caused by IgA nephropathy, diabetic nephropathy and lupus nephritis. CR002 neutralizes PDGF-D, a mediator known to stimulate mesangial cell proliferation and implicated in the pathogenesis of nephritis. Results from animal models of kidney inflammation suggest that neutralization of PDGF-D by CR002 can significantly reduce tissue scarring in the kidney and may possibly help to preserve kidney function. A phase I study in healthy male volunteers evaluating the antibody's safety, tolerability, pharmacokinetics and pharmacodynamics was completed earlier this year and results were submitted for presentation at a medical conference later this year. CuraGen plans to outlicense this product, which has been granted orphan drug designation for slowing the progression of IgA nephropathy and delaying kidney failure in patients affected by the disease. CR002 was generated using Abgenix's XenoMouse® technology (1-5).

1. *Restructuring at CuraGen*. DailyDrugNews.com (Daily Essentials) Oct 21, 2004.

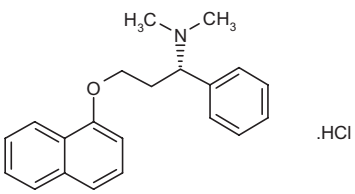
2. *CuraGen highlights pipeline progression*. DailyDrugNews.com (Daily Essentials) Oct 29, 2004.

3. *Orphan drug designation for CR-002 in IgA nephropathy*. DailyDrugNews.com (Daily Essentials) Nov 15, 2004.

4. *CuraGen reports Q1 R&D highlights*. CuraGen Press Release 2005, April 28.

5. *CuraGen reports Q2 R&D highlights*. CuraGen Press Release 2005, July 28.

Dapoxetine Hydrochloride



Alza (Johnson & Johnson) has submitted an NDA for dapoxetine hydrochloride, a new treatment for premature ejaculation. If approved by the FDA, dapoxetine would be the first prescription treatment designed specifically to treat premature ejaculation and will be marketed in the U.S. by Ortho-McNeil (1).

No pharmacokinetic drug interaction was seen with dapoxetine and ethanol in a randomized, double-blind, placebo-controlled, crossover study. Healthy male volunteers in the study received single doses of dapoxetine 60 mg plus placebo, dapoxetine 60 mg plus ethanol 0.5 g/kg, placebo plus ethanol 0.5 g/kg or placebo only. Mean peak plasma concentrations of dapoxetine and ethanol did not differ between monotherapy and co-administration. No serious adverse events were seen, although 1 subject experienced symptomatic tachycardia (2).

In a randomized, crossover drug interaction study, 24 healthy male volunteers were treated with single doses of dapoxetine 60 mg, dapoxetine 60 mg plus tadalafil 20 mg and dapoxetine 60 mg plus sildenafil 100 mg. The pharmacokinetics of dapoxetine were not altered significantly by the PDE5 inhibitors, and plasma concentrations of the PDE5 inhibitors were as expected during co-administration. The treatment combinations were also well tolerated (3).

The efficacy and safety of dapoxetine in the treatment of premature ejaculation was assessed in a multicenter, double-blind, randomized, placebo-controlled, crossover phase II clinical trial. A total of 166 heterosexual males aged 23-64 years in a stable monogamous relationship for at least 6 months and with a baseline intravaginal ejaculatory latency time (IELT) of < 2 min were treated with placebo or dapoxetine (60 or 100 mg) on demand for 2 weeks. The average IELT of the patients, which was 1.04 min at baseline, increased to 2.05 min with placebo and to 2.94 and 3.20 min with 60 and 100 mg of dapoxetine, respectively. Nausea was the adverse event most commonly found with dapoxetine, and most of the patients who discontinued the treatment did so while receiving 100 mg of dapoxetine. Based on these results, the 60-mg dose was selected for further evaluation in premature ejaculation (4) (Table IV).

Dapoxetine doses of 20, 40, 60 and 100 mg were investigated in two multicenter, randomized, double-blind, placebo-controlled phase II clinical trials in a total of 323 patients with premature ejaculation. All dapoxetine doses significantly improved IELT compared to placebo. Comparison of between-group effects and tolerability evaluation led to the choice of dapoxetine 30 and 60 mg for phase III investigation (5).

Two 12-week phase III trials enrolled a total of 2,614 patients with premature ejaculation. Both the 30- and 60-mg doses of dapoxetine significantly improved IELT, Control Over Ejaculation and Satisfaction with Sexual Intercourse over placebo. Adverse events with these dapoxetine doses included nausea and headache, and diarrhea and dizziness were also seen with the higher dose (6) (Table IV).

1. *NDA submission for premature ejaculation treatment dapoxetine hydrochloride*. DailyDrugNews.com (Daily Essentials) Dec 30, 2004.

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

Indication	Design	Treatments	n	Conclusions	Ref.
Premature ejaculation	Randomized Double-blind Crossover	Dapoxetine, 60 mg PRN x 2 wks Dapoxetine, 100 mg PRN x 2 wks Placebo	166	Dapoxetine was significantly more effective than placebo in increasing IELT in patients with premature ejaculation. Mean IELT increased from 1.0 min to 2.9 min with 60 mg dapoxetine, 3.2 min with 100 mg dapoxetine and 2.1 min with placebo	4
Premature ejaculation	Randomized Double-blind Multicenter Pooled/meta-analysis	Dapoxetine, 30 mg x 12 wks Dapoxetine, 60 mg x 12 wks Placebo	2614	Preliminary results suggested that dapoxetine was well tolerated and effective on first dose for the on-demand treatment of premature ejaculation	6

2. Modi, N.B. et al. *Dapoxetine for the treatment of premature ejaculation: Lack of interaction with ethanol*. J Urol 2005, 173(4, Suppl.): Abst 879.

3. Dresser, M. et al. *Dapoxetine for the treatment of premature ejaculation: Lack of interaction with PDE5 inhibitors*. J Urol 2005, 173(4, Suppl.): Abst 739.

4. Gittelman, M., Althof, S., Ho, K.F., Kell, S., Hellstrom, W. *Dapoxetine HCl for the treatment of premature ejaculation: A phase II, randomized, double-blind, placebo-controlled study*. J Sex Med 2004, 1(Suppl. 1): Abst O97.

5. Hellstrom, W.J.G. et al. *Dapoxetine for the treatment of men with premature ejaculation (PE): Dose-finding analysis*. J Urol 2005, 173(4, Suppl.): Abst 877.

6. Pryor, J.L. et al. *Efficacy and tolerability of dapoxetine in the treatment of premature ejaculation*. J Urol 2005, 173(4, Suppl.): Abst 740.

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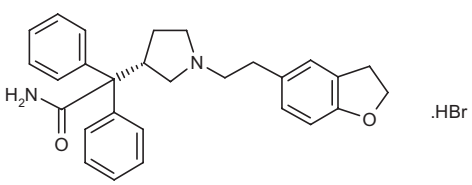
Darifenacin Hydrobromide



Novartis received European (all 25 member states, Norway and Iceland) and U.S. marketing approval for darifenacin hydrobromide (Emselex® in the E.U., Enablex® in the U.S.) in 2004 for the treatment of OAB. Darifenacin is a once-daily oral muscarinic M_3-selective receptor antagonist (M3 SRA) that works by selectively inhibiting the detrusor muscle that controls bladder contraction while sparing the M_1 and M_2 receptors believed to be involved in central nervous system (CNS) and cardiovascular function, respectively. The drug has been shown to reduce the number of weekly incontinence episodes by up to 77% *versus* placebo and to work without impairing cognitive function and without cardiovascular safety concerns. To date, 98 clinical trials have been conducted in more than 10,500 subjects and patients, of whom 7,146 were treated with darifenacin. Darifenacin has been shown to significantly improve all other key symptoms of OAB, including the number of times patients had to visit the bathroom each day, bladder capacity, frequency of urgency, severity of urgency and number of incontinence episodes leading to a change in clothing or pads. The company has an agreement with Procter & Gamble for the copromotion and further development of darifenacin extended-release tablets for OAB in the U.S. Novartis is also collaborating with Bayer Vital for the commercialization and distribution of darifenacin in Germany (1-9).

The selectivity for the muscarinic M_3 receptor subtype demonstrated by darifenacin may account for the lack of cognitive side effects observed in elderly subjects taking the drug in a randomized, double-blind, crossover trial. The 129 volunteers included in the study were 65 years of age or older and had no or mild cognitive impairment. In each treatment period they were given either controlled-release darifenacin (3.75, 7.5 or 15 mg once daily), immediate-release darifenacin (5 mg t.i.d.) or placebo for 14 days. Comparison of cognitive function tests given at baseline and after each treatment period revealed no differences between placebo and darifenacin for the primary endpoints of memory scanning sensitivity, speed of choice reaction time and word recognition sensitivity. Other endpoints, such as simple reaction time, digit vigilance speed or accuracy and word recognition speed, were also unaffected by darifenacin. Memory scanning speed improved with all treatments and the improvement was greater with placebo than with darifenacin 3.75 mg. Self-rated alertness, contentment and calmness were also not affected by darifenacin to a clinically relevant degree. Similar rates of treatment-related adverse events were seen in all treatment groups (10).

The results from this and the following studies are shown in Table V.

A multicenter, double-blind clinical trial randomized 439 patients with OAB to receive placebo or controlled-release darifenacin (7.5, 15 or 30 mg p.o.) once daily. After 12 weeks of treatment, darifenacin significantly reduced the weekly number of incontinence episodes and the number of nocturnal awakenings compared to placebo. Patients treated with darifenacin also reported an increase in the incidence of adverse events, but most of these were mild to moderate and the most common were dry mouth and constipation. No significant differences were found in the cardiovascular or CNS safety profiles of the study groups (11).

Pooled data from three double-blind, randomized, placebo-controlled clinical trials were used to determine the efficacy and safety of darifenacin in 900 female patients with OAB. The patients were given placebo or controlled-release darifenacin (7.5 or 15 mg p.o.) once daily for 12 weeks. Both darifenacin doses were significantly more effective than placebo in increasing bladder capacity, and in reducing micturition frequency, the median number of incontinence episodes and the median number of urgency episodes per day. The incidence of mild to moderate dry mouth and constipation also increased dose-dependently with darifenacin compared to placebo, whereas the incidence of cardiovascular and nervous system adverse events was similar in all study groups (12).

The effects of darifenacin on the quality of life of OAB patients were evaluated using data from three multicenter, double-blind, placebo-controlled clinical trials that enrolled 1,059 adult patients. Compared to placebo, once-daily darifenacin (7.5 or 15 mg) significantly reduced the number of incontinence episodes per week and improved all 9 domains in the King's Health Questionnaire (KHQ). The most common adverse events were dry mouth and constipation, but less than 1% of the patients discontinued the study because of them (13-17).

Pooled data from three double-blind, placebo-controlled clinical trials were used to compare the safety profiles of darifenacin and tolterodine in the treatment of OAB. Patients were randomized to receive placebo (n=388), tolterodine (2 mg b.i.d.; n=223) or darifenacin (7.5 or 15 mg once daily; n=337 and 334, respectively) for 12 weeks. The incidence of constipation was 6.2% with placebo, 12.6% with tolterodine and 14.8% and 21.3% with 7.5 mg and 15 mg of darifenacin, respectively. In all cases, constipation was easily managed and only required dietary modification or minor intervention. The percentage of patients who withdrew from the studies due to constipation was low in all study groups (18-20).

Darifenacin compared favorably with oxybutynin in a randomized, double-blind, placebo-controlled, crossover trial in 76 patients with OAB. The patients were treated for 2 weeks each with darifenacin (15 mg once daily), oxybutynin (5 mg t.i.d.) and placebo. Similar and significant improvements in incontinence episodes/week, urgency episode frequency and urgency severity were seen with both darifenacin and oxybutynin compared with placebo. Neither agent significantly reduced micturition frequency. Darifenacin was better tolerated than oxybutynin in 61 patients assessed for adverse effects. Dry mouth was significantly more common in patients treated with oxybutynin, while blurred vision and dizziness were reported in some oxybutynin-treated patients but not in darifenacin-treated patients. Constipation occurred with similar frequency with both active treatments (21).

1. *European approval recommended for Emselex*. DailyDrugNews.com (Daily Essentials) Aug 3, 2004.

2. *Novartis reports Q2 R&D highlights*. Novartis Press Release 2004, July 20.

3. *FDA approves Enablex for overactive bladder*. DailyDrugNews.com (Daily Essentials) Dec 27, 2004.

4. *Enablex launched in U.S*. DailyDrugNews.com (Daily Essentials) Feb 24, 2005.

5. *Novartis announces commercialization collaboration in Germany for Emselex® for the treatment of overactive bladder*. Novartis Press Release 2004, Dec 17.

6. *European approval for Emselex*. DailyDrugNews.com (Daily Essentials) Oct 28, 2004.

7. *Novartis and P&G to copromote Enablex in U.S*. DailyDrugNews.com (Daily Essentials) July 11, 2005.

8. *Novartis reflects on Q2 activities*. DailyDrugNews.com (Daily Essentials) Aug 9, 2005.

9. *Novartis reports Q2 R&D highlights*. Novartis Press Release 2005, July 14.

10. Lipton, R.B., Kolodner, K., Wesnes, K. *Assessment of cognitive function of the elderly population: Effects of darifenacin*. J Urol 2005, 173(2): 493.

11. Hill, S., Khullar, V. *Darifenacin, a muscarinic receptor antagonist with selectivity for M3 receptors, reduces incontinence and nocturia in patients with overactive bladder*. 34th Annu Meet Int Continence Soc (Aug 23-27, Paris) 2004, Abst 145.

12. Kerr, L., DelConte, A. *The effects of darifenacin on the improvement of symptoms of overactive bladder among female patients*. J Endourol 2004, 18(Suppl. 1): Abst MP 18/9.

13. Chapple, C., Kelleher, C., Perrault, L. *Quality of life effects of darifenacin, an M3 selective receptor antagonist, in patients with overactive bladder*. 27th Congr Soc Int Urol (Oct 3-7, Honolulu) 2004, Abst MP-19.03.

14. Abrams, P. et al. *Clinical relevance of quality of life data with darifenacin in patients with overactive bladder*. Int Urogynecol J 2005, 16(Suppl. 2): Abst 304.

15. Hill, S. et al. *Darifenacin in the treatment of overactive bladder: Dose-response effects on urinary symptoms in phase III trials*. 35th Annu Meet Int Continence Soc (Aug 26-Sept 1, Montreal) 2005, Abst 145.

16. Reese, P. et al. *Darifenacin provides clinically meaningful quality of life improvements in patients with overactive bladder assessed by minimal important difference (MID) analysis*. 35th Annu Meet Int Continence Soc (Aug 26-Sept 1, Montreal) 2005, Abst 326.

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

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized Double-blind Crossover	Darifenacin-CR, 3.75 mg p.o. o.d. x 2 wks (n=65) Darifenacin-CR, 7.5 mg p.o. o.d. x 2 wks (n=70) Darifenacin-CR, 15 mg p.o. o.d. x 2 wks (n=61) Darifenacin-IR, 5 mg p.o. t.i.d. x 2 wks (n=65) Placebo (n=66)	129	Darifenacin showed no effect on cognitive function in elderly healthy volunteers	10
Overactive bladder	Randomized Double-blind	Darifenacin, 7.5 mg p.o. o.d. x 12 wks (n=108) Darifenacin, 15 mg p.o. o.d. x 12 wks (n=107) Darifenacin, 30 mg p.o. o.d. x 12 wks (n=115) Placebo (n=109)	439	Once-daily darifenacin was well tolerated and improved the weekly number of incontinence episodes and the number of nocturnal awakenings inpatients with over-active bladder	11
Overactive bladder	Randomized Double-blind Pooled/meta-analysis	Darifenacin, 7.5 mg p.o. o.d. x 12 wks (n=288) Darifenacin, 15 mg p.o. o.d. x 12 wks (n=281) Placebo (n=331)	900	Compared with placebo, darifenacin dose-dependently decreased the number of incontinence episodes per week, the number of urgency episodes per day and micturition frequency in female patients with overactive bladder	12
Overactive bladder	Randomized Double-blind Multicenter Pooled/meta-analysis	Darifenacin, 7.5 mg p.o. o.d. x 12 wks (n=337) Darifenacin, 15 mg p.o. o.d. x 12 wks (n=334) Placebo (n=388)	1059	Darifenacin was significantly more effective than placebo in the severity of symptoms and their impact on quality of life in patients with overactive bladder. It effectively reduced urinary incontinence and urgency episodes and normalized micturition frequency	13, 15-17
Overactive bladder	Double-blind Multicenter Pooled/meta-analysis	Darifenacin, 7.5 mg o.d. x 12 wks (n=337) Darifenacin, 15 mg o.d. x 12 wks (n=334) Tolterodine, 2 mg b.i.d. x 12 wks (n=223) Placebo (n=388)	1282	Darifenacin was effective when compared to tolterodine in reducing incontinence episodes at all time points and did not increase the incidence of constipation in patients with overactive bladder	19, 20
Overactive bladder	Randomized Double-blind Crossover	Darifenacin, 15 mg p.o. o.d. x 2 wks Oxybutynin, 5 mg p.o. t.i.d. x 2 wks Placebo	76	Darifenacin was better tolerated and as effective as oxybutynin in reducing the number and severity of incontinence and urgency episodes in patients with overactive bladder	21
Overactive bladder	Open Multicenter	Darifenacin, 7.5 mg o.d. x 2 wks → 7.5 mg o.d. x 2 y Darifenacin, 7.5 mg o.d. x 2 wks → 15 mg o.d. x 2 y	716	Darifenacin was well tolerated and significantly improved the number of incontinence episodes per week, the number of micturitions per day, the volume passed per void and the severity of urgency in patients with overactive bladder. These effects were maintained throughout the 2-year study period	22, 23
Overactive bladder	Randomized Double-blind Multicenter	Darifenacin-CR, 7.5 mg p.o. o.d. x 12 wks Darifenacin-CR, 7.5 mg p.o. o.d. x 2 wks → [if additional efficacy required] 15 mg o.d. x 10 wks Placebo	395	Darifenacin was well tolerated and significantly reduced the number of incontinence episodes/week in patients with overactive bladder. Efficacy was improved with dose escalation	24, 26
Incontinence, urinary, Incontinence, urinary urge	Randomized Double-blind Multicenter	Darifenacin-CR, 30 mg p.o. o.d. x 2 wks (n=36) Placebo (n=36)	72	Darifenacin prolonged warning time compared with placebo in patients with urinary urgency, allowing more time to reach a suitable toilet and thus potentially reducing embarrassment	25

17. Abrams, P., Lheritier, K., Steel, M. *Approaches for determining the efficacy of treatment for overactive bladder: Assessment of responder rates to darifenacin in a pooled analysis of phase III studies*. Eur Urol Suppl 2005, 4(3): Abst 558.

