Drugs of the Future 2002, 27(9): 879-915

CCC: 0377-8282/2002

Annual Review 2002

Neurologic Drugs

N.E. Mealy, R. Castañer, L. Martín, M. del Fresno, L. Revel, M. Bayés, L.A. Sorbera, P. Cole, M. Cullell-Young, P.A. Leeson, J. Prous

Abstract

This month's *Annual Review* is dedicated to updated information on neurologic drugs. The following table lists 154 drugs under development in this area, some of which have been published in previous issues of the journal and others that have been marketed for an indication other than that discussed in the review. Information on the following 28 products is updated here: **cevimeline hydrochloride, CPI-1189, donepezil hydrochloride, ebselen, edaravone, etilevodopa, fampridine, FK-960, KW-6002, leteprinim potassium, modafinil, natalizumab, NXY-059, pregabalin, rasagiline mesilate, repinotan hydrochloride, retigabine, rivastigmine tartrate, rotigotine hydrochloride, safinamide mesilate, sapropterin dihydrochloride, SLV-308, stiripentol, T-588, talampanel, tomoxetine hydrochloride, xaliproden hydrochloride** and **zanapezil fumarate**.

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

Annual Review 2002: Neurologic Drugs

Drug	Source	Indication/Action	Phase
3,4 DAP	Jacobus	Lambert-Eaton myasthenic syndrome	II
ABP-150	MitoKor	Antiparkinsonian	I
ABR-215062	Active Biotech	Multiple sclerosis	II
ABT-089	Abbott	Alzheimer's dementia	I
		ADHD	I
AEOL-10150	Incara	Ischemic stroke	Clinical
AG-284	Corixa	Multiple sclerosis	II
AIT-034	NeoTherapeutics	Dementia	I
Alemtuzumab[2]	Ilex Oncology	Multiple sclerosis	II
AMP-397	Novartis	Antiepileptic	II
Ampalex	Cortex	ADHD	II
		Alzheimer's dementia	II
	Cortex/Servier	Cognition disorders	I
Apan	Praecis	Alzheimer's dementia	I
Argatroban Monohydrate[1,2]	Texas Biotechnology	Ischemic stroke	II
Aripiprazole[1]	Bristol-Myers Squibb	Alzheimer's disease	III
Atvogen	HemispheRx	Chronic fatigue syndrome	Prereg
BGC-728	BTG	Stroke	II
BIA-3-202	Portela	Antiparkinsonian	I
Botulinum Toxin Type B[2]	Eisai	Antispastic	L-2001
Bupropion Hydrochloride[1,2]	GlaxoSmithKline	ADHD	III
Cannabidiol	GW Pharmaceuticals	Epilepsy	I
Carabersat	GlaxoSmithKline	Antiepileptic	II
Cerebril	Neurochem	Hemorrhagic stroke	II
Cerebrolysin[2]	Ebewe	Ischemic stroke	II
		Alzheimer's dementia	II/III
Cevimeline Hydrochloride[1,2]	Snow Brand	Alzheimer's dementia	II
CGX-1007	Cognetix	Antiepileptic	I
CI-1017	Pfizer	Alzheimer's dementia	I/II
Cladribine	Ivax	Multiple sclerosis	II
Clioquinol[2]	Prana Biotechnology	Alzheimer's dementia	II
CM-101	CarboMed	Lesions of the spinal cord and related structures	I/II
Colostrinin	ReGen Therapeutics	Alzheimer's dementia	II
CPI-1189[1]	Centaur	Parkinson's dementia	II
		AIDS dementia	II
		Alzheimer's dementia	II
Crobenetine Hydrochloride	Boehringer Ingelheim	Ischemic stroke	I
CVT-E033	CV Technologies	ADHD	II
Dacliximab	Protein Design Labs	Multiple sclerosis	I/II
Dapsone[2]	Immune Network	Alzheimer's dementia	II
Dexanabinol	Pharmos	Mild cognitive impairment disorder	II
		Stroke	III
(*R*)-Didesmethylsibutramine	Sepracor	ADHA	II
DMXB-Anabaseine	Taiho	Alzheimer's dementia	I
Donepezil Hydrochloride[1,2]	Eisai	Vascular dementia	Prereg
DP-BAPTA-99	D-Pharm	Stroke	II
Dronabinol/Cannabidiol	GW Pharmaceuticals	Lesions of the spinal cord	II
	GW Pharmaceuticals	Multiple sclerosis	III
DU-127090	Solvay	Antiparkinsonian	III
DVD-111	David Pharmaceuticals	Stroke	I/II
		Cognition disorders	II
DVD-742	David Pharmaceuticals	Cognition disorders	II
DY-9760	Daiichi Pharmaceutical	Ischemic stroke	I
E-2007	Eisai	Multiple sclerosis	I
E-2051	Eisai	Ischemic stroke	I
E-2101	Eisai	Antispastic	I
Ebselen[1]	Daiichi Pharmaceutical	Stroke	Prereg
Edaravone[1]	Mitsubishi Pharma	Stroke	L-2001
		Hemorrhagic stroke	III
EN-101	Ester Neurosciences	Myasthenia gravis	I/II
Ensaculin Hydrochloride[1]	Schwabe	Alzheimer's dementia	II
Epoetin	Max-Planck-Gesellschaft	Stroke	I
Erlosamide	Schwarz	Antiepileptic	II