18. Thomas, S. et al. *Constipation and associated intervention in patients with overactive bladder treated with darifenacin or tolterodine*. Int Urogynecol J 2005, 16(Suppl. 2): Abst 306.

19. Thomas, S. et al. *Constipation and associated intervention in patients with overactive bladder treated with darifenacin or tolterodine*. 35th Annu Meet Int Continence Soc (Aug 26-Sept 1, Montreal) 2005, Abst 150.

20. Romanzi, L.J., Delconte, A. III., Kralidis, G. *Impact of darifenacin compared with tolterodine on incontinence episodes in patients with overactive bladder*. Obstet Gynecol 2005, 105(4, Suppl.): 88S.

21. Zinner, N., Tuttle, J., Marks, L. *Efficacy and tolerability of darifenacin, a muscarinic M3 selective receptor antagonist, versus oxybutynin in the treatment of overactive bladder (OAB)*. 27th Congr Soc Int Urol (Oct 3-7, Honolulu) 2004, Abst MP-19.05.

22. Steers, W. et al. *Efficacy of darifenacin in a 2-year long-term extension study in patients with overactive bladder*. 35th Annu Meet Int Continence Soc (Aug 26-Sept 1, Montreal) 2005, Abst 149 (Table V).

23. Steers, W. et al. *Long-term tolerability and safety of darifenacin demonstrated in a 2-year extension study in patients with overactive bladder*. 35th Annu Meet Int Continence Soc (Aug 26-Sept 1, Montreal) 2005, Abst 141 (Table V).

24. Steers, W. et al. *An investigation of dose titration with darifenacin, an M-selective receptor antagonist*. BJU Int 2005, 95(4): 580 (Table V).

25. Cardozo, L., Dixon, A. *Increased warning time with darifenacin: A new concept in the management of urinary urgency*. J Urol 2005, 173(4): 1214 (Table V).

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

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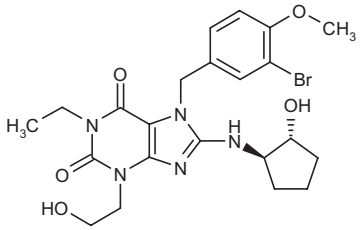
Devineni, D., Skerjanec, A., Woodworth, T.G. *Darifenacin has no clinically relevant effect on warfarin or digoxin pharmacodynamics/kinetics in healthy males*. Summer Meet Br Pharmacol Soc 2005, Abst P099.

Foote, J. et al. *Treatment of overactive bladder in the older patient: Pooled analysis of three phase III studies of darifenacin, an M3 selective receptor antagonist*. Eur Urol 2005, 48(3): 471.

Foote, J., Glavind, K., Kay, G. *Central nervous system (CNS)-related adverse even ts in patients with overactive bladder (OAB) treated with darifenacin versus tolterodine*. 27th Congr Soc Int Urol (Oct 3-7, Honolulu) 2004, Abst MP-19.07.

Skerjanec, A. et al. *Darifenacin, an M3 selective receptor antagonist (M3 SRA), does not prolong QT/QTC*. Clin Pharmacol Ther 2005, 77(2): Abst PI-8.

Dasantafil

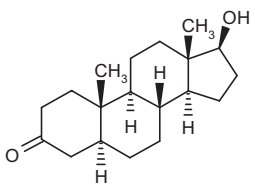


The PDE5 inhibitor dasantafil is in clinical development at Schering-Plough for the treatment of male erectile dysfunction.

DDP-200

DDP-200 is undergoing phase I clinical testing at Dynogen Pharmaceuticals for the treatment of OAB. A combination of two currently marketed neurological compounds, DDP-200 results in synergistic activity between two important neurological pathways and inhibition of bladder primary afferent C-fibers.

Dihydrotestosterone, Gel



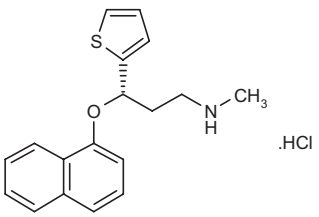
Ascend Therapeutics has secured exclusive North American development, marketing and commercialization rights from Besins International for the developmental pharmaceutical product Andrin (dihydrotestosterone), a novel transdermal treatment for late-onset hypogonadism and for preventing benign prostatic hyperplasia (BPH) and other chronic prostate conditions. Ascend has incorporated dihydrotestosterone into its proprietary Enhanced Hydroalcoholic Gel™ (EHG) technology to create Andrin. Andrin is being evaluated in phase II trials for the treatment of symptoms associated with low testosterone levels in older men. Evidence suggests that dihydrotestosterone may be effective in treating symptoms associated with androgen deficiency while having less of a stimulatory effect on the prostate than testosterone. Percutaneous administration means that dihydrotestosterone avoids first-pass liver metabolism. A double-blind,

placebo-controlled, randomized phase II is being conducted in conjunction with the University of Sydney, Australia, to evaluate the efficacy and safety of Andrin in preventing prostate growth in middle-aged men. Some 100 healthy men over the age of 50 will apply either the study drug or placebo gel to their shoulders, upper arms and thighs every day for 24 months. Preliminary results are expected in mid-2006. In previous Andrin trials, the volume of prostate growth was reduced (1, 2).

1. *Ascend Therapeutics acquires North American product rights for new product*. Ascend Therapeutics Press Release 2004, July 7.

2. *Ascend Therapeutics launches Andrin trial in Australia*. Ascend Therapeutics Press Release 2004, July 16.

Duloxetine Hydrochloride



Duloxetine hydrochloride (Yentreve®/Ariclaim®) was granted marketing authorization in the E.U. for the treatment of moderate to severe stress urinary incontinence (SUI) in women in 2004 and was subsequently launched in Germany, Denmark, Finland, Sweden and the U.K. The product is the first pharmaceutical widely approved to treat SUI and will help women reduce the number of leakages they experience and improve their quality of life. Ten studies in more than 2,000 women with SUI across 5 continents demonstrated that duloxetine effectively reduces the frequency of incontinence episodes by up to 53% and is generally well tolerated, with mild to moderate and manageable side effects, the most common of which is transient nausea. The balanced dual serotonin and norepinephrine reuptake inhibitor increases neurotransmitter concentration, which is believed to increase the tone and contraction of the urethral sphincter, helping to prevent accidental urine leakage due to physical activities such as sneezing, coughing, laughing, lifting or exercising. The product will be jointly copromoted in the E.U. by Lilly and Boehringer Ingelheim under the brand name Yentreve®, except for Greece, Italy, and Spain, where it will be marketed under the brand name Yentreve® by Lilly and as Ariclaim® by Boehringer Ingelheim. The two companies entered into a long-term agreement in November 2002 to jointly develop and commercialize duloxetine and the partnership covers most countries worldwide with few exceptions. In the U.S., the collaboration excludes neuroscience indications. Lilly withdrew its NDA in the U.S. for the SUI indication based on discussions with the FDA suggesting that the agency was not prepared to grant approval for duloxetine for the treatment of the SUI patient population based on the data package submitted. Duloxetine (Cymbalta®) has also been approved by the FDA and launched in the U.S. for the treatment of major depression in adults and for the management of diabetic peripheral neuropathic pain. The E.U. also authorized the marketing of the drug for major depressive episodes. The product will be marketed jointly by Lilly and partner Boehringer Ingelheim as Cymbalta® in most E.U. countries, except for Greece, Italy and Spain where Lilly will market it as Cymbalta® and Boehringer Ingelheim will market it as Xeristar®. It has also been recommended for approval in the E.U. for the management of diabetic peripheral neuropathic pain in adults (1-11). Shionogi is developing the drug in Japan for depression (phase III) and diabetic peripheral neuropathic pain (phase I/II).

A multicenter, double-blind, placebo-controlled clinical trial determined the effects of combining duloxetine hydrochloride with pelvic floor muscle training (PFMT) in the management of SUI. A total of 201 women aged 29-75 years with SUI were randomized to receive duloxetine (40 mg b.i.d.) alone, duloxetine combined with PFMT, PFMT alone or no active treatment for 12 weeks. The frequency of incontinence episodes in patients who completed the study decreased more with the duloxetine/PFMT combination (75.8%) compared to duloxetine alone (61.1%), PFMT alone (46.8%) or no active treatment (42.7%). The duloxetine/PFMT combination also tended to be more effective than duloxetine alone or PFMT alone in reducing pad use and improving the quality of life of the patients. Onset of action was more rapid with duloxetine alone than with PFMT alone. Most adverse events were mild and manageable, with nausea being the most common (12) (Table VI).

The results of two randomized, placebo-controlled trials of duloxetine treatment (40 mg b.i.d.) in women with SUI were analyzed based on baseline disease severity. Duloxetine was more effective than placebo in all patients regardless of baseline severity (weekly incontinence episode frequency below 7, 7-14, 14-21 or 21 or more) (13) (Table VI).

1. *FDA extends action date for Cymbalta*. DailyDrugNews.com (Daily Essentials) July 1, 2004.

2. *Cymbalta approved for major depressive disorder*. DailyDrugNews.com (Daily Essentials) Aug 9, 2004.

3. *Yentreve approved in E.U. for stress urinary incontinence*. DailyDrugNews.com (Daily Essentials) Aug 18, 2004.

4. *Cymbalta approved for diabetic peripheral neuropathic pain*. DailyDrugNews.com (Daily Essentials) Sept 8, 2004.

5. *European approval for duloxetine hydrochloride for major depressive episodes*. DailyDrugNews.com (Daily Essentials) Jan 10, 2005.

6. *New positive opinion for Cymbalta in Europe*. DailyDrugNews.com (Daily Essentials) Feb 21, 2005.

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

Indication	Design	Treatments	n	Conclusions	Ref.
Incontinence, urinary	Randomized Double-blind Multicenter	Duloxetine, 40 mg b.i.d. x 12 wks (n=52) Pelvic floor muscle training x 12 wks (n=50) Duloxetine, 40 mg b.i.d. + Pelvic floor muscle training x 12 wks (n=52) Placebo (n=47)	210	Combining twice-daily duloxetine with pelvic floor muscle training was more effective than either treatment alone in reducing the frequency of incontinence episodes and improving the quality of life in women with stress urinary incontinence	12
Incontinence, urinary	Pooled/meta-analysis	Duloxetine, 40 mg b.i.d. x 12 wks (n=484) Placebo (n=477)	961	Duloxetine was effective in women with stress urinary incontinence regardless of baseline disease severity	13
Incontinence, urinary	Randomized Double-blind Multicenter	Duloxetine, 40 mg b.i.d. x 4 wks → Duloxetine (n=34) Placebo x 4 wks → Duloxetine (n=31)	65	Duloxetine improved urethral closure during the filling phase and electrical activity of the striated urethral sphincter compared to placebo in female patients with stress urinary incontinence	14
Incontinence, urinary	Randomized Double-blind Multicenter	Duloxetine x 12 wks (n=958) Placebo (n=955)	1913	Duloxetine was effective in improving the number of dry days in women with both less severe stress urinary incontinence and a more severe form of the disease	15

7. *Lilly withdraws duloxetine NDA for stress urinary incontinence*. DailyDrugNews.com (Daily Essentials) Feb 2, 2005.

8. *Duloxetine recommended for approval in Europe*. DailyDrugNews.com (Daily Essentials) Sept 20, 2004.

9. *Lilly reports Q2 R&D highlights*. Eli Lilly and Co. Press Release 2004, July 22.

10. *Yentreve launched in Europe*. DailyDrugNews.com (Daily Essentials) Sept 15, 2004.

11. *Lilly launches Cymbalta*. DailyDrugNews.com (Daily Essentials) Aug 25, 2004.

12. Ghoniem, G.M. et al. *A randomized controlled trial of duloxetine alone, pelvic floor muscle training alone, combined treatment and no active treatment in women with stress urinary incontinence*. J Urol 2005, 173(5): 1647.

13. Taylor, M., Liu, C., Yalcin, I., Muram, D., Siddhanti, S. *Duloxetine efficacy in the treatment of various levels of stress urinary incontinence severity*. 27th Congr Soc Int Urol (Oct 3-7, Honolulu) 2004, Abst PD-6.05.

14. Bump, R., Benson, J.T., Brubaker, L., Brostrom, S., Hampel, C., Jannelli, M., Roberts, M., Schüessler, B., Van Kerrebroeck, P., Yalcin, I., Peng, G., Zhao, Y. *Biomechanical and electrophysiological effects of duloxetine in women with stress urinary incontinence*. 34th Annu Meet Int Continence Soc (Aug 23-27, Paris) 2004, Abst 269 (Table VI).

15. Bump, R., Hooper, C., Koke, S., Yalcin, I. *The effect of baseline severity on the efficacy of duloxetine in the treatment of women with stress urinary incontinence (SUI)*. 34th Annu Meet Int Continence Soc (Aug 23-27, Paris) 2004, Abst 275 (Table VI).

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

Additional References

Cardozo, L.D. et al. *The safety and effectiveness of duloxetine compared with placebo in women in the UK with stress urinary incontinence (SUI)*. Int Urogynecol J 2005, 16(Suppl. 2): Abst 339.

Jost, W.H., Manning, M., Marsalek, P., Junemann, K.P. *Pharmaceutical treatment of stress incontinence: New approaches via a direct effect of duloxetine on Onuf's nucleus*. Urologe (Ausg A) 2004, 43(10): 1249.

Khullar, V. et al. *An assessment of adverse events and withdrawals: Duloxetine compared with antimuscarinics for the treatment of urinary incontinence*. Int Urogynecol J 2005, 16(Suppl. 2): Abst 34.

Taylor, M., Liu, C., Yalcin, I., Muram, D., Siddhanti, S. *Duloxetine efficacy in the treatment of various levels of stress urinary incontinence severity*. 27th Congr Soc Int Urol (Oct 3-7, Honolulu) 2004, Abst UP-14.52.

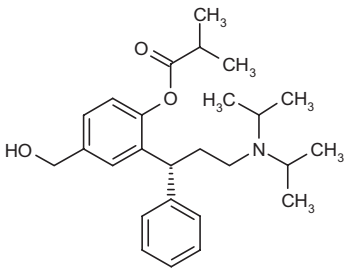
Van Kerrebroeck, P. *Duloxetine: An innovative approach for treating stress urinary incontinence*. BJU Int 2004, 94(Suppl. 1): 31.

Viktrup, L., Pangallo, B.A., Detke, M.J., Zinner, N.R. *Urinary side effects of duloxetine in the treatment of depression and stress urinary incontinence*. Prim Care Companion J Clin Psychiatry 2004, 6(2): 65.

FE-106483

FE-106483, an orally active, nonpeptide vasopressin agonist, is currently in phase II clinical trials at Ferring for the treatment of urinary incontinence.

Fesoterodine



A total of 1,900 patients with OAB participated in multicenter, double-blind, placebo-controlled phase III clinical trials that determined the benefits of the antimuscarinic drug fesoterodine in this indication. Each patient was given placebo, fesoterodine (4 or 8 mg) or extended-release fesoterodine (4 mg) once daily for 12 weeks. At the end of the treatment period, fesoterodine was significantly more effective than placebo in improving the average number of micturitions per 24 h, the average number of urge incontinence episodes per 24 h and treatment response (evaluated using a Treatment Benefit Scale). Dry mouth was the most common adverse event reported during the study. Schwarz Pharma is now preparing submissions for marketing approvals for OAB/urinary incontinence based on these data (1, 2).

As the metabolism of the active metabolite of fesoterodine, SPM-7605, is affected by the cytochrome P-450 (CYP) enzymes CYP3A4 and CYP2D6, the impact of CYP3A4 and CYP2D6 inhibition on the pharmacokinetics of fesoterodine was evaluated in healthy male subjects including extensive and poor CYP2D6 metabolizers. Inhibition of CYP2D6 led to approximately 2-fold increases in SPM-7605 AUC and C_{max} values. CYP3A4 inhibition with ketoconazole led to an approximately 2-fold increase in SPM-7605 AUC with C_{max} increases of 1.5- and 2.2-fold in poor and extensive CYP2D6 metabolizers, respectively. These increases in plasma concentrations did not appear to be clinically important, leading to the conclusion that fesoterodine dose adjustments are not necessary with genetic or pharmacological CYP inhibition (3).

Data from six phase I studies were retrospectively analyzed to determine the effect of fesoterodine on ECG parameters in 174 healthy volunteers. The study subjects had been given placebo or single or multiple doses (3 days) of oral fesoterodine at up to 28 mg. Fesoterodine was associated with dose-dependent increases in heart rate and a shortening of the measured Q-T interval. None of the study subjects had a corrected Q-T interval above 450 ms or a change of more than 60 ms (4).

A multicenter, double-blind, randomized, placebo-controlled phase II clinical trial assessed the efficacy and safety of fesoterodine in the treatment of urgency-frequency syndrome. A total of 728 patients were given placebo or fesoterodine (4, 8 or 12 mg) once daily for 12 weeks. Fesoterodine was significantly more effective than placebo in reducing both micturition frequency and the number of urge incontinence episodes per week. Dry mouth was the most commonly reported adverse event, which increased to 34% with the 12-mg dose. The incidence of other side effects, including constipation and vision disorders, was low. Based on these safety results, the authors concluded that the best efficacy/safety ratio was achieved with fesoterodine at daily doses of 4 and 8 mg (5).

A multicenter, double-blind, randomized clinical trial provided new data on the effects and safety of fesoterodine in the treatment of OAB. A total of 173 male and female OAB patients were randomized to receive placebo or fesoterodine (4, 8 or 12 mg) once daily for 8 weeks. All three fesoterodine dose levels were significantly more effective than placebo in reducing the number of urge urinary incontinence episodes per week and increasing the mean voided volume per micturition. The therapeutic benefits of fesoterodine increased with dose, were evident after only 2 weeks of treatment and were independent of the presence or absence of urodynamic detrusor overactivity. The most common adverse events were dry mouth (mostly mild or moderate), headache and gastrointestinal problems, and only 10 patients discontinued the study due to adverse events (6, 7) (Table VII).

1. *New phase III data on the efficacy of fesoterodine in OAB*. DailyDrugNews.com (Daily Essentials) April 20, 2005.

2. *Schwarz Pharma reports Q1 R&D highlights*. Schwarz Pharma Press Release 2005, April 27.

3. Cawello, W., Horstmann, R., Sachse, R. *Influence of CYP3A4 and CYP2D6 inhibition on fesoterodine treatment*. 33rd Annu Meet Am Coll Clin Pharmacol (ACCP) (Oct 3-5, Phoenix) 2004,

Table VII: Clinical studies of fesoterodine (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Overactive bladder	Randomized Double-blind Multicenter	Fesoterodine, 4 mg o.d. x 8 wks (n=44) Fesoterodine, 8 mg o.d. x 8 wks (n=47) Fesoterodine, 12 mg o.d. x 8 wks (n=39) Placebo (n=43)	173	Fesoterodine was well tolerated and dose-dependently improved the number of micturitions per 24 h and the number of urge urinary incontinence episodes per week in patients with overactive bladder. The benefits of fesoterodine were similar in patients with detrusor overactivity and in patients with normal filling cystometry	4, 5

Abst 8.

4. Sachse, R., Horstmann, R. *The novel antimuscarinic fesoterodine does not affect myocardial repolarization*. 33rd Annu Meet Am Coll Clin Pharmacol (ACCP) (Oct 3-5, Phoenix) 2004, Abst 7.

5. Chapple, C. *Fesoterodine, a new effective and well-tolerated antimuscarinic for the treatment of urgency-frequency syndrome: Results of a phase 2 controlled study*. 34th Annu Meet Int Continence Soc (Aug 23-27, Paris) 2004, Abst 142.

6. Rovner, E. et al. *Response to fesoterodine in overactive bladder (OAB) patients is independent of the urodynamic finding of detrusor overactivity*. 35th Annu Meet Int Continence Soc (Aug 26-Sept 1, Montreal) 2005, Abst 147.

7. Nitti, V. et al. *Fesoterodine is an effective antimuscarinic for patients with overactive bladder (OAB): Results of a phase 2 trial*. 35th Annu Meet Int Continence Soc (Aug 26-Sept 1, Montreal) 2005, Abst 306.

Original monograph – Drugs Fut 2003, 28(7): 647.

FG-3019

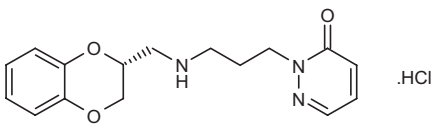
FG-3019 is a fully human monoclonal antibody against connective tissue growth factor (CTGF), a central mediator of fibrosis, designed to bind, neutralize and clear CTGF from the body. Discovered by the University of South Florida and in development by FibroGen, the antibody has completed phase I clinical trials for the treatment of idiopathic pulmonary fibrosis (IPF), the primary indication, and a phase Ib safety study is under way in patients with diabetic nephropathy. In addition, Taisho is evaluating FG-3019 in preclinical trials for the treatment of renal disorders. FibroGen has also filed an IND with the FDA seeking permission to begin clinical evaluation of FG-3019 for the treatment of pancreas cancer. The therapeutic activity FG-3019 in diabetic nephropathy and renal disorders is believed to be the result of CTGF's role in mediating multiple pathways that contribute to the development of diabetic nephropathy and the gradual destruction of kidneys. In terms of the anticancer activity of FG-3019, evidence implicates CTGF as a key mediator of tumor-stromal signaling involved in metastasis and the progression of certain cancers.

GPI-1485

Guilford has licensed to Symphony Neuro Development Company (SNDC) its rights to GPI-1485 for certain indications in the U.S. SNDC will invest up to USD 40 million to advance GPI-1485 through clinical development in Parkinson's disease, post-prostatectomy erectile dysfunction (PPED), HIV neuropathy and HIV dementia. The Parkinson's disease and PPED indications are in phase II, while the HIV indications are in preclinical development. Guilford has also issued to SNDC's investors 5-year warrants to purchase 1.5 million shares of Guilford's common stock. Guilford has received an exclusive purchase option from SNDC's investors allowing it to acquire all of the equity of SNDC. The option is generally exercisable between April 1, 2005, and March 31, 2007. The option may be paid in cash or a combination of cash and Guilford common stock provided that common stock does not constitute more than 50% of the option exercise price. RRD International will manage SNDC and will subcontract a portion of the ongoing development work to Guilford and other vendors. Guilford will perform certain services, including GPI-1485 manufacturing, process development, toxicology, patent and regulatory affairs work. GPI-1485 belongs to a class of small-molecule compounds called neuroimmunophilin ligands, which in preclinical experiments have been shown to repair and regenerate damaged nerves without affecting normal, healthy nerves (1).

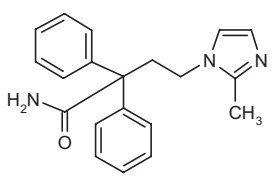
1. *Guilford licenses U.S. rights to GPI-1485 to Symphony Neuro Development Company*. DailyDrugNews.com (Daily Essentials) June 22, 2004.

GYKI-16084



Ivax is conducting phase II clinical trials with GYKI-16084 (Uroflux), a postsynaptic α_1/α_2-adrenoceptor antagonist, for the treatment of BPH. It is a prostate-specific antagonist of both adrenoceptors and appears to have reduced side effects compared to currently used drugs.

Imidafenacin



Imidafenacin (Staybla®, Uritos®, Ono-8025, KRP-1979), a selective muscarinic M_3/M_1 receptor antagonist, is being developed by Kyorin in partnership with Ono Pharmaceutical in Japan and with LG Life Sciences in Korea for the treatment of OAB. The drug is reported to have high efficacy, with fewer adverse effects such as dry

mouth. In Japan, it is awaiting manufacturing approval for the treatment of OAB (pollakiuria and urinary incontinence). LG Life Sciences has also been granted an exclusive right to investigate for a certain period the possibility of commercializing the drug in Europe, the U.S. and most other countries (1-3).

1. *Ono Pharmaceuticals reports Q4 R&D highlights*. Ono Pharmaceuticals Web Site 2004, May 18.

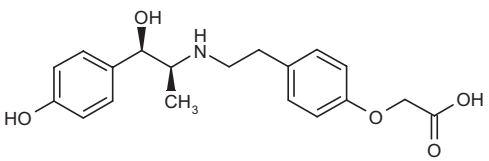
2. *Ono Pharmaceutical reports first-third quarter (April 1-December 31, 2004) R&D highlights*. Ono Pharmaceutical Press Release 2005, Feb 4.

3. *Kyorin and LG Life Sciences sign memorandum of understanding for KRP-197*. DailyDrugNews.com (Daily Essentials) Aug 4, 2005.

KUC-7483

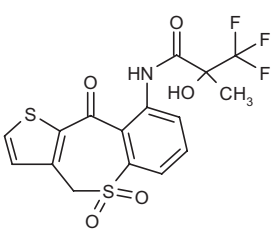
KUC-7483 is a β_3-adrenoceptor agonist currently being evaluated in phase I clinical trials as a treatment for urinary incontinence and OAB. Discovered by Kissei, Boehringer Ingelheim was granted exclusive rights to develop and market KUC-7483 worldwide, excluding Japan, Korea, China and Taiwan.

KUL-7211



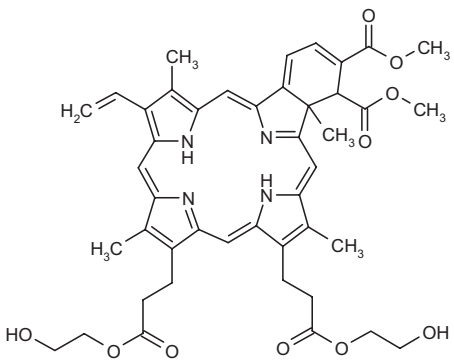
Kissei's KUL-7211 is a ureteral relaxant that acts through selective activation of β_2/β_3-adrenoceptors. It is in phase I trials for the relief of colic caused by urolithiasis and the acceleration of excretion of calculi.

KW-7158



KW-7158, a potassium channel activator, is currently undergoing phase II clinical trials for the oral treatment of urinary incontinence. Developed by Kyowa Hakko, KW-7158 is a tricyclic compound with a noncholinergic mechanism of action that works on sensory nerves in the bladder. KW-7158 is expected to have reduced side effects compared with the anticholinergic drugs currently used for the treatment of this disorder.

Lemuteporfin



Phase II clinical trials are in progress at QLT evaluating transurethral photodynamic therapy using the photosensitizer lemuteporfin (formerly QLT-0074) for the treatment of BPH.

Photodynamic therapy with lemuteporfin demonstrated activity in a multicenter, open phase I/II study in men with lower urinary tract symptoms (LUTS) related to BPH. In the study, 29 patients were administered lemuteporfin 0.2 mg injected transurethrally into each lobe of the prostate. After 30 min, the patients underwent transurethral laser light application at 689 nm. Patients were treated with escalating light doses (25, 50, 80, 120 and 150 J/cm^2) depending on safety. Maximum plasma lemuteporfin concentrations were seen immediately after light application and the drug was undetectable in most patients 2 h after application. The procedures were generally well tolerated. Five patients required catheterization for urinary retention. At 90 days, 14 of 21 patients had an improvement of at least 30% in American Urological Association (AUA) SI score and 8 had at least a 50% improvement (1).

1. Perez-Marrero, R. et al. *A phase I/II dose-escalation study to assess the safety, tolerability, and preliminary efficacy of transurethral photodynamic therapy with lemuteporfin in men with lower urinary tract symptoms due to benign prostatic hyperplasia*. J Urol 2005, 173(4, Suppl.): Abst 1556.

LI-301 (DMI-7958)

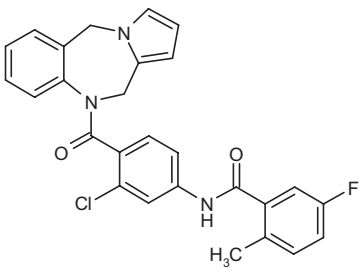
Enhance Biotech and DMI BioSciences are codeveloping a dual selective serotonin reuptake inhibitor (SSRI) and mu opioid receptor agonist for the treatment of pre-

mature ejaculation. Known as LI-301 at Enhance Biotech and as DMI-7958 at DMI, the product is in phase II clinical evaluation.

A definitive dose-ranging trial was commenced last year in preparation for a phase III study. The study is designed to evaluate the efficacy of three doses of LI-301/DMI-7968 on the IELT in subjects with premature ejaculation. The European study will involve over 80 couples and is an extension of promising earlier phase II work. Results are expected in the second quarter of this year (1).

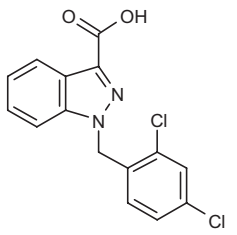
1. *Dose-ranging study for premature ejaculation compound LI-301*. DailyDrugNews.com (Daily Essentials) Oct 6, 2004.

Lixivaptan



Lixivaptan (VPA-985) is currently undergoing phase II clinical trials at CardioKine for the treatment of hyponatremia and water retention in patients with heart failure. Lixivaptan antagonizes the action of vasopressin on the V_2 receptors in the kidney collecting duct, causing a decrease in renal water reabsorption and urine osmolality and an increase in urine volume. The compound is expected to be beneficial in the treatment of disease states associated with water retention, such as congestive heart failure (CHF), cirrhosis and syndrome of inappropriate antidiuretic hormone (SIADH). CardioKine licensed lixivaptan from Wyeth in 2004.

Lonidamine, New Indication



Lonidamine (TH-070; Threshold Pharmaceuticals) is an indazole-3-carboxylic acid that inactivates hexokinase and interferes with glycolysis. The drug was originally launched almost 30 years ago for the treatment of solid tumors. The finding that glandular prostate epithelial cells, which are the cells that overgrow in benign prostatic hyperplasia (BPH), obtain energy solely from glycolysis suggested that lonidamine may show efficacy in this indication and it has advanced to phase III trials.

Researchers at the University of Bari, Italy, conducted a phase II clinical trial to determine the effects of oral lonidamine (150 mg once daily) in 30 patients with BPH. Compared to baseline, lonidamine given for 28 days decreased prostate volume by an average of 11.2%, improved mean maximum urine flow by 34.3% and decreased serum PSA levels and postvoid residual urine volume by an average of 17.8% and 52.5%, respectively. These improvements were still significant after 6 months of follow-up. Lonidamine was well tolerated and no drug-related adverse events were observed. Threshold Pharmaceuticals subsequently commenced a double-blind, randomized, placebo-controlled phase II clinical trial to determine the effects and safety of lonidamine in the management of BPH. The study will be conducted at 30 centers in the U.S. and will randomize approximately 200 BPH patients to receive placebo or one of four doses of lonidamine once daily for 28 days. With this study, the company hopes to confirm the results of the previous trial. The company has also begun a phase III trial as part of a registrational program for lonidamine. The study will measure the dosing, safety and efficacy of lonidamine in subjects with symptomatic BPH. The randomized, placebo-controlled, double-blind phase III trial will enroll men 50-80 years of age with symptomatic BPH across nearly 60 sites in selected European countries. Approximately 480 patients will participate in the study for up to 4.5 months. The primary objective is to evaluate the efficacy of lonidamine (50 or 150 mg) compared to placebo as measured by International Prostate Symptom Scores (I-PSS) in subjects with symptomatic BPH (1-3).

1. *New data confirm the benefits of TH-070 in symptomatic BPH*. DailyDrugNews.com (Daily Essentials) May 27, 2005.

2. *Threshold Pharmaceuticals initiates registrational program of TH-070 for treatment of benign prostatic hyperplasia*. Threshold Pharmaceuticals Press Release 2005, June 27.

3. *TH-070 begins phase III study for BPH*. DailyDrugNews.com (Daily Essentials) Aug 10, 2005.

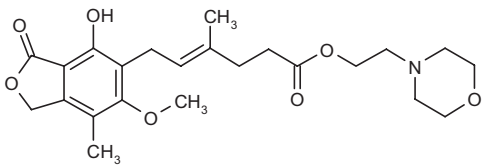
Original monograph – Drugs Fut 1979, 4(4): 265.

Additional References

Ditonno, P. et al. *Clinical evidence supporting the role of lonidamine for the treatment of BPH*. Rev Urol 2005, 7(Suppl. 7): S27.

Roehrborn, C.G. *The development of lonidamine for benign prostatic hyperplasia and other indications*. Rev Urol 2005, 7(Suppl. 7): S12.

Mycophenolate Mofetil, New Indication



Aspreva has commenced dosing in a pivotal phase III study evaluating mycophenolate mofetil (CellCept®) for the treatment of lupus nephritis. The phase III lupus management study aims to enroll 358 patients with biopsy-proven lupus nephritis at over 100 centers worldwide. The two-phase induction to the maintenance study is a randomized, open-label comparison of mycophenolate mofetil with the current standard of care cyclophosphamide for the first 6 months, followed by a double-blind comparison of mycophenolate mofetil with azathioprine for up to 3 years. This study will assess the efficacy and safety of mycophenolate mofetil in inducing and maintaining remission in patients with lupus nephritis. Results from the first phase of the study are expected in late 2006, with submission of a regulatory filing expected in mid- to late 2007. Mycophenolate mofetil, an IMP dehydrogenase (IMPDH) inhibitor, is an immunosuppressant used in combination with other immunosuppressive drugs for the prevention of rejection in patients receiving heart, kidney and liver transplants. It was first approved for use in combination therapy for the prevention of acute organ rejection in kidney transplantation in 1995 and has since been approved worldwide for the prevention of organ rejection in adult kidney, heart and liver transplantation. In some countries, it is also approved for pediatric kidney transplantation. Roche and Aspreva entered into a unique collaboration in October 2003 for Aspreva to further develop mycophenolate mofetil in autoimmune diseases. Aspreva has also initiated phase III studies of the immunosuppressant in myasthenia gravis and pemphigus vulgaris (1, 2).

Induction therapy with mycophenolate mofetil (up to 2 g/day) was compared to that with intravenous cyclophosphamide (given monthly) in a 1-year open study in 20 patients with severe lupus nephritis. Complete remission was achieved by 3 mycophenolate-treated and 1 cyclophosphamide-treated patients and partial remissions were also noted in 3 and 1 mycophenolate mofetil- and cyclophosphamide-treated patients, respectively. The probability of achieving partial remission at 9 months was higher with mycophenolate mofetil (80% *vs.* 25%) and the odds of failure at 11 months were higher with cyclophosphamide (73% *vs.* 20%) according to Kaplan-Meier analyses (3).

Mycophenolate mofetil demonstrated efficacy in treating 5 patients with diffuse proliferative lupus nephritis and chronic hepatitis C virus (HCV) infection. After failing other immunosuppressants, patients were treated with mycophenolate mofetil 500 mg b.i.d. (titrated up to 1500-2000 mg/day). Serum C-reactive protein fell and C3 levels were normalized in all patients, and an improvement of over 50% in proteinuria was seen in 4 patients. Responses lasted a mean of 8 months. Mycophenolate mofetil was well tolerated and prednisone doses were reduced in all patients (4).

Table VIII: Clinical studies of mycophenolate mofetil (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Nephritis, lupus	Open	Mycophenolate mofetil, 2 g/d x 1 [min.] y → Azathioprine	10	Mycophenolate mofetil was effective in patients with severe lupus nephritis. The risk of the recurrence of nephrotic syndrome was increased after withdrawal of mycophenolate mofetil	5
Nephritis, lupus	Open	Mycophenolate mofetil, 19-40 mg/kg/d x 3-20 mo + Prednisone, 0.3 mg/kg/d	12	Mycophenolate mofetil was effective in pediatric patients with lupus nephritis	6
Nephritis, lupus	Randomized Open	Mycophenolate mofetil, 2 [max.] g/d p.o. + Prednisolone, 1 mg/kg/d x 12 mo Cyclophosphamide i.v. 1x/mo + Prednisolone, 1 mg/kg/d x 12 mo	20	Preliminary results suggested that mycophenolate mofetil was as effective as cyclophosphamide as induction therapy in patients with severe lupus nephritis	7
Nephritis, lupus	Open	Mycophenolate mofetil, 2 g o.d. + Prednisone x 1 y → Mycophenolate mofetil, 1.5 g o.d. + Prednisone x 1 y	18	Mycophenolate mofetil combined with prednisone was effective in patients with lupus nephritis with a high activity index and partly effective in those with a high chronicity index	8
Nephritis, lupus	Open	Mycophenolate mofetil, 2 g/d p.o. x 8 [mean] mo + Prednisone	14	Mycophenolate mofetil was effective and should be considered for treating both new and resistant cases of lupus nephritis	9

1. *New phase III study of CellCept for myasthenia gravis*. DailyDrugNews.com (Daily Essentials) June 10, 2004.