Continued

Annual Review 2002: Neurologic Drugs

Drug	Source	Indication/Action	Phase
Etilevodopa[1]	TEVA	Antiparkinsonian	III
Fampridine[1]	Elan	Multiple sclerosis	III
	Acorda	Lesions of the spinal cord and related structures	III
Fibrillex	Neurochem	Alzheimer's dementia	II/III
FK-960[1]	Fujisawa	Alzheimer's dementia	II
Gacyclidine	Beaufour-Ipsen	Brain trauma	II
Galanthamine Hydrobromide[2]	Shire/Janssen	Vascular dementia	III
Ganaxolone	CoCensys	Antiepileptic	II
Ganglioside GM1[2]	Fidia	Lesions of the spinal cord and related structures	III
		Antiparkinsonian	III
Ganstigmine Hydrochloride	Chiesi	Alzheimer's dementia	II
GT-2331	Gliatech	ADHD	II
GW-320659	GlaxoSmithKline	ADHD	II
Inosiplex[2]	Helix BioPharma	Fatigue	I
IQ-201	Immune Network	Alzheimer's dementia	II
IR-208	Immune Response	Multiple sclerosis	I/II
JP-1730	Juvantia	Parkinson's disease	I
KT-7515	Cephalon	Antiparkinsonian	II/III
KW-6002[1]	Kyowa Hakko	Antiparkinsonian	II
Lanicemine Hydrochloride	AstraZeneca	Ischemic stroke	II
LAX-101	Amarin	Huntington's disease	III
LBS-Neurons	Layton Bioscience	Stroke	II
LDP-01	Millennium	Stroke	I
LDP-519	Millennium	Ischemic stroke	I
Leteprinim Potassium[1]	NeoTherapeutics	Alzheimer's dementia	III
		Lesions of the spinal cord and related structures	II
		Antiparkinsonian	II
Levodopa/Carbidopa/Entacapone	Orion	Parkinson's disease	Prereg
Licarbazepine[2]	Novartis	Antiepileptic	III
Liposome-Encapsulated Mitoxantrone	NeoPharm	Multiple sclerosis	I
MBP-8298	BioMS Medical	Multiple sclerosis	II
Mesopram	Schering AG	Multiple sclerosis	II
MKC-231	Mitsubishi Pharma	Alzheimer's dementia	II
Modafinil[1,2]	Cephalon	Alzheimer's dementia	II
		ADHD	III
Naproxen Sodium[2]	Bayer	Alzheimer's dementia	III
Natalizumab[1]	Biogen/Athena Neurosciences	Multiple sclerosis	III
NDD-094	Novartis	Alzheimer's dementia	II
Nefiracetam[1]	Daiichi Pharmaceutical	Alzheimer's disease	III
Neramexane Hydrochloride	Forest	Antiparkinsonian	II
		Stroke	II
Neurochem	Neurochem	Alzheimer's dementia	II
Neurodex	Avanir	Miscellaneous neurologic disorders	III
NeuroVax	Immune Response	Multiple sclerosis	I/II
Nicaraven[1]	Chugai	Stroke	Prereg
NIK-317	Nikken Chemicals	Antiepileptic	III
NIL-A	Guilford	Antiparkinsonian	II
Nitroflurbiprofen[1]	Nicox	Alzheimer's disease	II
NPS-1506	NPS Pharmaceuticals	Ischemic stroke	I
NPS-1776	NPS Pharmaceuticals/Abbott	Antiepileptic	I
NS-2330	NeuroSearch/Boehringer Ingelheim	Alzheimer's dementia	II
		Antiparkinsonian	II
NS-7	Nippon Shinyaku/Schering AG	Stroke	II
NXY-059[1]	AstraZeneca	Ischemic stroke	II
Ono-2506	Ono	Stroke	II
		Parkinson's disease	I
		Alzheimer's dementia	I
p-58	Phytopharm	Alzheimer's dementia	II
Phenserine	Axonyx	Alzheimer's dementia	II
Polynitroxylated Albumin	SynZyme	Hemorrhagic stroke	II

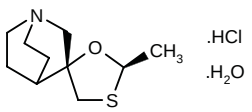
Continued

Annual Review 2002: Neurologic Drugs

Drug	Source	Indication/Action	Phase
Pregabalin[1]	Pfizer	Antiepiletic	III
Rasagiline Mesilate[1]	Teva	Antiparkinsonian	III
		Alzheimer's dementia	II
Recombinant Human Prourokinase	Abbott	Ischemic stroke	III
Repinotan Hydrochloride[1]	Bayer	Ischemic stroke	III
Retigabine[1]	Viatris	Antiepileptic	III
Revoxyn	Neuron Therapeutics	Stroke	I
Riluzole[1,2]	Aventis Pharma	Antiparkinsonian	III
Rivastigmine Tartrate[1,2]	Novartis	Vascular and Parkinson's dementia	III
Rofecoxib[1,2]	Merck & Co.	Alzheimer's dementia	III
Rotigotine Hydrochloride[1]	Schwarz	Antiparkinsonian	III
S-01139	Shionogi/GlaxoSmithKline	Ischemic stroke	II
		Hemorrhagic stroke	II
S-8510	Shionogi/GlaxoSmithKline	Alzheimer's dementia	II
		Vascular dementia	II
Safinamide Mesilate[1]	Newron	Antiepileptic	II
		Antiparkinsonian	II
Sapropterin Dihydrochloride[1,2]	Suntory	Extrapyramidal disorders	Prereg
Sarpogrelate Hydrochloride[1,2]	Mitsubishi Pharma	Stroke	III
SB-271046	GlaxoSmithKline	Alzheimer's dementia	I
SB-424323	GlaxoSmithKline	Stroke	II
SB-683698	GlaxoSmithKline	Multiple sclerosis	I
Sch-211803	Schering-Plough	Alzheimer's dementia	I
Sipatrigine	GlaxoSmithKline/CeNeS	Stroke	II
SL-251188	Sanofi-Synthélabo	Alzheimer's dementia	I
SLV-308[1]	Solvay	Antiparkinsonian	II
SMART Anti-E/P-Selectin Antibody	Protein Design Labs	Stroke	I
SMART Anti-L-Selectin	Protein Design Labs/Scil Biomedica	Stroke	II
Sodium Dichloroacetate	Questcor	Ischemic stroke	II/III
SPD-421	Shire Pharmaceuticals	Antiepileptic	II
SPD-473	Shire Pharmaceuticals	Parkinson's disease	II
SPD-502	Neurosearch/Shire Laboratories	Antiepileptic	I
		Ischemic stroke	I
SPD-503	Shire Laboratories	ADHD	II
SPH-3047	Sanochemia	Muscle spasms	I
Spheramine	Titan/Schering AG	Antiparkinsonian	II
SR-57667	Sanofi-Synthélabo	Alzheimer's dementia	I
		Antiparkinsonian	I
Stiripentol[1]	Biocodex	Antiepileptic	II
Sumanirole Maleate	Pharmacia	Antiparkinsonian	II
SUN-N4057	Suntory	Ischemic stroke	I
SX-3933	Dainippon Pharmaceutical	Alzheimer's dementia	I
T-2000	Taro	Antiepileptic	I
T-588[1]	Toyama	Alzheimer's dementia	II
Talampanel[1]	Ivax	Antiepileptic	II
T-Cell Receptor Peptide Based Vaccine	Immune Response	Multiple sclerosis	I/II
TCH-346	Novartis	Amyotrophic lateral sclerosis	II
		Antiparkinsonian	I
Tiplimotide	Neurocrine Biosciences	Multiple sclerosis	II
Tomoxetine Hydrochloride[1,2]	Lilly	ADHD	Prereg
Valrocemide	TEVA	Antiepileptic	II
VMDA-3601	Dong-A	Ischemic stroke	II
Xaliproden Hydrochloride[1]	Sanofi-Synthélabo	Amyotrophic lateral sclerosis	III
		Alzheimer's dementia	II
YKP-509	SK Corp.	Antiepileptic	I
Zanapezil Fumarate[1]	Takeda	Alzheimer's dementia	III
Zonampanel	Yamanouchi	Ischemic stroke	II
Zonisamide	Dainippon Pharmaceutical	Antiparkinsonian	II