2. *Phase III lupus management study of CellCept begins dosing*. DailyDrugNews.com (Daily Essentials) Aug 2, 2005.

3. Flores-Suárez, L.F., Villa, A.R. *Preliminary results of an open label randomised clinical trial comparing mycophenolate mofetil (MMF) vs. intravenous cyclophosphamide (IV-CYC) as induction therapy for severe lupus nephritis (LN)*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 1029.

4. Medina, F., Fuentes, J., Carranza, I., Portela, M., Barile, L., Fraga, A. *Mycophenolate mofetil: A potential treatment for diffuse prolipherative lupus nephritis (DPLN) and chronic hepatitis C virus infection*. 68th Annu Sci Meet Am Coll Rheumatol (Oct 16-21, San Antonio) 2004, Abst 1030.

5. Bullo, B., Boleslaw, R., Zbigniew, Z. *Mycophenolate mofetil (MMF) promising option in the treatment of lupus nephritis (LN) - 5-Year observation*. 42nd Congr Eur Renal Assoc - Eur Dialysis Transpl Assoc (June 4-7, Istanbul) 2005, Abst MP097 (Table VIII).

6. Caropreso, M.R., Malgieri, G., Nuzzi, F., Indaco, R., D'Armiento, M., Pecoraro, C., Balletta, M.M. *Mycophenolate mofetil (MMF) in the treatment of children with lupus nephritis (LN)*. 42nd Congr Eur Renal Assoc - Eur Dialysis Transpl Assoc (June 4-7, Istanbul) 2005, Abst MP100 (Table VIII).

7. Flores-Suarez, L.F., Villa, A.R. *Preliminary results of an open randomised clinical trial comparing mycophenolate mofetil (MMF) vs. intravenous cyclophosphamide (IV-CYC) as induction therapy for severe lupus nephritis (LN)*. Ann Rheum Dis 2004, 63(Suppl. 1): Abst THU0413 (Table VIII).

8. Grcevska, L.P., Dzikova, S.L., Zafirovska, K. *Mycophenolate mofetil/prednisone treatment in lupus nephritis with high histological activity and chronicity indexes*. 42nd Congr Eur Renal Assoc - Eur Dialysis Transpl Assoc (June 4-7, Istanbul) 2005, Abst MP090 (Table VIII).

9. Sanadgol, H. et al. *The efficacy of mycophenolate mofetil on treatment of lupus nephritis*. Nephrol Dial Transplant 2004, 19(5, Suppl.): Abst SP093 (Table VIII).

Original monograph – Drugs Fut 1995, 20(4): 356.

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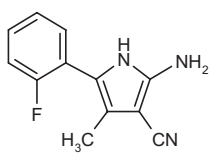
NM-100061

NM-100061 cream is in phase II clinical trials at NexMed for the topical treatment of premature ejaculation. NexMed is currently seeking a codevelopment partner for this compound.

NS-8



NS-8 is a pyrrole derivative in phase I trials in Europe and Japan for the treatment of OAB. The compound is a calcium-sensitive potassium channel opener that increases bladder volume without affecting the cardiovascular system by selectively inhibiting the afferent micturition reflex. Discovered by Nippon Shinyaku, Apogepha was granted exclusive development rights for Europe in 2003.

NX-1207

Data from Nymox's phase I/II and pivotal phase II U.S. trials of NX-1207 for BPH indicate that it has potential as a frontline treatment for this condition. The phase I/II trials in a total of 20 men aged 45-65 with BPH were designed to include only the more difficult cases which did not respond to optimal medical therapy. They studied the effect of NX-1207 over a period of 30 days. Patients were assessed for the drug effect on symptoms, such as frequent urination, urination at night, difficulty with urination, and for the drug effect on prostate size measurements. Overall there was a highly significant improvement in symptom scores and shrinkage in prostate size in the 30-day studies. Symptom score reduction and prostate size reduction both reached statistical significance. There were no significant adverse side effects from the drug. Following these promising results, NX-1207 was advanced to pivotal phase II testing in the U.S. One-year follow-up results from the multicenter phase II trials indicated statistically significant symptomatic improvement in subjects treated with NX-1207. Patients were evaluated using the American Urological Association (AUA) symptom score after 1 year. The mean AUA score in patients treated with NX-1207 showed an 8.8-point improvement compared to controls. This reached statistical significance and exceeded results from the most recent 30-day phase I/II study of NX-1207, in which there was a 6.9-point improvement in AUA score. Subjects followed for up to 2 years post-treatment showed even further statistically significant symptom improvement of 9.3 points (1-8).

1. *NX-1207 shows potential as a front-line treatment for BPH in phase I/II trials*. DailyDrugNews.com (Daily Essentials) July 2, 2004.

2. *Phase II protocol for NX-1207 accepted by FDA*. DailyDrugNews.com (Daily Essentials) July 19, 2004.

3. *Further positive phase I/II data for NX-1207 in BPH*. DailyDrugNews.com (Daily Essentials) Aug 2, 2004.

4. *Positive one-year data for NX-1207 in BPH*. DailyDrugNews.com (Daily Essentials) Sept 13, 2004.

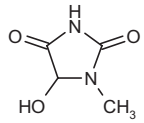
5. *NX-1207 shows promise for BPH*. DailyDrugNews.com (Daily Essentials) March 29, 2005.

6. *NX-1207 shows long-term efficacy in improving the symptoms of BPH*. DailyDrugNews.com (Daily Essentials) June 14, 2005.

7. *Interim safety results of pivotal study of NX-1207 for BPH*. DailyDrugNews.com (Daily Essentials) Aug 10, 2005.

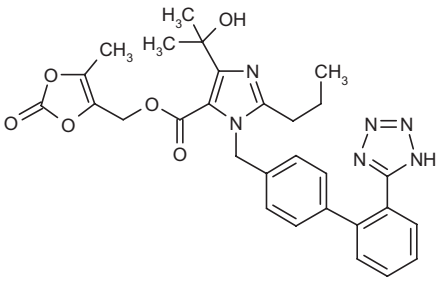
8. *Update on pivotal trial of Nymox's NX-1207 for benign prostatic hyperplasia*. Nymox Pharmaceutical Corp. Press Release 2005, Sept 14.

NZ-419



NZ-419 is an antioxidant in phase II clinical trials at Nippon Zoki for the prevention of advanced renal failure.

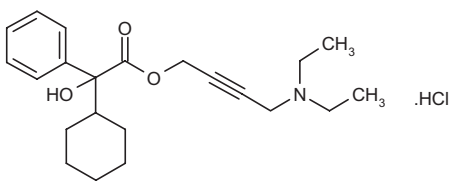
Olmesartan Medoxomil, New Indication



Olmesartan medoxomil, an angiotensin AT_1 antagonist discovered by Sankyo, is currently available in several countries, including the U.S., the U.K. and Japan, for the oral treatment of hypertension. Phase III clinical trials are under way to evaluate its use in the treatment of diabetes-related kidney dysfunction and chronic glomerulonephritis.

Original monograph – Drugs Fut 1997, 22(11): 1205.

Oxybutynin, Gel



Antares Pharma has initiated a phase II trial of oxybutynin-based Anturol™ (AP-1034) for the treatment of OAB. The randomized, open-label, dose-ranging trial is being conducted in Germany and will enroll 48 volunteers. Three different doses will be tested over 20 days. The trial is expected to be completed before the end of December 2005. A phase III trial is anticipated for early 2006, and would be followed by an NDA filing. Anturol™ utilizes Antares Pharma's proprietary Advanced Transdermal Delivery (ATD™) hydroalcoholic gel technology designed to allow delivery of active substances across the skin using a combination of permeation enhancers. The oxybutynin formulation is a cosmetic-quality, clear and odorless gel designed to be rapidly absorbed through the skin following once-a-day application on the abdomen, shoulders or thighs (1, 2).

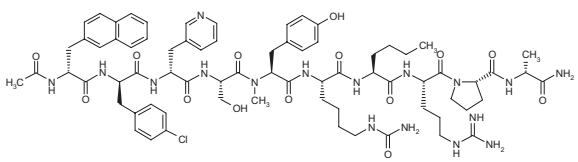
1. *Antares Pharma files IND for oxybutynin ATD.* DailyDrugNews.com (Daily Essentials) March 21, 2005.

2. *Anturol begins phase II study for overactive bladder syndrome.* DailyDrugNews.com (Daily Essentials) Sept 12, 2005.

Oxybutynin, Transvaginal Ring

Barr Laboratories is developing a transvaginal ring formulation of oxybutynin for the treatment of urinary incontinence. Currently in phase II clinical development, the company obtained worldwide marketing rights to the product from Schering AG in 2004.

Ozarelix



AEterna Zentaris's fourth-generation LHRH antagonist ozarelix (D-63153, SPI-153), administered as a depot formulation, is currently undergoing three clinical trials in Europe and the U.S. The trials include one phase II trial in Europe in hormone-sensitive prostate cancer and another phase II trial in Europe in benign prostatic hyperplasia, together with a phase I/II study in the U.S. in hormone-sensitive prostate cancer that was initiated in collaboration with North American partner Spectrum Pharmaceuticals. The open-label, multicenter phase II trial in prostate cancer is designed to evaluate the effects of ozarelix on hormone levels, in particular testosterone, as well as objective antitumor effects, in 48 patients. In a prior phase I trial evaluating multiple doses in 18 male volunteers, ozarelix injections were well tolerated and demonstrated an immediate and dose-dependent suppression of plasma testosterone levels, reaching castrate levels within the first 12 h of application. The duration of suppression was dose-dependent, with a single injection of the highest dose leading to testosterone suppression for 27 days. The multicenter phase II trial to evaluate the safety and efficacy of ozarelix as a treatment for patients with BPH is designed to evaluate both objective parameters, such as improvement in urine flow and shrinkage of prostate volume, and various symptoms of BPH over a

period of several months. The U.S. phase I/II study will provide additional information regarding the optimum dose range for testosterone suppression. Ozarelix, which allows for chronic intermittent treatment, could improve clinical symptoms of these diseases and may have advantages over other LHRH antagonists related to improved solubility and decreased potential for histamine release. AEterna Zentaris granted an exclusive license to Spectrum in August 2004 to develop and market ozarelix for all potential indications in North America (including Canada and Mexico) and India. AEterna Zentaris received an upfront payment and is eligible to receive milestone payments and royalties. AEterna Zentaris retains exclusive rights for the rest of world and will share with Spectrum upfront and milestone payments, royalties or profits from potential sales in Japan (1-11).

1. *AEterna Zentaris unveils new name, progress and plans*. DailyDrugNews.com (Daily Essentials) June 1, 2004.

2. *Spectrum acquires North American, Indian rights to D-631153*. DailyDrugNews.com (Daily Essentials) Aug 17, 2004.

3. *Spectrum Pharmaceuticals reports Q2 R&D highlights*. Spectrum Pharmaceuticals Press Release 2004, Aug 16.

4. *European phase II study of SPI-153 for hormone-dependent prostate cancer*. DailyDrugNews.com (Daily Essentials) April 14, 2005.

5. *SPI-153 enters phase II trial for BPH*. DailyDrugNews.com (Daily Essentials) April 18, 2005.

6. *AEterna Zentaris reports Q1 R&D highlights*. AEterna Zentaris Press Release 2005, May 4.

7. *Phase I/II prostate cancer study of SPI-153 gets green light*. DailyDrugNews.com (Daily Essentials) June 2, 2005.

8. *Ozarelix begins U.S. phase I/II trial for hormone-dependent prostate cancer*. DailyDrugNews.com (Daily Essentials) July 28, 2005.

9. *Enrollment completed in phase II study of ozarelix for prostate cancer*. DailyDrugNews.com (Daily Essentials) Aug 31, 2005.

10. *AEterna Zentaris reports Q2 R&D highlights*. AEterna Zentaris Press Release 2005, Aug 3.

11. *Spectrum Pharmaceuticals reports Q2 R&D highlights*. Spectrum Pharmaceuticals Press Release 2005, Aug 9.

Pamirosin

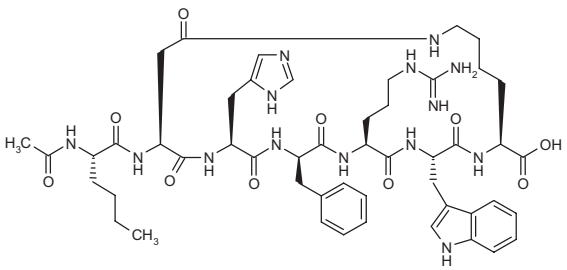
Schwarz Pharma has discontinued its phase II trial with the uroselective α_{1A}-adrenoceptor antagonist pamirosin (SPM-969) for the treatment of BPH due to unclear preclinical findings. As the preclinical findings need further evaluation, the program has been placed on hold until final resolution (1). The compound was licensed from Ranbaxy (RBx-2258) in 2002 for the U.S., Europe and Japan.

1. *Discontinuation of phase II pamirosin trial for BPH*. DailyDrugNews.com (Daily Essentials) Nov 11, 2004.

PD-217014

The calcium channel modulator PD-217014 was last reported to be in phase II clinical trials at Pfizer for the treatment of overactive bladder (OAB) and irritable bowel syndrome (IBS).

PT-141



King Pharmaceuticals and Palatin Technologies have entered into a strategic alliance to jointly develop and commercialize Palatin's PT-141 for the treatment of male and female sexual dysfunction. PT-141, a synthetic peptide analogue of α-MSH, is the first melanocortin receptor agonist under development to treat sexual dysfunction.

Table IX: Clinical studies of PT-141 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Erectile dysfunction	Open	Sildenafil, 50-100 mg Sildenafil, 50-100 mg + PT-141, 7.5-10 mg i.n.	32	Combining PT-141 with sildenafil was more effective than sildenafil alone in increasing the duration of erectile activity in patients with erectile dysfunction. No serious or significant adverse events were reported with any study regimen	4
Erectile dysfunction	Randomized Crossover	Sildenafil, 25 mg + PT-141, 7.5 mg i.n. Sildenafil, 25 mg + Placebo Placebo		Sildenafil combined with PT-141 was safe, well tolerated and effective in patients with erectile dysfunction	5

Varying doses of the new chemical entity are being evaluated in phase II trials in men with erectile dysfunction (ED) and women experiencing female sexual dysfunction (FSD). The mechanism of action of PT-141 may offer benefits over current products for the treatment of ED because it acts on the pathway that controls sexual function without acting directly on the vascular system. Unlike PDE5 inhibitors which are contraindicated in patients taking nitrates, clinical data indicate that PT-141 should not have any drug interactions with nitrates. The nasal formulation of PT-141 currently under development appears to result in a rapid onset of action. Under their agreement, Palatin has granted King a co-exclusive license to PT-141 in North America and an exclusive right to collaborate on the licensing or sublicensing of PT-141 outside North America. King and Palatin will share all development and marketing costs and all net profits derived from net sales of PT-141 in North America based on an agreed percentage. King and Palatin will seek a partner for PT-141 for territories outside North America and will jointly share in revenues generated from those territories. The companies are conducting two double-blind, placebo-controlled phase IIb trials of PT-141 in patients with ED: a phase IIb trial to evaluate the safety and efficacy of PT-141 in 560 nondiabetic patients suffering from mild to severe ED, which is expected to conclude in mid-2006, and another study in 265 diabetic patients with ED, which is expected to conclude in the second half of 2006. Both trials will involve an at-home 3-month treatment period and a range of PT-141 intranasal doses between 5 and 15 mg (1-3).

A recent clinical trial evaluated the potential benefits of combining sildenafil citrate (Viagra®) with PT-141 in the treatment of ED. Thirty-two patients were given sildenafil (50 or 100 mg) alone or combined with intranasal PT-141 (7.5 or 10 mg), and their erectile activity was monitored for 6 h after dosing in the absence of visual sexual stimulation. Compared to sildenafil alone, the combination of sildenafil plus PT-141 increased the duration of erectile activity by an average factor of 5.3 without inducing any serious or significant adverse events (4) (Table IX).

In another randomized, crossover study, erectile responses in men with ED were significantly enhanced when intranasal PT-141 7.5 mg was added to treatment with sildenafil citrate 25 mg p.o. Patients enrolled in the study had responded to sildenafil and received sildenafil and PT-141, sildenafil plus placebo spray and placebo tablets plus placebo spray. During the 6-h postdose period, erectile activity was assessed during two 30-min episodes of visual sexual stimulation. PT-141 was found to improve RigiScan® findings compared to sildenafil alone and did not increase or cause new adverse events (5) (Table IX).

1. *King and Palatin to jointly develop, commercialize PT-141*. DailyDrugNews.com (Daily Essentials) Aug 18, 2004.

2. *Phase IIa trials of PT-141 in FSD and ED complete enrollment*. DailyDrugNews.com (Daily Essentials) Jan 18, 2005.

3. *Phase IIb studies begin for PT-141 for erectile dysfunction*. DailyDrugNews.com (Daily Essentials) Aug 9, 2005.

4. *PT-141 reported to increase the efficacy of sildenafil in ED*. DailyDrugNews.com (Daily Essentials) March 24, 2005.

5. Diamond, L.E. et al. *Co-administration of low doses of intranasal PT-141, a melanocortin receptor agonist, and sildenafil to men with erectile dysfunction results in an enhanced erectile response*. J Urol 2005, 173(4, Suppl.): Abst 1057.

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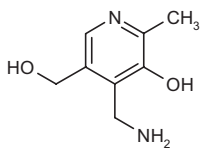
Pyridoxamine



Pyridoxamine, a small molecule that has been shown to be highly active against multiple pathways of advanced glycation end product (AGE) formation, is currently in phase III development in the U.S. by BioStratum (Pyridorin™) for the oral treatment of diabetic nephropathy. The product is exclusively licensed to Kowa (K-163) for development, manufacturing and marketing in Japan

Table X: Clinical studies of pyridoxamine (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Diabetes, Nephropathy, diabetic	Randomized Double-blind Multicenter Pooled/meta-analysis	Pyridoxamine, 250 [max.] mg b.i.d. + Standard therapy x 6 mo Placebo	84	Pyridoxamine delayed renal disease progression and was thus beneficial in patients with type 1 or 2 diabetes with nephropathy	2, 3
Diabetes, Nephropathy, diabetic	Randomized Double-blind Multicenter	Pyridoxamine, 50 mg b.i.d. p.o. + Standard therapy x 6 mo Placebo + Standard therapy x 6 mo	128	Pyridoxamine was active, safe and well tolerated in patients with type 1 or type 2 diabetes and overt nephropathy	4

and other Asian markets; in Japan it is in phase I clinical testing. In 2002, the FDA granted fast track status to pyridoxamine for the treatment of diabetic kidney disease.

The results of two multicenter, randomized, double-blind, placebo-controlled trials have demonstrated the benefit of pyridoxamine treatment in patients with type 1 or 2 diabetes and overt nephropathy. The studies included patients with mild to moderate or moderate to severe nephropathy who received placebo or escalating doses of pyridoxamine (50 mg b.i.d. for 2 weeks, 100 mg b.i.d. for 2 weeks and 250 mg b.i.d. for 20 weeks). Two weeks after ending treatment, urinary TGF-β1 levels had declined by 24.6% from baseline in pyridoxamine-treated patients, while these levels were increased by 51.8% in placebo-treated patients. The preservation of renal function with pyridoxamine appeared to be due at least in part to reductions in TGF-β1 levels (1).

1. Wassenberg, J.J., Fox, J.W., Degenhardt, T.P., Szabo, J., Khalifah, R.G. *Pyridoxamine (Pyridorin™) reduces urinary TGF-beta1 in phase 2 clinical studies (PYR-205/207) on type 1 and type 2 diabetic patients with overt nephropathy*. J Am Soc Nephrol 2004, 15: Abst SU-PO914.

2. Distiller, L.A., Malik, R.A., Degenhardt, T.P., Szabo, J.R., Khalifah, R.G., Schotzinger, R.J. *Clinical investigation of pyridoxamine in type 1 and type 2 diabetic patients with overt diabetic nephropathy (PYR-205/207)*. 40th Annu Meet Eur Assoc Study Diabetes (EASD) (Sept 5-9, Munich) 2004, Abst 232 (Table X).

3. McGill, J.B., Degenhardt, T.P., Szabo, J.R., Khalifah, R.G., Schotzinger, R.J. *A phase 2 clinical investigation of pyridoxamine (Pyridorin) in type 1 and type 2 diabetic patients with overt diabetic nephropathy (PYR-205/207)*. Diabetes 2004, 53(Suppl. 2): Abst 581-P (Table X).

4. Bell, D.S.H. et al. *Investigation of the safety and efficacy of pyridoxamine (Pyridorin ™) in patients with diabetic nephropathy (PYR-206)*. 64th Annu Meet Sci Sess Am Diabetes Assoc (ADA) (June 4-8, Orlando) 2004, Abst 504-P (Table X).

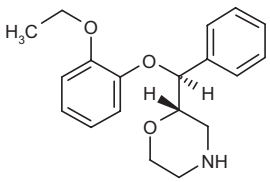
R-873

R-873 is in early clinical development at Roche for the treatment of erectile dysfunction (ED). The drug is a small-molecule G-protein-coupled receptor (GPCR) agonist.

R-1484

A GPCR modulator from Roche, R-1484 is being evaluated in phase I clinical trials for the treatment of stress urinary incontinence.

(+)-(*S,S*)-Reboxetine



(+)-(*S,S*)-Reboxetine is a norepinephrine reuptake inhibitor developed by Pfizer and presently in phase II clinical trials for the treatment of stress urinary incontinence.

REC-0545

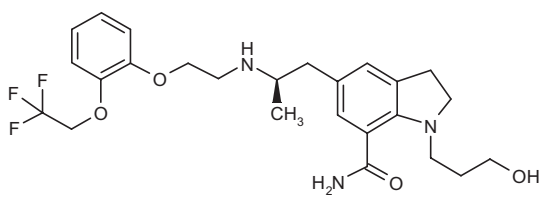
Recordati is conducting proof-of-concept clinical trials with REC-0545, a potent and selective 5-HT_{1A} receptor antagonist with potential for the treatment of OAB/urinary incontinence. REC-0545 increases bladder volume capacity without blunting bladder contractility, in contrast to anticholinergics.

Sevelamer Carbonate

Genzyme initiated a short-term clinical trial of sevelamer carbonate in patients with end-stage renal disease to evaluate the product's equivalence to Renagel® (sevelamer hydrochloride). The company also anticipates launching a study later this year to evaluate sevelamer carbonate's potential to benefit patients with chronic kidney disease (1).

1. *Genzyme Corp. reports Q1 R&D highlights*. Genzyme Corp. Press Release 2005, April 21.

Silodosin



Recordati has entered into a license agreement with Kissei for the development and marketing of silodosin (KMD-3213), a new compound discovered by Kissei for the treatment of symptoms associated with BPH, in all

European countries. Recordati obtains exclusive rights to silodosin for Europe, where it will complete its clinical development (now in phase II) and handle marketing and commercialization. Silodosin is a uroselective α_{1A}-adrenoceptor antagonist which relaxes smooth muscles in the prostate and the urethra, thereby decreasing urinary resistance and alleviating symptoms associated with BPH. An NDA has been filed for the drug in Japan, where it has been developed in collaboration with Daiichi Pharmaceutical. Watson is developing the product for the North American market and has commenced enrollment for two large phase III studies to evaluate the efficacy and safety of silodosin 8 mg once daily in patients with signs and symptoms of BPH. These multicenter, double-blind, placebo-controlled trials, which will run for 12 weeks, will evaluate a total of 1,200 patients with signs and symptoms of BPH in the U.S. The primary objective is to demonstrate that the effectiveness of 8 mg silodosin given once daily for 12 weeks is superior to placebo for the relief of BPH symptoms, as measured by a baseline-to-endpoint change in the total score of the I-PSS. A long-term open-label extension study will also be available for patients who complete these double-blind studies. Watson plans to submit an NDA for silodosin in 2008 (1-3).

In a multicenter, double-blind phase III trial in Japan, 457 patients with BPH and LUTS were randomized to receive silodosin 4 mg b.i.d., tamsulosin 0.2 mg once daily or placebo for 12 weeks. The change in I-PSS, which was the primary efficacy measure, was –8.3 with silodosin, as compared to –6.8 and –5.3 with tamsulosin and placebo, respectively. More silodosin-treated patients achieved a reduction of at least 25% in I-PSS (76.4%, 65.6% and 50.6%, respectively). Silodosin also significantly improved quality of life compared to placebo. Hypotension-related adverse events occurred with similar frequency in the silodosin and tamsulosin groups, while abnormal ejaculation occurred more often with silodosin and was the most frequent adverse event in that group (4).

1. *Recordati to develop silodosin for BPH in Europe*. DailyDrugNews.com (Daily Essentials) Dec 15, 2004.

2. *Recordati acquires Merckle's branded pharmaceutical business in Germany*. DailyDrugNews.com (Daily Essentials) Jan 20, 2005.

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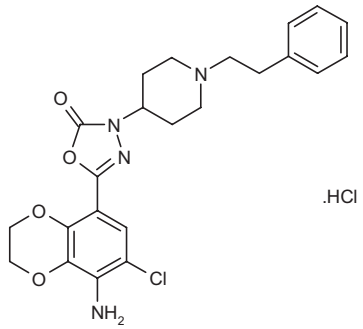
4. Yoshida, M. et al. *Silodosin, a new effective alpha1A-adrenoceptor selective antagonist for the treatment of benign prostatic hyperplasia: Results of a phase 3 randomized, placebo-controlled, double-blind study*. J Urol 2005, 173(4, Suppl.): Abst 1642.

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

SL-65.0155



The 5-HT_4 partial agonist SL-65.0155 is in phase II trials at Sanofi-Aventis for the treatment of Alzheimer's-type dementia and urge urinary incontinence.

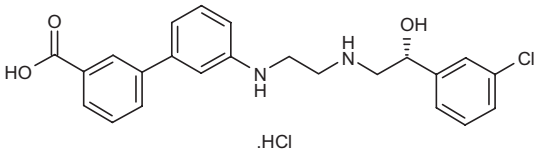
SLV-320

SLV-320, an adenosine A_1 receptor antagonist from Solvay, is being tested in phase II trials as a potential therapeutic for acute congestive heart failure and renal failure.

SLx-2101

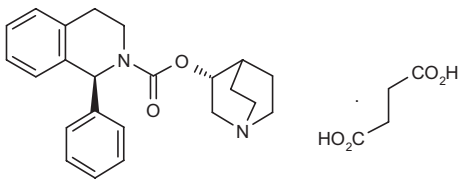
Surface Logix recently conducted a phase I trial for SLx-2101, a novel, selective, oral PDE5 inhibitor progressing into phase II development for male erectile dysfunction and pulmonary arterial hypertension (PAH). The single-center, randomized, double-blind study evaluated the safety, tolerability, pharmacokinetics and pharmacodynamics of orally administered SLx-2101 in healthy male subjects. SLx-2101 was well tolerated under the test conditions. Pharmacokinetic data from the five dose levels demonstrated the rapid appearance of SLx-2101 and the active metabolite SLx-2081 in plasma, levels exceeding the IC_{50} for PDE5 inhibition for at least 36 h at all dose levels. This study also demonstrated efficacy in established models of endothelial function (peripheral arterial tone and erectile function). An additional repeated-dose phase I study and a phase IIa study in erectile dysfunction are scheduled for the end of 2005, with a phase IIa study in PAH scheduled for next year. SLx-2101 was designed using Surface Logix's proprietary small-molecule Pharmacomer™ Technology. Numerous preclinical animal models have demonstrated that it is a highly potent and selective compound with rapid cellular and tissue response and an extended duration of action.

Solabegron Hydrochloride



Solabegron hydrochloride is a β_3-adrenoceptor agonist developed by GlaxoSmithKline and currently in phase II trials for the treatment of type 2 diabetes and in early clinical trials for the treatment of overactive bladder (OAB).

Solifenacin Succinate



An investigational muscarinic antagonist, solifenacin succinate is indicated for the treatment of OAB. Solifenacin works to decrease bladder activity by inhibiting contraction of the smooth muscle wall surrounding the bladder. Micturition normally occurs following stimulation of acetylcholine muscarinic M_3 receptors within the detrusor muscle wall. As a potent and selective muscarinic receptor antagonist, solifenacin acts specifically at the M_3 receptor site. Initial data have shown solifenacin to be more bladder-selective than its predecessors. It is this selective mode of action that gives solifenacin the potential to limit commonly experienced anticholinergic side effects. These developments could translate into higher patient compliance with the potential for better long-term results. Solifenacin has been shown to have a favorable risk/benefit ratio. At a once-daily oral dose of 5 mg/day, clinical data have shown solifenacin to be effective in reducing the symptoms of OAB, with an incidence of dry mouth comparable to that associated with placebo. Results from phase I, II and III clinical trials have shown solifenacin to have a promising efficacy and safety profile for the treatment of overactive bladder. First launched in the E.U. in 2004, Astellas Pharma launched solifenacin (Vesicare®) in the U.S. early this year following approval in November 2004 for the treatment of OAB with symptoms of urgency, frequency and urge incontinence. It is marketed and copromoted by the company's U.S. subsidiary and partner GlaxoSmithKline. Astellas promotes the drug targeting specialists such as urologists and gynecologists, while in the primary care market promotion will be conducted mainly by GSK and partly by Astellas. In Japan, an NDA was filed with the Ministry of Health, Labor and Welfare in August 2004 (1-9).

Recent data from a landmark clinical trial discussed during a satellite symposium at the 2005 Congress of the European Association of Urology revealed that solifenacin is superior to tolterodine in the treatment of OAB. The STAR study was a multicenter, double-blind clinical trial conducted at 117 European sites that randomized 1,355 OAB patients to receive a flexible dose regimen of once-daily solifenacin (5 or 10 mg/day) or extended-release tolterodine (tolterodine ER, 4 mg once daily) for 12 weeks. Compared to tolterodine ER, solifenacin showed similar efficacy in reducing micturition frequency and the number of nocturia episodes, but was associated with significantly greater reductions in volume voided per micturition, frequency of urge incontinence, number of urgency episodes and number of incontinence episodes. At the end of the study, more solifenacin-treated patients showed a reduction of at least 50% in incontinence episodes (74.1% *vs.* 66.5%) or were restored to continence (58.7% *vs.* 48.9%); these effects were associated with a lower need for incontinence pads and greater reductions in urge incontinence. Solifenacin was estimated to be 65% more effective than tolterodine at treating urge incontinence, which is considered to be the most troublesome symptom of OAB. The greater benefits found with solifenacin also resulted in a better patient perception of improvements in their bladder condition. Overall, 48% of patients given solifenacin requested the dose be increased from 5 to 10 mg/day after 4 weeks' treatment due to insufficient efficacy. Dose increase was also requested by 51% of patients given tolterodine ER, but this was not available during the study. No significant differences were found between the safety profiles of solifenacin and tolterodine. Both drugs were well tolerated, and most adverse events were mild or moderate (10, 11).

Twenty-four young and 23 elderly healthy volunteers participated in an open-label, crossover clinical trial that determined the effects of age and gender on the pharmacokinetics of solifenacin succinate (5 or 10 mg once daily for 14 days). Both the peak plasma concentration and the area under the curve of solifenacin increased with time in both study populations. No clinically relevant differences were found between elderly and young subjects, or between males and females, for peak plasma concentration, area under the curve, time to peak plasma concentration and half-life of solifenacin. The authors of the study did not recommend the introduction of solifenacin dose adjustments due to age or gender (12).

The long-term efficacy and safety of solifenacin succinate in the treatment of incontinence associated with OAB were evaluated using pooled data from two pivotal double-blind, randomized clinical trials that administered solifenacin (5 or 10 mg p.o.) or placebo once daily to 1,640 patients. After 12 weeks of treatment, a subset of 943 patients with an average of 2.6-3.0 incontinence episodes per day at baseline showed significant improvements in their number of incontinence episodes with both solifenacin doses compared to placebo. The percentage of patients who became continent at the end of the study

was also greater with solifenacin (51% *vs.* 38% with placebo). Open-label administration of solifenacin for another 40 weeks in an extension study further reduced the number of incontinence episodes and increased the continence rate. Most adverse events were mild or moderate, the most common being dry mouth (13) (Table XI).

Data from two phase III studies and a long-term extension study in patients with OAB show that treatment with solifenacin significantly improved the patients' quality of life. The studies were multicenter, randomized, double-blind trials lasting 12 weeks and included a total of 1,984 patients. The extension study included 1,637 of these patients who were treated for up to 40 additional weeks. In the phase III studies, the change from baseline with either solifenacin 5 or 10 mg once daily was significantly superior to that with placebo on 5 of 10 domains of the King's Health Questionnaire. When the data were pooled, both doses provided significant improvement over placebo in 9 of 10 domains (general health perception, incontinence impact, role limitations, physical limitations, social limitations, emotions, sleep/energy, severity measures and symptom severity; only the personal relationships domain was not affected). In the extension study, improvements in 9 of the 10 domains ranged from 35% to 48% with solifenacin. The incremental improvement during the extension study accounted for 28-35% of the overall improvement from baseline of the 12-week studies (14) (Table XI).

Pooled data from four randomized, placebo-controlled phase III clinical trials were used to determine the effects of solifenacin in 975 OAB patients without incontinence at baseline. Compared to placebo, solifenacin (5 and 10 mg once daily) given for 12 weeks significantly reduced the average number of urgency episodes and micturitions per day and increased the mean volume voided per micturition. A solifenacin dose of 10 mg/day also significantly reduced mean number of nocturia episodes per day. The percentage of patients who achieved resolution or normalization of urgency, frequency or nocturia was greater in the two solifenacin study groups than in the placebo group (15).

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

Indication	Design	Treatments	n	Conclusions	Ref.
Overactive bladder	Randomized Double-blind Multicenter Pooled/meta-analysis	Solifenacin, 5 mg p.o. o.d. x 52 wks Solifenacin, 10 mg p.o. o.d. x 52 wks Placebo	943	Long-term administration of solifenacin for up to 1 year was well tolerated and improved incontinence in patients with overactive bladder	13
Overactive bladder	Pooled/meta-analysis	Solifenacin, 5 mg o.d. x 12 wks Solifenacin, 10 mg o.d. x 12 wks Placebo	1984	Solifenacin significantly improved the quality of life for patients with overactive bladder	14
Overactive bladder	Randomized Double-blind Pooled/meta-analysis	Solifenacin, 5 mg p.o. o.d. x 12 wks Solifenacin, 10 mg p.o. o.d. x 12 wks Tolterodine, 2 mg p.o. b.i.d. x 12 wks Placebo	1874	Solifenacin was significantly more effective than tolterodine or placebo in reducing urgency in patients with overactive bladder and mild, moderate or severe frequency	16
Overactive bladder	Randomized Double-blind Multicenter	Solifenacin, 5 mg o.d. x 12 wks (n=299) Solifenacin, 10 mg o.d. x 12 wks (n=307) Placebo (n=301)	907	Both doses of solifenacin significantly improved urinary frequency, urgency and incontinence and were well tolerated,while 10 mg reduced the episodes of nocturia in patients with overactive bladder	18
Overactive bladder	Randomized Double-blind	Solifenacin, 5 mg 1x/d (n=548) Solifenacin, 10 mg 1x/d (n=550) Placebo 1x/d (n=526)	1624	Solifenacin therapy was associated with reductions in urgency episodes and was effective in patients with overactive bladder	19
Overactive bladder	Double-blind Open	Solifenacin, 5 mg p.o. o.d. x 40 wks Solifenacin, 5 mg p.o. o.d. x 4 wks → 5 mg p.o. o.d. x 36 wks Solifenacin, 5 mg p.o. o.d. x 4 wks → 10 mg p.o. o.d. x 36 wks	1802	Solifenacin was effective and well tolerated and showed higher patient satisfaction in patients with overactive bladder	20
Overactive bladder	Randomized Double-blind Multicenter Pooled/meta-analysis	Solifenacin, 5 mg p.o. o.d. x 12 wks (n=552) Solifenacin, 10 mg p.o. o.d. x 12 wks (n=554) Placebo (n=534)	1640	Solifenacin improved quality of life and reduced symptoms in patients with overactive bladder	21

Pooled results from two double-blind, randomized, placebo-controlled trials indicate that solifenacin reduces urgency episodes in patients with OAB regardless of baseline severity. In the 12-week trials, patients were treated with placebo, solifenacin (5 or 10 mg b.i.d.) or tolterodine (2 mg b.i.d.). Among the 1,874 patients experiencing urgency at baseline, tolterodine and solifenacin significantly reduced urgency episodes compared with placebo, with differences of –0.64, –0.99 and –1.21 for tolterodine and the solifenacin 5- and 10-mg doses, respectively. Both solifenacin doses were associated with significant reductions in subsets of patients with mild, moderate and high frequency at baseline; the same was not true for tolterodine. The differences from placebo among patients with high baseline urgency episode frequency were –1.03, –2.48 and –2.71 in the tolterodine and the solifenacin 5- and 10-mg dose groups, respectively (16) (Table XI).