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

Cevimeline Hydrochloride



The selective muscarinic M_1 receptor agonist cevimeline hydrochloride (SNI-2011, AF-102B, SND-5008 and SNK-508) was introduced in the U.S. in 2000 by Daiichi Pharmaceutical, under license from Snow Brand Milk Products, as Evoxac™ for the treatment of Sjögren's syndrome. The companies are also collaborating on the development of cevimeline for the treatment of Alzheimer's disease, for which it is in phase III clinical evaluation.

Elucidation of the pharmacological properties of cevimeline in mice, rats and cats indicated that the drug has muscarinic effects on general behavior and the central nervous system at doses 10 times higher than those required for saliva secretion (1).

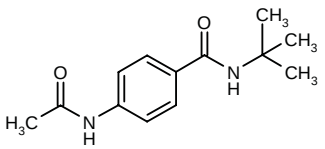
Muscarinic M_1 receptor activation has been reported to inhibit the secretion of β-amyloid (Aβ) in cell culture and may therefore represent a therapeutic approach to the treatment of Alzheimer's disease. The effects of cevimeline were therefore assessed on cerebrospinal fluid (CSF) Aβ levels in 19 Alzheimer's disease patients. A statistically significant decrease in Aβ levels was seen in the group as a whole; specifically, 14 patients showed a 22% decrease in CSF Aβ levels, 2 no change and 3 an increase in total Aβ CSF levels. In contrast, neither the acetylcholinesterase inhibitor physostigmine nor the anti-inflammatory agent hydroxychloroquine had a significant effect in Alzheimer's disease patients. These findings point to potential long-term beneficial effects of M_1 agonists in Alzheimer's disease (2).

1. Arisawa, H., Imai, E., Fujise, N., Fukui, K., Masunaga, H. *General pharmacological profile of the novel muscarinic receptor agonist SNI-2011, a drug for xerostomia in Sjögren's syndrome. 1st communication: Effects on general behavior and central nervous system.* Arzneim-Forsch Drug Res 2002, 52(1): 14.

2. Nitsch, R.M., Deng, M., Tennis, M., Schoenfeld, D., Growdon, J.H. *The selective muscarinic M_1 agonist AF102B decreases levels of total Aβ in CSF of patients with Alzheimer's disease*. 5th Int Conf Prog Alzheimer Parkinson Dis (March 31-April 5, Kyoto) 2001, Abst A-9-2.

Original monograph - Drugs Fut 2000, 25(6): 558.

CPI-1189



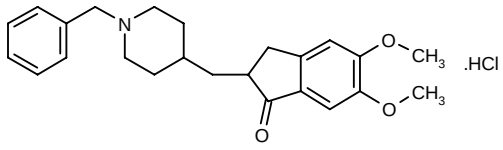
Centaur has obtained proof of concept in its dementia trials of CPI-1189, an oral agent which potentially inhibits neuroinflammation.

Statistically and clinically significant improvements in cognitive function were obtained on psychomotor tests conducted in double-blind, placebo-controlled phase IIa clinical studies in AIDS dementia and Parkinson's dementia patients. Results from these studies also support the safety of CPI-1189 upon long-term use, including 5 months of daily dosing in AIDS patients and 3 months of dosing in Parkinson's patients. Based on these positive results, Centaur plans to proceed to phase IIb studies of CPI-1189 in patients with Alzheimer's disease (1).

1. *Centaur's CPI-1189 shows efficacy in phase IIa trials in patients with dementia.* DailyDrugNews.com (Daily Essentials) May 16, 2001.

Original monograph - Drugs Fut 2001, 26(7): 647.

Donepezil Hydrochloride



Eisai has submitted a supplemental NDA to the FDA for donepezil hydrochloride (Aricept®) for the treatment of vascular dementia. The acetylcholinesterase inhibitor is currently approved for the symptomatic treatment of Alzheimer's disease (1).

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

Indication	Design	Treatments	n	Conclusions	Ref.
Vascular dementia	Randomized, double-blind, multicenter	Donezepil, 5 mg/d x 24 wk Donezepil, 5 mg/d x 1 wk → 10 mg/d x 23 wk Placebo	603	Donezepil was well tolerated and effective in patients with possible and probable vascular dementia	3
Dementia, vascular dementia	Randomized, double-blind, multicenter, pooled/meta-analysis	Donepezil, 5 mg/d x 24 wk (n=406) Donepezil, 10 mg/d x 24 wk (n=421) Placebo (n=392)	1219	Donezepil was effective in improving cognition and global function in patients with probable or possible dementia during the entire treatment period, with the 10 mg/d dose showing greater improvements	5, 6
Dementia, vascular dementia	Randomized, double-blind	Donepezil, 5 mg/d x 24 wk (n=208) Donepezil, 10 mg/d x 24 wk (n=215) Placebo (n=193)	616	Donepezil was well tolerated and effective in improving cognition and clinical status in patients with vascular dementia	7
Dementia	Open, multicenter	Memantine, 20 mg/d x 0.5 (mean) y + Donepezil, 10 mg/d x 0.6 (mean) y Memantine, 20 mg/d x 0.5 [mean] y + Rivastigmine, 4.5 mg/d x 0.6 [mean] y Memantine, 20 mg/d x 0.5 (mean) y + Tacrine, 160 mg/d x 0.6 (mean) y	158	Cotreatment with memantine and cholinesterase inhibitors such as donepezil was safe, well tolerated and generally effective in improving or stabilizing dementia	9
Dementia, Alzheimer's dementia	Open	Donepezil, 5 mg/d x 3 mo Donepezil, 10 mg/d x 3 mo	913	Donepezil was effective, well tolerated and improved the quality of life of most of the Alzheimer's disease patients enrolled	10

Results from a study in 12 patients with vascular dementia followed for 3 months on treatment with donepezil 5 mg/day have been reported. In all but 1 patient, improvement or stabilization was seen in mental status on the Mini-Mental State Examination (MMSE). Behavioral improvement was also reported by caregivers and no side effects were seen (2).