A pharmaceutical composition for transdermal delivery of solifenacin succinate has been claimed for the treatment of urinary incontinence. The claim further embodies the use of at least one fatty acid ester or terpene, the inclusion of which was discovered to substantially augment the permeability of such a composition (17).

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van Kerrebroeck, P. et al. *Antimuscarinic therapy for overactive bladder syndrome: Possible benefits of switching to solifenacin*. 35th Annu Meet Int Continence Soc (Aug 26-Sept 1, Montreal) 2005, Abst 571.

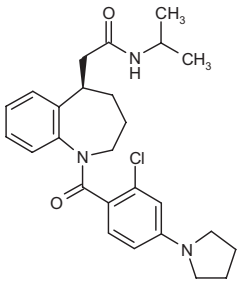
SOU-001 (AA-10020)

The U.K.'s Medicines and Healthcare products Regulatory Agency (MHRA) has approved the initiation of a placebo-controlled, randomized phase II study of SOU-001 (AA-10020), which is targeted for the oral treatment of stress urinary incontinence (SUI). The phase II study will evaluate efficacy, safety and tolerability of single oral doses of SOU-001 in female volunteers with SUI. SOU-001 is the first successful demonstration of Sosei's DRP® (Drug Reprofiling Platform®). Previously it was developed up to phase II for a certain cardiovascular indication by a Japanese pharmaceutical company. Sosei's DRP®, in collaboration with a U.K.-based profiling partner (Arachnova), identified SUI as its new potential indication in 2001. Sosei has now acquired exclusive worldwide rights for the development and commercialization of this compound. Since reprofiling, Sosei has conducted an encouraging volunteer study to validate the effect using the intravenous route, and has undertaken toxicological studies and pharmaceutical studies to develop an oral formulation. A phase I safety, tolerability and pharmacokinetic study in volunteers was completed in 2004 which confirmed SOU-001 could be used as an oral treatment (1, 2).

1. *Sosei's phase I trial of SOU-001 cleared to begin in U.K.* DailyDrugNews.com (Daily Essentials) June 17, 2004.

2. *Sosei cleared to begin U.K. phase II study for SOU-001.* DailyDrugNews.com (Daily Essentials) June 22, 2005.

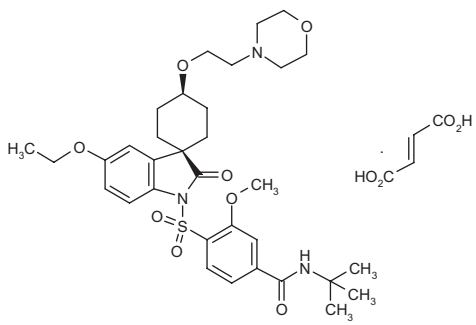
SOU-003 (OPC-51803)



Sosei has inlicensed a urology compound, OPC-51803 (SOU-003), from Otsuka. Sosei has been granted the rights to develop and commercialize the compound globally, except for Japan and other Asian countries where Otsuka retains the rights. Sosei also has copromotion rights in Japan, while Otsuka retains a copromotion option in the U.S. and Europe. SOU-003 is an orally active small molecule with selective vasopressin V_2 receptor-agonist activity which increases water reabsorption in the kidneys. The safety of SOU-003 has been confirmed in several phase I studies in healthy volunteers and in various types of incontinence patients by Otsuka. Sosei plans to begin a phase II study to select the optimal dose in nocturia and nocturnal enuresis patients during the second half of 2005. The compound is expected to reduce the urine production rate at night, which should avoid interruptions to sleep and improve the quality of life of sufferers. A small-molecule oral treatment such as SOU-003, with higher bioavailability than the currently available treatment desmopressin, is likely to provide a treatment with a more reliable effect. SOU-003 also has the potential for other indications, including diabetes insipidus. The agreement provides the right for Sosei to explore all indications (1).

1. *Sosei inlicenses urology drug from Otsuka*. DailyDrugNews.com (Daily Essentials) Feb 25, 2005.

SR-121463



Sanofi-Aventis's vasopressin V_2 receptor antagonist SR-121463 (satavaptan fumarate) is currently undergo-

ing phase III clinical trials for the treatment of hyponatremia in patients with cirrhotic ascites.

The HypoCAT phase IIb study of SR-121463 in 110 hyponatremic patients with cirrhotic ascites met its primary endpoint of change in serum sodium levels on day 5 compared to baseline. The NormoCAT phase IIb study in 148 normonatremic patients with cirrhotic ascites met its primary endpoint of change in body weight gain at the end of treatment compared to baseline. In both studies, SR-121463 induced an increase in 24-h urine volume as compared to placebo. Pooled safety data from HypoCAT and NormoCAT confirm the good safety profile observed in phase IIa testing (1).

SR-121463 was found to increase serum sodium levels in a phase II study in patients with syndrome of inappropriate antidiuretic hormone secretion (SIADH). Patients first received placebo or doses of 25 or 50 mg once daily for up to 5 days and then open-label SR-121463 25 or 50 mg once daily for 23 days. This was followed by open-label treatment with 12.5, 25 or 50 mg once daily for at least 1 year. During double-blind treatment, 79%, 83% and 13% of patients given SR-121463 25 and 50 mg and placebo, respectively, had normalized serum sodium levels or an increase in serum sodium of at least 5 mmol/l. Serum sodium responses were maintained in both the short-term and long-term open-label treatment phases. The active treatment was also well tolerated (2).

1. *Sanofi-Aventis reports Q2 R&D highlights*. Sanofi-Aventis Press Release 2005, Aug 31.

2. Soupart, A., Gross, P., Legros, J.-J., Alfoldi, S., Annane, D., Heshmati, H.M., Decaux, G. *Successful long-term treatment of hyponatremia in syndrome of inappropriate antidiuretic hormone secretion with SR121463B, an orally active, nonpeptide, vasopressin V2-receptor antagonist*. J Am Soc Nephrol 2004, 15: Abst SU-PO140.

Sulodexide, New Indication

Keryx Biopharmaceuticals has initiated its pivotal phase III and phase IV program with KRX-101 (sulodexide), the company's lead drug candidate, for the treatment of diabetic nephropathy. This program is being conducted under the Subpart H guidelines for accelerated approval pursuant to a special protocol assessment (SPA) with the FDA. The phase III portion of the program is a randomized, double-blind, placebo-controlled study comparing 200 mg daily of KRX-101 with placebo in patients with persistent microalbuminuria. The phase III study is designed to enroll approximately 1,000 patients, with recruitment expected to take 12-18 months. The objective is to determine the safety and efficacy of KRX-101 in the treatment of patients with type 2 diabetes and persistent microalbuminuria despite being treated with a maximum approved or tolerated dose of an angiotensin II receptor blocker (ARB) or angiotensin-converting enzyme (ACE) inhibitor. Patients will be on treatment for 6 months, followed by 2 months of evaluation off treatment. During the treatment and off-treatment evaluation period, all patients in the study population are expected to continue to receive maximum approved or tolerated doses of ACEs or ARBs. Patients who are not already on maximum approved or tolerated doses of ACEs or ARBs for 120 days are required to go into a 120-day run-in period prior to randomization in order to stabilize blood pressure and to confirm persistent microalbuminuria. The primary endpoint is therapeutic success at 6 months, defined as conversion from microalbuminuria to normoalbuminuria as measured by albumin/creatinine ratio (ACR), with at least a 25% reduction in ACR relative to baseline ACR or a 50% reduction in ACR relative to baseline ACR. The phase IV portion of the program, beginning at the same time, is a randomized, double-blind, placebo-controlled study also comparing 200 mg daily of KRX-101 with placebo in patients with persistent macroalbuminuria or overt nephropathy. The phase IV study is designed to enroll approximately 2,200 patients and it is expected that it will take approximately 24 months to complete enrollment. The objective of this study is to determine the efficacy of KRX-101 in reducing the rate of progression of renal disease and adverse clinical sequelae in patients with nephropathy due to type 2 diabetes, despite being treated with a maximum approved or tolerated dose of an ARB. All patients in the study population are expected to continue to receive maximum approved or tolerated doses of ARBs during the course of the study. The phase IV study is expected to be completed post-FDA approval of KRX-101. The KRX-101 pivotal program is being conducted by The Collaborative Study Group (CSG). Participating in the KRX-101 studies are over 250 U.S., European and Asian-Pacific clinical centers. KRX-101 is a first-in-class oral heparinoid consisting of a low-molecular-weight heparin and active dermatan sulfate for the treatment of diabetic nephropathy. It belongs to the proposed new glycosaminoglycan class of nephroprotective drugs. Unlike various members of this chemical family, KRX-101 is given orally and, in this form, has demonstrated little if any anticoagulant effects to date. More than 20 studies have been published assessing the safety and efficacy of KRX-101 in diabetic nephropathy and other vascular conditions. A randomized, double-blind, placebo-controlled phase II study of the use of KRX-101 for the treatment of diabetic nephropathy was conducted in 223 patients in Europe, and showed a dose-dependent reduction in proteinuria or urinary albumin excretion rates. In May 2005, interim data analysis from an ongoing U.S.-based phase II study confirmed the activity of KRX-101 as a potentially effective treatment for diabetic nephropathy in patients who were on maximum approved or tolerated doses of ACEs and ARBs. Keryx holds an exclusive license to KRX-101 (from originator Alfa Wassermann) in the territories of North America, Japan, Australia, Israel and certain other markets. A potential launch for KRX-101 could take place in late 2007 (1-3). Sulodexide was origi-

Table XII: Clinical studies of SVT-40776 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized	SVT-40776, 0.125 mg p.o. o.d. (n=6) SVT-40776, 0.25 mg p.o. o.d. (n=6) SVT-40776, 0.5 mg p.o. o.d. (n=6) Placebo (n=6)	24	Oral SVT-40776 was well tolerated and only induced dry mouth in healthy volunteers who reached maximum free plasma drug levels > 36 pg/ml	1

nally introduced for the treatment of lipid and thrombotic disorders.

1. *KRX-101 phase II/III program recommended to continue to phase III*. DailyDrugNews.com (Daily Essentials) Jan 14, 2005.

2. *Keryx finalizes SPA agreement for KRX-101*. DailyDrugNews.com (Daily Essentials) March 31, 2005.

3. *KRX-101 enters pivotal phase III and phase IV programs*. DailyDrugNews.com (Daily Essentials) July 11, 2005.

SVT-40776

Salvat has advanced SVT-40776, a selective muscarinic M_3 receptor antagonist being developed for the treatment of urinary incontinence, into phase II evaluation. In phase I trials the compound showed excellent pharmacokinetic and safety results. SVT-40776 has a unique profile, exhibiting a reduced potential for dry mouth, a complete absence of cardiac effects, a long elimination half-life (> 30 h) and a low metabolic rate resulting in minimal interindividual plasma level variations in both young and elderly volunteers. Preclinical studies have demonstrated the high bladder selectivity and potency of the compound. Salvat believes that SVT-40776 may become the first of a new generation of drugs to treat overactive bladder (1).

A placebo-controlled study evaluated the pharmacokinetics and safety of multiple oral doses of SVT-40776 (0.125, 0.25 or 0.5 mg once daily) in 24 healthy female volunteers. The drug was rapidly absorbed and peak plasma levels were reached within 4 h after administration. SVT-40776 had a median half-life of 64-67 h and a linear pharmacokinetic profile at multiple doses, supporting a once-daily dosing regimen. The most common adverse events were constipation and visual disturbances; dry mouth was only reported in patients given a daily dose of 0.5 mg, whereas a daily dose of 0.125 mg induced no antimuscarinic adverse reactions (2) (Table XII).

1. *SVT-40776 progresses into phase II for urinary incontinence*. DailyDrugNews.com (Daily Essentials) June 17, 2004.

2. Rigau, D. et al. *A double-blind, placebo controlled, randomised, multiple oral dose, dose escalation trial investigating the safety, tolerability and pharmacokinetics of SVT-40776 in healthy postmenopausal women*. 35th Annu Meet Int Continence Soc (Aug 26-Sept 1, Montreal) 2005, Abst 112.

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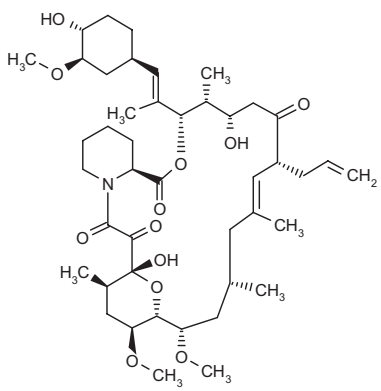
TA-5538

Phase I trials of Tanabe Seiyaku's tachykinin NK_1 antagonist TA-5538, which has shown potential as a treatment for OAB, are under way in Europe (1).

1. *Tanabe Seiyaku reports Q1 R&D highlights*. Tanabe Seiyaku Co., Ltd. Press Release 2005, May 12.

Tacrolimus



The immunosuppressant tacrolimus (FK-506, Prograf®, Protopic®) continues to undergo active clinical development worldwide by Astellas Pharma for a variety of conditions in different formulations, including psoriasis (gel/cream) and asthma (inhalation). Phase III trials are under way in Japan for the oral treatment of lupus nephritis. Tacrolimus has been available in Japan since 1993 and is currently used for the prophylaxis of organ rejection in transplant recipients, the prophylaxis of rejection in bone marrow transplant recipients and the treatment of generalized myasthenia gravis. The ointment formulation

was subsequently launched for the treatment of atopic dermatitis. An oral formulation was recently approved and launched in Japan for the treatment of rheumatoid arthritis and is also under review for use in ulcerative colitis.

Original monograph – Drugs Fut 1989, 14(8): 746.

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Gonzalez-Crespo, M.R., Praga, M., Morales, E., Mateo, I. *Tacrolimus in the treatment of diffuse proliferative glomerulonephritis in systemic lupus erythematosus*. Annu Eur Congr Rheumatol (EULAR) (June 8-11, Vienna) 2005, Abst AB0155.

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Mok, C.C. et al. *Tacrolimus for induction therapy of diffuse proliferative lupus nephritis: An open-labeled pilot study*. Kidney Int 2005, 68(2): 813.

Papez, K., Mills, M., White, S., Brophy, P., Kershaw, D. *Tacrolimus in steroid resistant nephrotic syndrome*. Annu Meet Pediatr Acad Soc (May 1-4, San Francisco) 2004, Abst 3237.

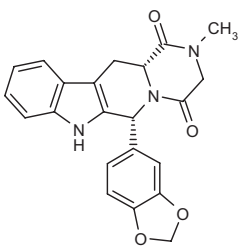
Papez, K., Mills, M., White, S., Brophy, P., Kershaw, D. *Tacrolimus in steroid resistant nephrotic syndrome*. 37th Annu Meet Am Soc Nephrol (ASN) (Oct 27-Nov 1, St. Louis) 2004, Abst SU-PO110.

Politt, D. et al. *Tacrolimus- (FK 506) based immunosuppression in severe systemic lupus erythematosus*. Clin Nephrol 2004, 62(1): 49.

Qu, L., Wang, S., Lin, W., Chen, Y., Li, X., Chen, J. Tacrolimus: *A new treatment for nephrotic syndrome*. Nephrology (Carlton) 2005, 10(Suppl.): Abst T-PO30034.

Wang, L.P., Chen, J., Zhuang, Y. *A report of tacrolimus (FK506) for diffuse proliferative lupus nephritis (DPLN) refractory to other immunosuppressive agent*. 37th Annu Meet Am Soc Nephrol (ASN) (Oct 27-Nov 1, St. Louis) 2004, Abst PUB027.

Tadalafil, New Indication

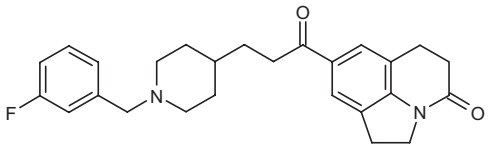


Following the success of its selective PDE5 inhibitor tadalafil (Cialis®) for ED, Lilly Icos has been increasing its research and development to pursue additional indications, including benign prostatic hyperplasia (phase II) and pulmonary arterial hypertension (phase III) (1).

1. *Lilly ICOS reports Q2 R&D highlights*. Lilly ICOS Press Release 2005, July 21.

Original monograph – Drugs Fut 2001, 26(1): 15.

TAK-802

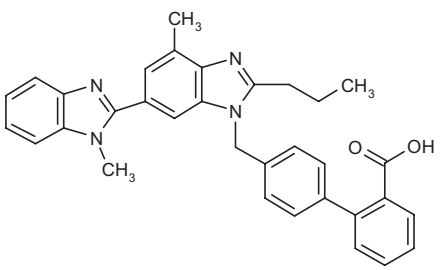


Takeda has discontinued the development of TAK-802, an acetylcholinesterase (AChE) inhibitor that had reached phase II clinical testing for the oral treatment of hypoactive bladder.

TD-6301

TD-6301 is currently being evaluated in early clinical trials at Theravance for the treatment of OAB. In preclinical studies, TD-6301 demonstrated greater inhibition of bladder contraction and less inhibition of salivation than comparable products, indicating that it may be more bladder-selective with respect to dry mouth.

Telmisartan, New Indication



Boehringer Ingelheim and Astellas Pharma reported last year that the large-scale phase III Japanese INNOVATION study of telmisartan (Micardis®) has completed enrollment, with over 1,800 subjects recruited. The study compares 40 or 80 mg of telmisartan and placebo in type 2 diabetic patients with incipient nephropathy to evaluate its inhibitory effect on the transition to overt nephropathy. This study involves not only hypertensive patients but also normotensive patients. By controlling blood pressure of all subjects, including those in the

placebo group, the renoprotective effect of telmisartan will be evaluated independently of its antihypertensive effect. Results are expected in 2006. Angiotensin II receptor blockers such as telmisartan are expected to inhibit the progression of nephropathy by blocking the action of angiotensin II at the receptor level, suppressing the increase in intraglomerular pressure, and other mechanisms. Based on its strong and persistent binding to angiotensin II receptors and its continuous antihypertensive effect over 24 h, telmisartan is expected to provide a significant renoprotective effect. Since almost 100% of telmisartan is excreted in bile, the need for dose adjustment will be reduced even in patients with impaired renal function. The INNOVATION study is part of the PROTECTION™ (Program of Research to shOw Telmisartan Endorgan proteCTIOn poteNtial) Program, being conducted globally by Boehringer Ingelheim to evaluate the organ protective effects of telmisartan. The ONTARGET™ trial program and the PRoFESS® trial for stroke prevention are also being conducted, involving over 54,000 subjects. Telmisartan is currently marketed for the treatment of hypertension by Boehringer Ingelheim under the brand name Micardis® in more than 84 countries all over the world; it is comarketed with Bayer in some European countries, with Astellas in Japan and with Abbott in the U.S. It is also marketed by GlaxoSmithKline under the brand name Pritor® in 30 countries (1, 2).

1. *INNOVATION study of Micardis completes enrollment*. DailyDrugNews.com (Daily Essentials) July 28, 2004.

2. *Telmisartan shows promise in the management of early morning blood pressure surge*. DailyDrugNews.com (Daily Essentials) June 30, 2005.

Original monograph – Drugs Fut 1997, 22(10): 1112.

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Aranda, P., Aranda, F.J., Frutos, M.A., Lopez de Novales, E., Aranda, P.J., Ruilope, L.M. *Long-term renoprotective effects of usual versus high dose of telmisartan in non-diabetic nephropathies*. Am J Hypertens 2004, 17(5, Part 2): Abst P-148.

Barnett, A.H. et al. *Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy*. New Engl J Med 2004, 351(19): 1952.

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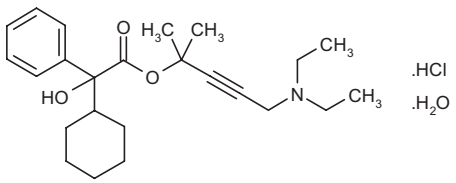
Schmieder, R.E. et al. *Effects of telmisartan versus ramipril on endothelium function of the renal vasculature in type 2 diabetes*. 42nd Congr Eur Renal Assoc - Eur Dialysis Transpl Assoc (June 4-7, Istanbul) 2005, Abst MP127.

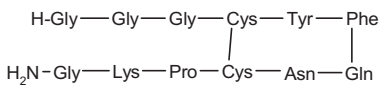
Schmieder, R.E. et al. *Effects of telmisartan versus ramipril on endothelium function of the renal vasculature in type 2-diabetes*. Nephrology (Carlton) 2005, 10(Suppl.): Abst M-PO20027.

Temiverine Hydrochloride



Temiverine hydrochloride (NS-21, Urespan) is an anticholinergic agent and potassium channel blocker that has been submitted for review in Japan by Nippon Shinyaku for the treatment of OAB.

Terlipressin, New Indication



The FDA has granted fast track status and orphan drug designation for terlipressin for the treatment of patients with type 1 hepatorenal syndrome (HRS), or the development of renal dysfunction in patients with end-stage liver cirrhosis. Protein Design Labs' (PDL) wholly owned subsidiary ESP Pharma has acquired from Orphan Therapeutics exclusive marketing, sales and distribution rights for terlipressin in the U.S. and Canada. Orphan Therapeutics holds the U.S. IND for terlipressin and is conducting a phase III trial in the U.S. and Europe. The ongoing phase III study is a double-blind, placebo-controlled trial of terlipressin in patients with type I HRS (OT-0401). Patients receive placebo or terlipressin given intravenously as 1-2 mg every 6 h. Therapy is continued until creatinine decreases to 1.5 mg/dl or less for at least 48 h, or for a total of 14 days, unless treatment fails or the patient undergoes liver transplantation. Terlipressin is a synthetic 12-amino-acid peptide derived from the natural hormone lysine-vasopressin. Due to its constrictive activity on vascular and extravascular smooth muscle cells (V_1 agonist), it reduces blood flow in the splanchnic area, and

thereby lowers portal blood pressure. Although not available in the U.S., terlipressin has been marketed by Ferring for more than 20 years outside the U.S. and is considered a standard of care for the treatment of esophageal variceal hemorrhage (1-3).

1. *Orphan drug status for intravenous terlipressin for type 1 hepatorenal syndrome*. DailyDrugNews.com (Daily Essentials) Nov 12, 2004.

2. *Fast track designation for terlipressin in type 1 hepatorenal syndrome*. DailyDrugNews.com (Daily Essentials) April 22, 2005.

3. *Protein Design Labs reports Q1 R&D highlights*. Protein Design Labs Press Release 2005, May 2.

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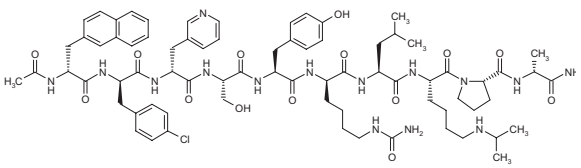
Teverelix



Phase IIa trials for sustained-release teverelix (antarelix) in prostate cancer and benign prostatic hyperplasia (BPH) are under way at Ardana Bioscience, which acquired full global rights to the gonadotropin-releasing hormone (GnRH) antagonist, as well as intellectual property relating to the underlying microcrystalline suspension technology, from AEterna Zentaris. Phase I trials were previously completed successfully in healthy male volunteers, establishing the dosing regimens necessary to achieve different levels of testosterone suppression. Ardana recently held a pre-IND application meeting with the FDA to discuss the development for prostate cancer of teverelix LA. Recent results from two phase II studies in patients with prostate cancer showed that teverelix LA successfully suppressed serum testosterone to the required levels for treatment. An additional phase II study outside the U.S. is expected to commence soon, with results due in the first half of 2006. The FDA has confirmed that serum testosterone levels can serve as a reliable surrogate marker for efficacy in the treatment of prostate cancer. The pre-IND meeting reached agreement on the path forward for the development of teverelix LA for the treatment of prostate cancer, which will allow Ardana to meet its registration timelines and previously announced launch target of the end of 2009. Teverelix may also have application in the treatment of female indications such as endometriosis and fibroids, and a phase I trial in healthy female volunteers is under way (1-3). An immediate-release formulation of the drug has completed phase I trials for the prevention of premature ovulation in controlled ovarian stimulation and assisted reproductive technology.

Eighty-one patients with BPH participated in a double-blind, randomized, placebo-controlled phase II clinical trial that evaluated the efficacy of subcutaneous doses of teverelix LA. Compared to placebo, patients treated with teverelix LA showed greater reductions in their mean I-PSS both at 2 weeks (12.6% *vs.* 5.7%) and at 16 weeks (33.9% *vs.* 7.4%). Response to treatment, which was defined as a reduction of at least 25% in baseline symptom scores, was achieved in 76% of patients given teverelix LA. Other effects associated with the use of teverelix LA included significant improvements in maximum urine flow rate, quality of life and prostate size. Few patients reported adverse events during the study (4).

1. *AEterna reports Q1 R&D highlights*. AEterna Laboratories Press Release 2004, May 4.

2. *AEterna Zentaris reports Q2 R&D highlights*. AEterna Zentaris Press Release 2004, Aug 11.

3. *Ardana holds pre-IND meeting for Teverelix LA*. DailyDrugNews.com (Daily Essentials) Sept 12, 2005.

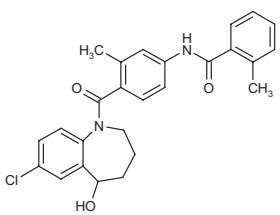
4. *Ardana announces successful results in a phase II study of Teverelix LA in benign prostatic hyperplasia*. Ardana Biosciences Press Release 2005, May 26.

TJN-598

TJN-598 had reached phase II development at Tsumura for the oral treatment of chronic glomerulonephritis, but in March 2005 development was discontinued based on preliminary efficacy and safety results (1).

1. *Tsumura discontinues development of TJN-598*. DailyDrugNews.com (Daily Essentials) 2005, March 10.

Tolvaptan

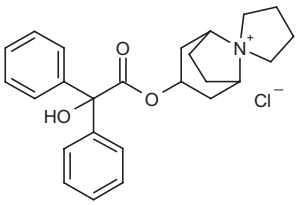


Tolvaptan (OPC-41061) is an orally active vasopressin V_2 receptor antagonist in phase III clinical devel-

opment by Otsuka for the treatment of congestive heart failure (CHF) and hyponatremia. The agent is also in early clinical development for polycystic kidney disease.

Original monograph – Drugs Fut 2002, 27(4): 350.

Trospium Chloride



Following FDA approval, Indevus launched trospium chloride (Sanctura®) in the U.S. last year for the treatment of OAB with symptoms of urge urinary incontinence, urgency and urinary frequency. Originally copromoted with Pliva's U.S. subsidiary Odyssey Pharmaceuticals, the latter was subsequently acquired by Saturn Pharmaceuticals, which then changed its name to Esprit Pharma. This resulted in certain amendments to the original agreement between Indevus and Odyssey, including increased royalties due Indevus. FDA approval was based on a review of data from clinical studies conducted in the U.S. and Europe involving approximately 3,000 subjects. A quarternary ammonium compound, trospium belongs to the muscarinic receptor antagonist class of anticholinergic compounds which relax smooth muscle tissue in the bladder, thereby decreasing bladder contractions. The drug is currently marketed in Europe. Indevus licensed exclusive U.S. rights to trospium chloride from Madaus in late 1999. Long-term treatment with trospium chloride provides extended relief from the symptoms of OAB and is well tolerated, according to new data from a 12-month phase III study that included a 3-month, randomized, double-blind, placebo-controlled phase, followed by a 9-month open-label period. During the initial 12-week period, patients were treated with either trospium chloride or placebo. Patients on trospium chloride had a statistically significant reduction in the frequency of urination and urge incontinence episodes, as well as an increase in volume voided, compared to placebo-treated patients. At the end of the 12-week period, trospium chloride-treated patients continued treatment for an additional 9 months, while placebo-treated patients were switched to trospium chloride. Following treatment for up to 1 year, patients continuing on trospium chloride treatment maintained comparable and sustained efficacy for the entire treatment period. Patients who crossed over from placebo to trospium chloride rapidly experienced a similar degree of efficacy that was also sustained for the entire 9-month period. Regardless of initial treatment, at 12 months the mean reduction in frequency of urination for all patients ranged from 18 to 21 voids per week, and the mean reduction in urge incontinence episodes ranged from 64% to 72% per day compared to baseline. All patients experienced an increase of 27-28 ml in volume voided at the end of the study. Treatment was well tolerated, and the most frequently reported adverse events were dry mouth (11.3%) and constipation (8.8%). A total of 523 patients were studied in the original 12-week trial, which was included in the NDA. A total of 407 of these patients opted to continue treatment in the open-label phase of the trial (1-5).

Indevus has initiated a phase III program for Sanctura XR™ in patients with OAB. Sanctura XR™ is a once-daily formulation of the currently marketed Sanctura®. The new phase III program consists of two 12-week, double-blind, placebo-controlled studies totaling 1,200 adults enrolled at approximately 120 U.S. sites. The trials will evaluate the effects of once-daily dosing of trospium chloride on urinary frequency, urge incontinence and other related symptoms associated with OAB. An NDA filing remains on track for the second half of 2006. Initiation of the phase III program triggered a USD 10 million milestone payment from Esprit Pharma, Indevus's copromotion partner for trospium chloride (6).

A total of 148 patients participated in a multicenter, double-blind, placebo-controlled pilot phase II clinical trial

Table XIII: Clinical studies of trospium chloride (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Incontinence, urinary, Overactive bladder	Randomized Double-blind Multicenter	Trospium, 20 mg p.o. b.i.d. x 12 wks (n=329) Placebo (n=329)	658	Trospium was well tolerated and effective for overactive bladder associated with urge incontinence, and improvement was apparent within the first days of treatment	8
Incontinence, urinary, Overactive bladder	Randomized Double-blind Multicenter	Trospium, 20 mg b.i.d. x 51 wks (n=262) Placebo x 12 wks → Trospium, 20 mg b.i.d. x 9 mo (n=261)	523	Trospium was well tolerated and offered sustained efficacy starting from week 1 in patients with symptomatic overactive bladder, reducing the number of voids and urge incontinence episodes and the severity of urge episodes, and improving quality of life	9

Table XIV: Clinical studies of udenafil (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Erectile dysfunction	Randomized Double-blind Multicenter	Udenafil, 100 mg PRN [max. o.d.] x 12 wks Udenafil, 200 mg PRN [max. o.d.] x 12 wks Placebo	319	Udenafil was well tolerated and significantly more effective than placebo in improving erectile function in patients with erectile dysfunction	2

that established the effects and safety profile of the once-daily formulation of the muscarinic receptor antagonist trospium chloride (Sanctura XR™) in the treatment of OAB. Sanctura XR™ improved all the signs and symptoms of OAB, together with the quality of life of the patients. The efficacy of Sanctura XR™ was similar to that reported in previous clinical trials for the currently marketed formulation (Sanctura®) given twice daily. The most common anticholinergic adverse events associated with Sanctura XR™ were dry mouth and constipation (7).

1. *Good efficacy and safety shown for long-term use of Sanctura*. DailyDrugNews.com (Daily Essentials) Aug 4, 2004.

2. *Sanctura distribution under way*. DailyDrugNews.com (Daily Essentials) Aug 17, 2004.

3. *Conversion of Sanctura agreement*. DailyDrugNews.com (Daily Essentials) Oct 21, 2004.

4. *Indevus announces agreement for Saturn Pharmaceuticals to acquire marketing rights to Sanctura from Odyssey Pharmaceuticals; Indevus signs amendment and consent agreement and receives enhanced economic terms*. Indevus Press Release 2005, May 16.

5. *Indevus announces closing of Sanctura® transaction; Sanctura marketing rights acquired by Esprit Pharma (formerly known as Saturn Pharmaceuticals)*. Indevus Press Release 2005, July 1.

6. *Sanctura XR enters phase III program for overactive bladder*. DailyDrugNews.com (Daily Essentials) Sept 13, 2005.

7. *Phase II data supports the use of Sanctura XR for overactive bladder*. DailyDrugNews.com (Daily Essentials) June 20, 2005.

8. Rudy, D. et al. *A multicenter, randomized, placebo-controlled trial of trospium chloride in overactive bladder patients*. 34th Annu Meet Int Continence Soc (Aug 23-27, Paris) 2004, Abst 144 (Table XIII).

9. Zinner, N. et al. *Trospium chloride improves overactive bladder symptoms: A multicenter phase III trial*. J Urol 2004, 171(6, Part 1): 2311 (Table XIII).

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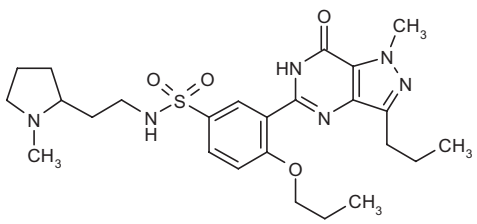
Udenafil



Dong-A PharmTech has filed an IND to commence U.S. clinical trials of its new PDE5 inhibitor udenafil (DA-8159, Zydena) for ED. The U.S. clinical program will start with a double-blind, placebo-controlled, dose-confirmation phase II study in approximately 300 patients. The 12-week at-home study will evaluate ED patients of all severities. Dong-A PharmTech's oral udenafil is awaiting approval in Korea. Korean studies in approximately 300 patients have shown that udenafil produced highly significant improvement in erectile function after 12 weeks of therapy, with up to a 91% vaginal penetration success rate and up to a 67% intercourse completion rate compared to 29% for the placebo group. Additionally, 40% of the patients in the previous studies at the high dose level returned to normal function after 12 weeks on drug compared to only 9% on placebo. The overall patient satisfaction as measured by the standard Global Assessment Question (GAQ) was up to 86% in the high-dose group compared to 26% in the placebo group. Previous phase I studies in the U.K. and Korea showed that udenafil has a unique pharmacokinetic profile (t_{max} = 1.0-1.5 h, $t_{1/2}$ = 11-13 h), suggesting that it may have a relatively rapid onset and sufficiently long duration of action to provide efficacy for up to 24 h. Prior studies have also demonstrated a selectivity profile for udenafil that is similar to sildenafil, but unlike tadalafil it does not inhibit the PDE11 isozyme and thus would not be expected to produce significant myalgia (1).

A multicenter, double-blind, randomized clinical trial administered placebo or udenafil (100 or 200 mg) as needed, but not more than once daily, to 319 patients with mild to severe ED. After 12 weeks of treatment, the baseline Erectile Function domain scores in the IIEF of the patients increased significantly with both udenafil doses compared to placebo. The average success rate in maintaining erections until successful intercourse increased from 19.2% to 66.8% and from 17.4% to 66.9% with 100

and 200 mg of udenafil, respectively. The percentage of patients who achieved normal erectile function at the end of the study was almost 40% with 200 mg of udenafil and 9% with placebo. The most common drug-related adverse events were mild to moderate flushing and headache; none of the patients experienced severe or serious adverse events during the treatment period (2) (Table XIV).

1. *Dong-A PharmTech files IND for new PDE5 inhibitor for erectile dysfunction*. DailyDrugNews.com (Daily Essentials) April 1, 2005.

2. Kim, S.W., Yang, D.Y. et al.Paick, J.S. *Efficacy and tolerability of DA-8159 in patients with erectile dysfunction*. J Sex Med 2004, 1(Suppl. 1): Abst O56.

UK-390957/UK-464273

The 5-HT reuptake inhibitor UK-390957 and the calcium channel modulator UK-464273 were last reported by Pfizer to be in phase II trials for premature ejaculation.

YM-178

Astellas Pharma's YM-178, a β_3-adrenoceptor agonist, is in phase II development in Europe for the oral treatment of OAB.