In a randomized, double-blind, placebo-controlled study enrolling 603 patients with a diagnosis of vascular dementia treated with donepezil 5 or 10 mg/day or placebo for 24 weeks, significant improvement in cognitive function compared to placebo was seen in the donepezil groups, as measured by the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and the MMSE. Donepezil was also superior to placebo when improvement was measured using the Clinician's Interview-Based Impression of Change scale (CIBIC-plus), and significantly reduced functional deterioration on donepezil was detected using the Alzheimer's Disease Functional Assessment of Change Scale (ADFACS). The withdrawal rate due to adverse events was similar on placebo and the low dose of donepezil (11.1%), and somewhat higher on donepezil 10 mg/day (21.8%) (3, 4). The results of this study and some that follow are summarized in Table I.

A combined analysis from 2 double-blind, randomized, placebo-controlled studies in 1219 patients with probable or possible vascular dementia treated with donepezil 5 or 10 mg/day or placebo for 24 weeks was reported. Patients treated with donepezil showed significantly improved cognition compared to placebo. The higher dose of the drug was associated with greater improvement in patients with probable vascular dementia compared to those with possible vascular dementia. Donepezil-treated patients also had greater improvements in global function and functional benefits over placebo-treated patients and the treatment was well tolerated. Unlike Alzheimer's disease patients, little or no decline in cognition was seen during the course of the study in placebo-treated patients with vascular dementia (5, 6).

Donepezil was evaluated in 616 patients with probable or possible vascular dementia in a 24-week, randomized, double-blind, placebo-controlled trial. Donepezil was administered at 5 mg/day for 28 days and then escalated to 10 mg/day in some patients. Cognitive function was significantly improved by both donepezil doses at the end of the study and the drug was well tolerated in this population (7).

A study compared the safety profile of donepezil in patients with vascular dementia and patients with Alzheimer's disease and found that the incidence of adverse events was higher in the vascular dementia groups than in the corresponding Alzheimer's disease groups. The authors of the study interpreted this finding as evidence that vascular dementia patients are "sicker" as a group than patients with Alzheimer's disease, and reported that the drug was well tolerated by both groups of patients (8).

The safety of a combination of memantine and cholinesterase inhibitors in the treatment of dementia and Alzheimer's disease was assessed in an open-label, observational postmarketing surveillance study in 158 patients suffering from dementia. Memantine was

combined with donepezil, rivastigmine or tacrine, and the tolerability of the treatment was generally good or very good. The combination of memantine and other drugs was safe, with only 6 patients reporting adverse events and all of these resolved without sequelae and without discontinuation of treatment. The combination was also effective, as physicians considered that the condition of the patients had improved or remained stable in 93% of the cases. These were the first results to suggest a good clinical tolerability of the combination of an uncompetitive NMDA antagonist such as memantine with cholinesterase inhibitors such as donepezil in the treatment of Alzheimer's disease and vascular dementia (9).

A postmarketing surveillance study was performed in Alzheimer's disease patients with or without concomitant cerebrovascular disease who were switched from other antidementia treatments to donepezil (5 or 10 mg/day). The study enrolled 913 patients who were observed for 3 months. At that time, the mean MMSE score increased by 2.2 points and quality of life was considered to be improved in 70% of patients, improvement being obtained in both those with and those without cerebrovascular disease. Donepezil was well tolerated in the study (10).

1. *Aricept sNDA submitted for vascular dementia*. DailyDrugNews.com (Daily Essentials) Sept 5, 2002.

2. Sisak, E. *Donepezil treatment in vascular dementia*. 2nd Int Congr Vasc Dement (Jan 24-27, Salzburg) 2002, Abst.

3. Pratt, R.D., Perdomo, C.A. *Donepezil improves cognitive function in patients with vascular dementia: Results from Study 307, a 24-week, randomized, double-blind, placebo-controlled trial*. 54th Annu Meet Am Acad Neurol (April 13-20, Denver) 2002, Abst S20.005.

4. Roman, G.C., Pratt, R.D., Perdomo, C.A. et al. *Donepezil improves cognition in patients with vascular dementia: Results from Study 307, a 24-week, randomized, double-blind, placebo-controlled trial*. 8th Int Conf Alzheimer's Dis Relat Disord (July 20-25, Stockholm) 2002, Abst 212.

5. Perdomo, C.A., Pratt, R.D. *A comparison of the effects of donepezil in patients with probable and possible vascular dementia: A combined analysis of two 24-week, randomized, double-blind, placebo-controlled trials*. 54th Annu Meet Am Acad Neurol (April 13-20, Denver) 2002, Abst P05.115.

6. Pratt, R.D., Perdomo, C.A. *Donepezil provides significant benefits on cognition, global function, and activities of daily living in patients with possible and probable vascular dementia*. Cerebrovasc Dis 2002, 13(Suppl. 3): Abst P276.

7. Salloway, S., Pratt, R.D. *Donepezil-treated patients with vascular dementia demonstrate cognitive and global benefits: Results from Study 308, a 24-week, randomized, double-blind, placebo-controlled trial*. 8th Int Conf Alzheimer's Dis Relat Disord (July 20-25, Stockholm) 2002, Abst 219.

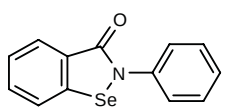
8. Pratt, R., Perdomo, C. et al. *Donepezil is well tolerated in patients with vascular dementia: A comparison of safety and tolerability results from randomized, placebo-controlled clinical trials in vascular dementia patients and Alzheimer's disease patients*. 8th Int Conf Alzheimer's Dis Relat Disord (July 20-25, Stockholm) 2002, Abst 218.

9. Hartmann, S., Möbius, H.-J. *Tolerability of memantine in combination with cholinesterase inhibitors in Alzheimer's disease and vascular dementia*. 8th Int Conf Alzheimer's Dis Relat Disord (July 20-25, Stockholm) 2002, Abst 317.

10. Frolich, L., Klinger, T., Berger, F.M. *Treatment with donepezil in Alzheimer patients with and without cerebrovascular disease*. 2nd Int Congr Vasc Dement (Jan 24-27, Salzburg) 2002, Abst.

Original monograph - Drugs Fut 1991, 16(1): 16.

Ebselen



The seleno-organic compound ebselen, which exerts antioxidant activity through a glutathione peroxidase-like mechanism, is under regulatory review in Japan for the treatment of subarachnoid hemorrhage and acute stroke. It was developed by Daiichi Pharmaceutical under license from Aventis.

An *in vitro* study using PC-12 cells (catecholamine-containing neurons) has shown that ebselen reduced oxidative stress-induced neuronal cell death via suppression of c-Jun *N*-terminal kinase (JNK) activity and the activator protein-1 (AP-1) signaling pathway. Ebselen inhibited H_2O_2-induced JNK without affecting extracellular signal-regulated kinase (ERK) or p38 activation. The agent also suppressed H_2O_2-induced increases in DNA binding activity of AP-1 and significantly increased recovery of cells from H_2O_2-induced apoptosis. The agent may therefore be effective in the treatment of ischemic cerebral disorders involving neuronal cell death (1). In rats with transient focal ischemia, i.v. ebselen at a dose of 1 mg/kg by bolus plus 1 mg/kg/h significantly decreased gray and white matter damage and neurological deficits. The principal mechanism of action appeared to be attenuation of free radical damage (2).

Intrastriatal injection of quinolinic acid in rats increased the striatal content of thiobarbituric acid reactive species (TBARS) and induced convulsions and contralateral rotational behavior. Injection of ebselen 15 min before quinolinic acid eliminated TBARS production without affecting the behavioral effects, indicating that ebselen acts on postreceptor events (3).

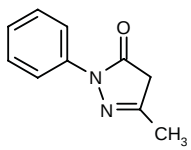
1. Yoshizumi, M., Kogame, T., Suzaki, Y. et al. *Ebselen attenuates oxidative stress-induced apoptosis via the inhibtion of the c-Jun N-terminal kinase and activator protein-1 signalling pathway in PC12 cells*. Br J Pharmacol 2002, 136(7): 1023.

2. Imai, H., Masayasu, H., Dewar, D., Graham, D.I., Macrae, I.M. *Ebselen protects both gray and white matter in a rodent model of focal cerebral ischemia*. Stroke 2001, 32(9): 2149.

3. Rossato, J.I., Zeni, G., Mello, C.F., Rubin, M.A., Rocha, J.B.T. *Ebselen blocks the quinolinic acid-induced production of thiobarbituric acid reactive species but does not prevent the behavioral alterations produced by intra-striatal quinolinic acid administration in the rat*. Neurosci Lett 2002, 318(3): 137.

Original monograph - Drugs Fut 1984, 9(10): 741.

Edaravone



Edaravone (Radicut®, MCI-186) is a free radical scavenger and antioxidant that was recently introduced by Mitsubishi Pharma in Japan for use in patients with acute stroke.

Neuroprotection with edaravone (3, 6 and 9 mg/kg) was investigated in rat pups subjected to hypoxic-ischemic injury. Examination 24 h and 7 days after the insult revealed that edaravone dose-dependently protected against brain damage (1).

The combined neuroprotective effect of argatroban and edaravone against postischemic hypoperfusion was assessed in gerbils after 15 min of forebrain ischemia. Either drug alone significantly increased postischemic cerebral blood flow and attenuated brain edema after reperfusion, but only the combination increased the survival ratio and protected neuronal cells from damage. It appears that anticoagulants and free radical scavengers reciprocally function to inhibit the progression of ischemic cell damage (2).

A study examined the effect of edaravone on local cerebral blood flow in acute stroke patients. Twenty patients presenting within 24 h of cerebral thrombosis were given an i.v. drip infusion of edaravone before and after SPECT to measure medial and regional cerebral blood flow. The results suggested that edaravone had no direct acute effect on cerebral blood flow after cerebral infarction (3).

Japanese investigators have described findings related to immunoneuropathic and neurodegenerative diseases and the effects of the free radical scavenger edaravone. They determined the levels of 3-nitrotyrosine (3-NT) in patients with amyotrophic lateral sclerosis (ALS), Guillain-Barre syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, Fisher's syndrome and other disorders, including Alzheimer's disease. They found that about half the cases of ALS had elevated 3-NT levels, as did some patients with Guillain-Barre syndrome and immunoneuropathy, indicating a role for oxidative stress in nerve cell damage in these diseases. Moreover, treatment with edaravone (30 mg/day for 14 days) resulted in significant reductions in 3-NT levels in 2 of 5 ALS patients. Based on these findings, it is suggested that antioxidant and free radical-scavenging drugs may have potential in intractable neuropathies. Edaravone may thus merit further evaluation for the treatment of immunoneuropathy and neurodegenerative diseases (4).

Edaravone was safe and improved neurological deficits in acute ischemic stroke patients, resulting in improvements in activities of daily living and disability (5).

1. Ikeda, T., Xia, Y.X., Kaneko, M., Sameshima, H., Ikenoue, T. *Effect of the free radical scavenger, 3-methyl-1-phenyl-2-pyrazolin-5-one (MCI-186), on hypoxia-ischemia-induced brain injury in neonatal rats*. Neurosci Lett 2002, 329(1): 33.

2. Jin, Y.J., Mima, T., Raicu, V., Park, K.C., Shimizu, K. *Combined argatroban and edaravone caused additive neuroprotection against 15 min of forebrain ischemia in gerbils*. Neurosci Res 2002, 43(1): 75.

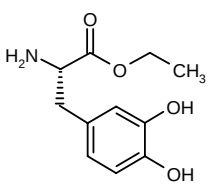
3. Ueda, T. et al. *Local cerebral blood flow response to edaravone (Radicut) in acute cerebral infarction*. Jpn J Stroke 2002, 24(1): Abst P178.

4. Yoshino, H., Asano, A., Kimura, A. *Determination of 3-nitrotyrosine in CSF of patients with ALS and neuroimmunologic disorders and the effect of free radical scavenger, edaravon, on the levels of 3NT in CSF*. Neuroimmunology 2002, 10(1): 132.

5. Tanaka, M. *Pharmacological and clinical profile of the free radical scavenger edaravone as a neuroprotective agent*. Folia Pharmacol Jpn 2002, 119(5): 301.

Original monograph - Drugs Fut 1996, 21(10): 1014.