Annual Update 2004/2005 - Treatment of Genitourinary Cancers

According to the National Cancer Institute (NCI), the genitourinary cancer group includes urinary cancers, such as bladder and kidney (renal) cancers, and male reproductive cancers, such as penile, prostate and testicular cancers, among others (1).

Prostate cancer is the most common genitourinary cancer and the second leading cause of cancer-related death among men in the U.S. and the E.U., after lung cancer (2, 3). African-American men are more likely to be diagnosed with prostate cancer and to die from it than caucasian Americans, although the reasons for this ethnic disparity are not clear (3). Early detection through prostate cancer screening tests has led to an increase in the survival rate for this type of cancer in recent years.

In the table that follows, drugs under active development for genitourinary cancer are shown (*Source: Prous Science Integrity*®).

References

1. NCI website (www.cancer.gov)

2. *New European cancer figures for 2004*. International Agency for Research on Cancer (WHO) Press Release 159, Feb 17, 2005.

3. *Annual report to the nation on the status of cancer, 1975-2002, featuring population-based trends in cancer treatment*. J Natl Cancer Inst 2005, 97(19): 1407.

Pepi Hurtado, PhD

Treatment of Genitourinary Cancers

Condition	Phase	Drug	Target	Source
Bladder carcinoma *in situ*	I/II	Mycobacterium cell wall-DNA complex		Bioniche Life Sciences
Bladder cancer	III	Lapatinib	Epidermal growth factor receptor (EGFR)	GlaxoSmithKline
	III	Vinflunine	Tubulin	Pierre Fabre
	III	Carboplatin[1]	DNA	National Cancer Institute (US)
	III	Mitomycin[1]	DNA	National Cancer Institute (US)
	II/III	Celecoxib[1]	Cyclooxygenase type 2	National Cancer Institute (US)
	II/III	Bexidem		IDM
	II	Tocosol paclitaxel	Microtubule	Sonus
	II	Plitidepsin	Vascular endothelial growth factor (VEGF)	PharmaMar
	II	Pemetrexed disodium[1]	Thymidylate synthase, Phosphoribosylglycinamide formyltransferase (GAR TFase), Dihydrofolate reductase	National Cancer Institute (US)
	II	Irinotecan hydrochloride[1]	DNA topoisomerase I	National Cancer Institute (US)
	II	Genistein	Epidermal growth factor receptor (EGFR), Cystic fibrosis transmembrane conductance regulator (CFTR) channels, DNA topoisomerase II	National Cancer Institute (US)
	II	Gefitinib[1]	Epidermal growth factor receptor (EGFR)	National Cancer Institute (US)

Continuation

Treatment of Genitourinary Cancers

Condition	Phase	Drug	Target	Source
Bladder cancer	II	Apaziquone	DNA	Spectrum Pharmaceuticals
	I/II	Oncomyc-NG	MYC	AVI BioPharma
	I/II	Gallium maltolate	Ribonucleoside-diphosphate reductase	Titan
	I	Proxinium	Endothelial cell adhesion molecule (EpCAM)	Viventia Biotech
	I	CG-0070		Cell Genesys
	I	AMG-706	Vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2, VEGFR-3), Platelet-derived growth factor receptor (PDGFR)	Amgen
	I	Ad5CMV-p53		Introgen/National Cancer Institute (US)
Kidney cancer	III	Lapatinib	Epidermal growth factor receptor (EGFR)	GlaxoSmithKline
	II	Talactoferrin alfa		Agennix
	II	SRL-172		SR Pharma
	II	Panitumumab	Epidermal growth factor receptor (EGFR)	Abgenix
	II	NSC-330507	Heat shock protein 90 (HSP90)	National Cancer Institute (US)
	II	Ixabepilone	Microtubule	Bristol-Myers Squibb/National Cancer Institute (US)
	II	Irinotecan hydrochloride[1]	DNA topoisomerase I	Medical University of South Carolina
	II	Gemcitabine[1]	Ribonucleoside-diphosphate reductase, Pyrimidine	National Cancer Institute (US)
	II	Flt3-L		National Cancer Institute (US)
	II	Dolastatin 10	Tubulin	National Cancer Institute (US)
	I/II	RNA-loaded dendritic cell vaccine		Argos Therapeutics
	I/II	Interleukin-2 XL		Flamel Technologies
	I	ZRx-101		ZelleRx
	I	Spisulosine		PharmaMar
	I	Edodekin alfa		National Cancer Institute (US)
	I	EC-17		Endocyte
	I	AGRO-100		Antisoma
Renal cell carcinoma	Prereg.	Sunitinib malate	Vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2), Platelet-derived growth factor receptor β (PDGFRβ, Flt3)	Pfizer
	Prereg.	Sorafenib	Raf kinase, Vascular endothelial growth factor receptor (VEGFR), Platelet-derived growth factor receptor (PDGFR)	Bayer/Onyx
	III	Temsirolimus	mTOR	Wyeth Pharmaceuticals
	III	MAb G250	G250	Wilex
	III	HSPPC-96		Antigenics
	II	Tegafur/gimeracil/oteracil[1]	Thymidylate synthase, Pyrimidine	Taiho
	II	Thalidomide[1]		National Cancer Institute (US)
	II	SB-485232		GlaxoSmithKline
	II	Ranpirnase		Alfacell
	II	MVA-Muc1-IL-2	MUC-1	Transgene
	II	MVA-5T4		Oxford BioMedica
	II	Motexafin gadolinium		Pharmacyclics
	II	MG-98	DNMT1	MGI Pharma/MethylGene
	II	IMO-2055	Toll-like receptor 9 (TLR9)	Hybridon
	II	GTI-2040	RRM2	Lorus Therapeutics
	II	Erlotinib hydrochloride[1]	Epidermal growth factor receptor (EGFR)	Genentech/National Cancer Institute (US)
	II	Depsipeptide	Histone deacetylase (HDAC)	Gloucester Pharmaceuticals

Continuation

Treatment of Genitourinary Cancers

Condition	Phase	Drug	Target	Source
Renal cell carcinoma	II	CP-461	Phosphodiesterase 2A (PDE2A), Phosphodiesterase 5A (PDE5A)	OSI Pharmaceuticals
	II	Carboxyamidotriazole		National Cancer Institute (US)
	II	Bay-59-8862	Microtubule	Bayer
	II	Axitinib	Vascular endothelial growth factor receptor (VEGFR), Platelet-derived growth factor receptor (PDGFR)	Pfizer
	II	Atrasentan	Endothelin ET_A receptor	National Cancer Institute (US)
	I/II	Temsirolimus	mTOR	National Cancer Institute (US)
	I/II	Idronoxil	Sphingosine kinase, BIRC4, Tumor NADH oxidase (tNOX)	Marshall Edwards
	I/II	CNTO-328	Interleukin-6 (IL-6)	Centocor
	I	PHP		Curacyte
	I	Interleukin-21		ZymoGenetics
	I	Innacell gammadelta		Innate Pharma
	I	Incyclinide	Gelatinase A (MMP-2), Gelatinase B (MMP-9)	National Cancer Institute (US)
	I	FolateImmune	Folate receptor	Endocyte
Metastatic kidney cancer	III	Bevacizumab[1]	Vascular endothelial growth factor (VEGF)	Genentech
	II	Carboplatin[1]	DNA	National Cancer Institute (US)
	II	Volociximab	CD49e/CD29 (integrin $\alpha_5\beta_1$)	Protein Design Labs
	II	MDX-010	CD152 (CTLA4)	Medarex
Penile cancer	II	Irinotecan hydrochloride[1]	DNA topoisomerase I	EORTC
	II	Docetaxel[1]	Microtubule	National Cancer Institute (US)
	II	Cisplatin[1]	BIRC4, TNFSF6, DNA	EORTC
Prostate cancer	R-2005	Triptorelin	Gonadotropin-releasing hormone (GnRH, LHRH)	Debiopharm
	Prereg.	Histrelin acetate	Gonadotropin-releasing hormone (GnRH, LHRH)	Paladin/Valera Pharmaceuticals
	Prereg.	Abarelix	Gonadotropin-releasing hormone (GnRH, LHRH)	Praecis
	III	Vinorelbine[1]	Tubulin	Pierre Fabre/Novacea
	III	Toremifene[1]	Estrogen receptor (ER)	GTx
	III	Taxotere[1]		Sanofi-Aventis
	III	Satraplatin	DNA	GPC Biotech/Spectrum Pharmaceuticals
	III	GVAX Prostate		Cell Genesys
	III	Goserelin[1]	Gonadotropin-releasing hormone (GnRH, LHRH)	National Cancer Institute (US)
	III	DCVax-Prostate		Northwest Biotherapeutics
	III	Bevacizumab[1]	Vascular endothelial growth factor (VEGF)	Genentech
	III	APC-8015		Dendreon
	II/III	Thalidomide[1]		Celgene/National Cancer Institute (US)
	II/III	DN-101		Novacea
	II/III	Atrasentan	Endothelin ET_A receptor	Abbott
	II/III	(*R*)-Flurbiprofen	NF-κB	Myriad Genetics
	II	ZD-4054	Endothelin ET_A receptor	National Cancer Institute (US)
	II	Volociximab	CD49e/CD29 (integrin $\alpha_5\beta_1$)	Protein Design Labs
	II	Trabectedin		PharmaMar
	II	Tesmilifene hydrochloride	Estrogen receptor (ER), Histamine receptor	YM BioSciences
	II	Temsirolimus	mTOR	National Cancer Institute (US)
	II	Tegafur/gimeracil/oteracil[1]		Taiho
	II	Tasidotin hydrochloride	Microtubule	Genzyme
	II	Squalamine	Na^+/H^+ exchanger (NHE), Vascular endothelial growth factor (VEGF)	Genaera

Continuation

Treatment of Genitourinary Cancers

Condition	Phase	Drug	Target	Source
Prostate cancer	II	Sorafenib	Raf kinase, Vascular endothelial growth factor receptor (VEGFR), Platelet-derived growth factor receptor (PDGFR)	National Cancer Institute (US)
	II	Seocalcitol		Cougar Biotechnology
	II	Sabarubicin hydrochloride	DNA topoisomerase II	Menarini
	II	Reolysin		Oncolytics Biotech
	II	Rebimastat	Interstitial collagenase (MMP-1), Gelatinase A (MMP-2), Gelatinase B (MMP-9), Membrane-type matrix metalloproteinase-1 (MMP-14)	National Cancer Institute (US)
	II	Prostvac VF	Prostate-specific antigen (PSA)	Therion/National Cancer Institute (US)
	II	Plitidepsin	Vascular endothelial growth factor (VEGF)	PharmaMar
	II	PI-88	Vascular endothelial growth factor (VEGF), Basic fibroblast growth factor (bFGF, FGF-2), heparanase	Progen
	II	Perifosine	Protein kinase B (PKB/Akt)	AEternaZentaris/National Cancer Institute (US)
	II	Pentrys		AustCancer
	II	Patupilone	Microtubule	Novartis
	II	Ozarelix	Gonadotropin-releasing factor (VEGF), Basic fibroblast growth factor (bFGF, FGF-2), heparanase	AEterna Zentaris/Spectrum Pharmaceuticals
	II	Onyvax P		Onyvax
	II	OGX-011		OncoGeneX Technologies/Isis Pharmaceuticals
	II	Oblimersen sodium	BCL2	Genta
	II	NSC-640488		Antisoma
	II	NSC-330507	Heat shock protein 90 (HSP90)	Kosan
	II	MVA-Muc1-IL-2	MUC-1	Transgene
	II	MT-201	Endothelial cell adhesion molecule (EpCAM)	Micromet
	II	Modrenal	Estrogen receptor (ER) β	Bioenvision
	II	MDX-010	CD152 (CTLA4)	Medarex
	II	Liposome-encapsulated doxorubicin	DNA topoisomerase II	University of Kentucky
	II	J591		BZL Biologics
	II	Ispinesib mesilate	Kinesin-like spindle protein (KSP, Eg5)	National Cancer Institute (US)
	II	Irofulven	Caspase -8 and -9	MGI Pharma
	II	Imatinib mesilate[1]	Abl kinase, Platelet-derived growth factor receptor α (PDGFRα, Kit)	Novartis
	II	Idronoxil	Sphingosine kinase, BIRC4, Tumor NADH oxidase (tNOX)	Marshall Edwards
	II	GTI-2501	RRM1	Lorus Therapeutics
	II	GTI-2040	RRM2	Lorus Therapeutics, National Cancer Institute (US)
	II	GnRH Pharmaccine	Gonadotropin-releasing hormone (GnRH, LHRH)	Aphton
	II	Globo H-KLH vaccine		Sloan-Kettering Institute
	II	Genistein	Epidermal growth factor receptor (EGFR), Cystic fibrosis transmembrane conductance regulator (CFTR) channels, DNA topoisomerase II	National Cancer Institute (US)
	II	Fenretinide	Retinoic acid receptor (RAR) β and γ	National Cancer Institute (US)

Continuation

Treatment of Genitourinary Cancers

Condition	Phase	Drug	Target	Source
Prostate cancer	II	Erlotinib hydrochloride[1]	Epidermal growth factor receptor (EGFR)	Genentech/National Cancer Institute (US)
	II	Exisulind	cGMP phosphodiesterase	OSI Pharmaceuticals/National Cancer Institute (US)
	II	Eflornithine hydrochloride[1]	Ornithine decarboxylase	National Cancer Institute (US)
	II	Doxercalciferol[1]		National Cancer Institute (US)
	II	Desoxyepothilone B	Microtubule	Kosan/Roche
	II	Depsipeptide	Histone deacetylase (HDAC)	Gloucester Pharmaceuticals
	II	Degarelix	Gonadotropin-releasing hormone (GnRH, LHRH)	Ferring
	II	CTL-102		Innovata
	II	CP-461		OSI Pharmaceuticals
	II	CM-31747	Sigma1 and sigma2 receptor	Sanofi-Aventis
	II	CC-5013	TNF-α	Celgene
	II	Bortezomib[1]	Proteasome, NF-κB	Millennium Pharmaceuticals
	II	Bevacizumab[1]		National Cancer Institute (US)
	II	Avorelin	Gonadotropin-releasing hormone (GnRH, LHRH)	Mediolanum
	II	Arsenic trioxide[1]		National Cancer Institute (US)
	II	AP-23573	mTOR	Ariad Pharmaceuticals
	II	Antineoplaston A10		Burzynski Research Institute
	II	Antarelix	Gonadotropin-releasing hormone (GnRH, LHRH)	Ardana Bioscience/AEterna Zentaris
	II	Amonafide	DNA topoisomerase II	ChemGenex Pharmaceuticals
	II	AdV-tk		Advantagene
	I/II	Oncomyc-NG	MYC	AVI BioPharma
	I/II	Norelin		YM BioSciences
	I/II	MLN-2704		Millennium Pharmaceuticals
	I/II	Lexidronam[1] Sm 1531		Cytogen/Northwestern University/ University of Maryland
	I/II	GPI-0100		Galenica/Memorial Sloan-Kettering Cancer Center
	I/II	Gemcitabine[1]	Ribonucleoside-diphosphate reductase, Pyrimidine	Lilly/Sanofi-Aventis
	I/II	Gefitinib[1]	Epidermal growth factor receptor (EGFR)	National Cancer Institute (US)
	I/II	EMD-273066		EMD Pharmaceuticals
	I/II	Combretastatin A-4 phosphate	Tubulin	OxiGene
	I/II	ABR-215050		Active Biotech
	I/II	^{90}Yttrium-DOTA-huJ591		BZL Biologics
	I/II	^{111}In-DOTA-huJ591		BZL Biologics
	I	UBITh	Gonadotropin-releasing hormone (GnRH, LHRH)	United Biomedical
	I	Thermodox	DNA topoisomerase II	Celsion
	I	Talactoferrin alfa		Agennix
	I	SSR-125329A	Sigma receptor	Sanofi-Aventis
	I	Spisulosine		PharmaMar
	I	Rhodamine 123		University of Tennessee, Memphis
	I	rhIGFBP-3	Insulin-like growth factor (IGF)	Insmed
	I	RC-8800		Rejuvenon
	I	PSMA vaccine	Prostate-specific antigen (PSA)	Cytogen/Progenics
	I	Prostate cancer vaccine		GlaxoSmithKline
	I	NBI-56418	Gonadotropin-releasing hormone (GnRH, LHRH)	Neurocrine Biosciences
	I	NBI-42902	Gonadotropin-releasing hormone (GnRH, LHRH)	Neurocrine Biosciences
	I	Mycobacterium cell wall-DNA complex		Bioniche Life Sciences
	I	Motexafin lutetium		National Cancer Institute (US)
	I	Ketoconazole	Aromatase, Androgen receptor	National Cancer Institute (US)
	I	Kahalalide F		PharmaMar
	I	INSM-18	Insulin-like growth factor-I (IGF-I) receptor	Insmed/University of California, San Francisco
	I	Ad5CMV-p53		Introgen

Continuation

Treatment of Genitourinary Cancers

Condition	Phase	Drug	Target	Source
Prostate cancer	I	Abiraterone acetate	Cytochrome P-450 CYP17 (17α-hydroxylase/C17-20 lyase)	BTG
	I	Abiraterone	Cytochrome P-450 CYP17 (17α-hydroxylase/C17-20 lyase)	Cougar Biotechnology
Metastatic prostate cancer	Prereg.	Atrasentan	Endothelin ET_A receptor	Abbott
	II	PCK-3145 derivative		Procyon Biopharma
	II	PCK-3145		Procyon Biopharma
	II	MDX-070		Medarex
	II	Ixabepilone	Microtubule	Bristol-Myers Squibb/National Cancer Institute (US)
	II	hLM609	CD51/CD61 (integrin $\alpha_v\beta_3$)	MedImmune
	II	GCAN-101		GammaCan
	II	Diflomotecan	DNA topoisomerase I	Ipsen
	II	Depsipeptide	Histone deacetylase (HDAC)	Astellas Pharma
	II	CC-4047	TNF-alpha	Celgene
	I/II	TERT-RNA Vaccine	Telomerase reverse transcriptase	Geron/Duke University
	I/II	Gallium maltolate	Ribonucleoside-diphosphate reductase	Titan
	I	LAMP-TERT-RNA Vaccine	Telomerase reverse transcriptase	Geron/Duke University
Testicular cancer	II/III	Bleomycin sulfate[1]		National Cancer Institute (US)
	II	Ixabepilone	Microtubule	National Cancer Institute (US)

[1]Launched for another indication.