Etilevodopa



Lundbeck, under license from Teva, is conducting phase III clinical trials with etilevodopa (L-DOPA ethyl ester, levodopa ethyl ester, TV-1203) in Europe as a potential treatment for Parkinson's disease (1-3).

A crossover pharmacokinetic study enrolled 29 Parkinson's disease patients with response fluctuations to compare the parameters of etilevodopa in dispersable tablet, oral solution and dissolved dispersable tablet formulations combined with carbidopa and levodopa plus carbidopa tablet formulations. The etilevodopa/carbidopa formulations had shorter t_{max} values and significantly larger AUC values in the first hour postdose than levodopa/carbidopa. Peak plasma levels were significantly higher with the etilevodopa/carbidopa dispersable tablet. Etilevodopa/carbidopa tablets demonstrated pharmacokinetics equivalent to the etilevodopa/carbidopa oral solution (4).

The effect of the improved absorption of etilevodopa over levodopa was assessed in a multicenter, randomized, double-blind study in 62 Parkinson's disease patients with delayed "on" or no "on" response fluctuations. Patients were given etilevodopa solution plus carbidopa tablets or the standard levodopa/carbidopa (250/25 mg) tablets for 4 weeks, with only the morning and afternoon levodopa/carbidopa doses replaced with etilevodopa/carbidopa. In a 2-week extension, carbidopa 25 mg was added to the replaced doses. Etilevodopa decreased the latency from dose ingestion to turning "on" after the morning and afternoon doses, and afternoon no "on" episodes were also reduced by etilevodopa compared with levodopa/carbidopa. The effect of etilevodopa/carbidopa treatment was enhanced by the addition of carbidopa (5).

1. *Neurological drugs in Lundbeck's pipeline*. DailyDrugNews.com (Daily Essentials) Sept 20, 2001.

2. *Important advances in the Lundbeck pipeline during 2000*. DailyDrugNews.com (Daily Essentials) Jan 10, 2001.

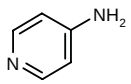
3. *Teva finalizes separate agreements with Aventis and Lundbeck*. DailyDrugNews.com (Daily Essentials) Feb 16, 2001.

4. Djaldetti, R. et al. *Pharmacokinetic profiles of different forms of levodopa ethylester (solution, dispersible swallowed tablet, dissolved tablet) compared with levodopa tablets*. Parkinsonism Relat Disord 2001, 7(Suppl. 1): Abst P-TU-178.

5. Djaldetti, R., Inzelberg, R., Giladi, N. et al. *Oral solution of levodopa ethylester for treatment of response fluctuations in patients with advanced Parkinson's disease*. Mov Disord 2002, 17(2): 297.

Original monograph - Drugs Fut 2001, 26(3): 219.

Fampridine



Fampridine-SR, a sustained-release form of 4-aminopyridine (4-AP), is being developed by Acorda under a license agreement with Elan. Acorda obtained the rights to develop fampridine for therapeutic use in SCI from the Canadian Spinal Research Organization (CSRO). The company has chosen spasticity as the lead indication for fampridine, with NDA submission planned for 2003 (1).

Acorda has initiated two phase III studies of fampridine-SR in chronic spinal cord injury (SCI). The trials will enroll a total of 360 patients at more than 70 SCI centers in the U.S. and Canada and aim to evaluate the safety and efficacy of fampridine-SR in the treatment of moderate to severe spasticity associated with chronic SCI. Fampridine enhances conduction in damaged nerves, and is the first compound to restore some neurological function to people with SCI. Fampridine-SR is an oral formulation designed for twice-daily dosing. It restores nerve conduction by blocking exposed potassium channels in demyelinated axons. In previous SCI clinical trials, fampridine-SR reduced spasticity, improved sexual function and bowel and bladder control. It is also being evaluated in phase II trials for the treatment of symptoms associated with multiple sclerosis (2).

Fampridine blocked the slow afterhyperpolarization seen after high-frequency dendritic or somatic firing in rat CA1 hippocampal pyramidal neurons. The effect was altered by varying the type of anion used in the electrode solution (3).

Experiments in neonatal rats showed that treatment of motor nerve terminals with fampridine before nerve injury prevented motoneuron death. Treatment of soleus and extensor digitorum longus muscles 3 days before crushing of the sciatic nerve improved reinnervation in treated versus untreated muscles (4).

Fampridine was found to concentration-dependently increase free cytosolic calcium concentrations in type I astrocytes, neurons and skeletal muscle cells under basal conditions. The agent also potentiated capacitative calcium entry severalfold in astrocytes and muscle cells, but not in neurons, possibly explaining some of its neurotransmission-enhancing effects (5).

Fampridine (10 mg i.m. b.i.d. for 28 days) was administered to 15 patients with relapsing-remitting multiple sclerosis to assess the agent's effects on neurological and cognitive deficits. Treatment improved cognitive functions, including verbal and nonverbal memory and executive functions, as well as physical disability. The investigators concluded that fampridine may improve cognitive functions by enhancing cholinergic transmission at

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

Indication	Design	Treatments	n	Conclusions	Ref.
Multiple sclerosis	Open	Fampridine, 10 mg bid x 28 d	15	Fampridine improved cognitive functions and physical disability in multiple sclerosis patients	6
Multiple sclerosis	Open	Galantamine, 5 mg bid + Fampridine, 10 mg bid x 1 mo	15	Galantamine and fampridine significantly improved cognitive deficits in patients with multiple sclerosis	7
Spinal cord compression	Randomized, double-blind, crossover	Fampridine, 5 mg/d tid (uptitrated over 4 wk to maximum 0.5 mg/kg) → Placebo x 4 wk Fampridine, 5 mg/d tid (uptitrated over 4 wk to maximum 0.5 mg/kg) → Placebo x 4 wk	20	Fampridine did not improve the functional status of spinal cord injury patients, and no subset of patients appeared to benefit more from treatment	8
Multiple sclerosis	Randomized, double-blind, crossover	Fampridine, 32 mg/d x 6 mo Placebo	54	Fampridine did not alter fatigue scores in any of the multple sclerosis patients, although those with higher fampridine serum levels achieved a significant decrease in fatigue	9
Spinal cord compression	Open	Fampridine, 10 mg sd	13	While baseline low-frequency heart rate variability power was lower in spinal cord injury patients compared with controls, it increased in patients after treatment with fampridine to the level of controls	11
Spinal cord compression	Randomized, double-blind, crossover	Fampridine, 10 mg sd Placebo	25	Fampridine administered after transcranial magnetic stimulation appeared to enhance central motor conduction in patients with spinal cord injury	12
Spinal cord injury	Randomized, double-blind, multicenter	Fampridine, 25 mg bid x 8 wk (2 wk uptitration, 4 wk maintenance and 2 wk tapering) Fampridine, 40 mg bid x 8 wk (2 wk uptitration, 4 wk maintenance and 2 ws tapering) Placebo	91	Fampridine was well tolerated and effective in improving the subjects' global impression and bowel function	13

central nervous synapses (6, 7). The results of these studies and some of those that follow are summarized in Table II.

Twenty patients with chronic, incomplete SCI were treated with fampridine (titrated up to a maximum of 0.5 mg/kg) in a randomized, double-blind, crossover trial. Patients received fampridine for 4 weeks and then 4 weeks of placebo, or placebo and then fampridine. The agent did not improve the functional status of the patients, and no subset of patients appeared to benefit more from treatment (8).

A randomized, double-blind, placebo-controlled trial examined whether fampridine at a dose of 32 mg/day could decrease daily living fatigue in 54 patients with progressive multiple sclerosis. After 6 months of treatment, a significant effect on fatigue was measured in patients with high serum levels of fampridine (9).

The pharmacokinetics and safety of multiple oral doses of fampridine-SR were assessed in an open-label, 4-week study in 16 patients with chronic SCI. The participants received doses of 10, 15, 20 or 25 mg b.i.d. for 1 week. The drug was absorbed slowly, peak plasma levels being reached at 2.6-3.2 h, with a mean plasma elimination half-life of 5.5-7.5 h. Fampridine-SR was generally well tolerated and adverse events were mild to moderate, leading to withdrawal in 2 patients (10).

Heart rate and heart rate variability were measured in 13 patients with long-standing SCI and in 13 able-bodied volunteers after a single dose of fampridine 10 mg. While baseline low-frequency heart rate variability power was lower in SCI patients compared with controls, it increased in patients after treatment with fampridine to the level of controls (11).

In a double-blind, placebo-controlled trial in patients with SCI, motor evoked potentials were elicited with transcranial magnetic stimulation delivered before and after administration of fampridine 10 mg. Fampridine appeared to improve the impaired central motor conduction in some patients, possibly by improving conduction deficits at the site of injury and by increasing cortical excitability (12).

Fampridine-SR has been shown to improve neurological function in patients with chronic SCI or multiple sclerosis. A double-blind, parallel-group study confirmed that fampridine-SR (25 mg b.i.d.) is well tolerated and results in significant improvements in bowel function and in Subject Global Impression scores (13).

1. *Acorda chooses spasticity as fampridine lead indication*. DailyDrugNews.com (Daily Essentials) Jan 17, 2002.

2. *Fampridine-SR enters two phase III trials for chronic spinal cord injury*. DailyDrugNews.com (Daily Essentials) July 3, 2002.

3. Andreasen, M. *Inhibition of slow Ca^{2+}-activated K^+ current by 4-aminopyridine in rat hippocampal CA1 pyramidal neurones*. Br J Pharmacol 2002, 135(4): 1013.

4. Dekkers, J., Waters, J., Vrbova, G., Greensmith, L. *Treatment of the neuromuscular junction with 4-aminopyridine results in improved reinnervation following nerve injury in neonatal rats*. Neuroscience 2001, 103(1): 267.

5. Grimaldi, M., Atzori, M., Ray, P., Alkon, D.L. *Mobilization of calcium from intracellular stores, potentiation of neurotransmitter-induced calcium transients, and capacitative calcium entry by 4-aminopyridine*. J Neurosci 2001, 21(9): 3135.

6. Nikolova, G., Traykov, L., Yancheva, S., Georgiev, D., Kmetska, K., Petrova, L., Dobreva, D. *Therapeutic efficacy of 4-aminopyridine on neurological and cognitive deficit in multiple sclerosis*. 17th World Congr Neurol (June 17-22, London) 2001, Abst P1305.

7. Traykov, L., Nikolova, G., Dobreva, D., Georgiev, D., Kmetska, K., Petrova, T., Yancheva, St. *Therapeutic efficacy of galanthamine and 4-aminopytidine on cognitive deficit in patients with multiple sclerosis*. Pharmacol Toxicol 2001, 89(Suppl. 1): Abst 551.

8. Van Der Bruggen, M.A., Huisman, H.B., Beckerman, H., Bertelsmann, F.W., Polman, C.H., Lankhorst, G.J. *Randomized trial of 4-aminopyridine in patients with chronic incomplete spinal cord injury*. J Neurol 2001, 248(8): 665.

9. Rossini, P.M., Pasqualetti, P., Pozzilli, C., Grasso, M.G., Millefiorini, E., Graceffa, A., Carlesimo, G.A., Zibellini, G., Caltagirone, C. *Fatigue in progressive multiple sclerosis: Results of a randomized, double-blind, placebo-controlled, crossover trial of oral 4-aminopyridine*. Multiple Scler 2001, 7(6): 354.

10. Hayes, K.C., Potter, P.J., Hsieh, T.C., Katz, M.A., Blight, A.R. *Open-label, multiple-dose study to determine the pharmacokinetics and safety of fampridine-SR in patients with chronic spinal cord injury*. 126th Annu Meet Am Neurol Assoc (Sept 30-Oct 3, Chicago) 2001, 76.

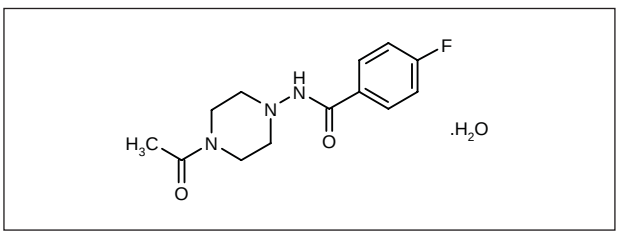
11. Segal, J.L., Warner, A.L., Brunnemann, S.R., Bunten, D.C. *4-Aminopyridine influences heart rate variability in long-standing spinal cord injury*. Am J Ther 2002, 9(1): 29.

12. Wolfe, D.L., Hayes, K.C., Hsieh, J.T.C., Potter, P.J. *Effects of 4-aminopyridine on motor evoked potentials in patients with spinal cord injury: A double-blinded, placebo-controlled crossover trial*. J Neurotrauma 2001, 18(8): 757.

13. Lammertse, D., Graziani, V., Katz, M.A., Blight, A.R. *Clinical evaluation of oral fampridine-SR (sustained-release 4-aminopyridine) in patients with chronic motor-incomplete spinal cord injury*. 54th Annu Meet Am Acad Neurol (April 13-20, Denver) 2002, Abst P01.035.

Original monograph - Drugs Fut 1980, 5(2): 221.

FK-960



Fujisawa's FK-960 is being evaluated in late-stage clinical trials in the U.S. and Japan as an antidementia agent. The compound exhibits a novel mechanism of action, activating the somatostatinergic system and thereby accelerating synaptic transmission.

An *in vitro* study recording intracellular excitatory postsynaptic potentials (EPSPs) and currents (EPSCs) from CA1 neurons in the rat hippocampus showed that FK-960 (100 nM) significantly enhanced the amplitude of EPSPs. No effects were observed on membrane potential, resistance or early GABAergic inhibitory postsynaptic current. Since FK-960 had no effect on the decay phase of EPSCs, indicating no effect on desensitization or deactivation, it was suggested that the agent acts on postsynaptic AMPA receptors. The effects of FK-960 on EPSPs were blocked by methyllycaconitine and α-bungarotoxin, suggesting that the agent, via modulation of α_7 nicotinic acetylcholine receptors, upregulates the action of acetylcholine at synapses in the hippocampus (1).

An *in vitro* study recording depolarization-induced Ca^{2+} current from *Xenopus* oocytes expressing a combination of rabbit α_1, human $\alpha_2\delta_1$ and human β_{1B} subunits of the N-type calcium channel showed that FK-960 significantly potentiated the α_{1B} current in a reversible, concentration-dependent manner. Maximum effects were observed at a concentration of 100 nM. The agent had a fast onset of action but did not alter activation or steady-state inactivation of the channel. The α_{1A} current was also potentiated by FK-960 treatment, although to a lesser extent. The agent had no effects on the α_{1C} or α_{1E} current (2).

Results from a study in rat hippocampal slices showed that FK-960 significantly increased the release of somatostatin in response to high potassium concentrations. The agent had no effect on basal somatostatin release or the release of acetylcholine, 5-HT, D-aspartate or GABA (3).

Using several animal models of cognitive deficits, researchers assessed the effects of FK-960 alone and in combination with the cholinesterase inhibitor donepezil. FK-906 (0.1-10 mg/kg i.p.) was able to significantly improve memory deficits in scopolamine-treated rats, rats with bilateral basal forebrain lesions and aged rats, whereas donepezil (0.032-3.2 mg/kg i.p.) showed significant efficacy in the first two models but not in aged rats. Combining low noneffective doses of both agents

resulted in significant improvement in memory impairment in the basal forebrain-lesioned rats, and concomitant administration of optimal doses of each agent (1 mg/kg FK-960 and 0.32 mg/kg donepezil) was associated with marked improvement in memory deficits compared to either agent alone (4).

Compounds that activate α_7 nicotinic acetylcholine receptors have been found to modulate excitatory synaptic transmission. These compounds are expected to be useful for the treatment of cerebral diseases such as dementia, amnesia, psychosis, schizophrenia or Parkinson's disease. A preferred compound is FK-960 (5).

1. Hodgkiss, J.P., Kelly, J.S. *Effect of FK960, a putative cognitive enhancer, on synaptic transmission in CA1 neurons of rat hippocampus*. J Pharmacol Exp Ther 2001, 297(2): 620.

2. Kanadzu, M. et al. *Specific potentiation of alpha$_{1B}$ (N-type) Ca^{2+} channel current by a potential antidementia drug, FK960*. Jpn J Pharmacol 2001, 85(Suppl. I): Abst P-368.

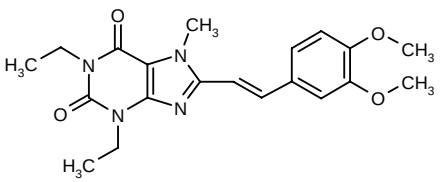
3. Inoue, T., Wang, F., Moriguchi, A., Shirakawa, K., Matsuoka, N., Goto, T. *FK960, a novel potential anti-dementia drug, enhances high K^+-evoked release of somatostatin from rat hippocampal slices*. Brain Res 2001, 892(1): 111.

4. Tokita, K., Matsuoka, N., Goto, T. *Combination of novel anti-dementia drug FK960 with a cholinesterase inhibitor synergistically improves memory deficits in rat model of dementia*. Soc Neurosci Abst 2001, 27: Abst 319.16.

5. Kelly, J.S. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Agent for modulating excitatory synaptic transmission comprising a cpd. having alpha$_7$ nicotinic acetylcholine receptor activation property*. WO 0220016.

Original monograph - Drugs Fut 1997, 22(8): 830.

KW-6002



The current treatment of Parkinson's disease, based mainly on dopamine replacement with levodopa, is hampered by the development of dyskinesias and loss of efficacy over the long term. Kyowa Hakko's KW-6002 is a selective adenosine A_{2A} receptor antagonist which may offer an alternative or a complement to L-DOPA therapy.

Two U.S.-based phase IIa clinical trials of KW-6002 in the treatment of Parkinson's disease have been completed. As monotherapy or combination therapy with levodopa or dopamine agonists, it has been shown to improve the symptoms of the disease in a parkinsonian monkey model, without increasing the incidence or severity of dopaminergic-related side effects or inducing or worsening dyskinesia. Kyowa Hakko is currently preparing for pivotal phase IIb and phase III trials in the U.S. and worldwide (1).

KW-6002 (0.1-30 mg/kg) was given alone and in combination with pergolide (0.003-0.1 mg/kg) and apomorphine (0.5 mg/kg) to rats which were then examined in the prepulse inhibition paradigm. According to the study results, KW-6002 does not possess psychotomimetic effects and does not potentiate those of dopamine agonists, suggesting that the two types of treatments can be used in combination to treat Parkinson's disease (2).

Hypolocomotion induced in rats by haloperidol was reversed by 0.3-3 mg/kg KW-6002, which also substantially increased locomotor activity in drug-naive rats. KW-6002 (1-10 mg/kg) produced ipsilateral rotations in drug-naive hemiparkinsonian rats, while in rats sensitized with apomorphine, KW-6002 produced contralateral rotations (3).

Studies in MPTP-treated marmosets demonstrated improvement in motor disability on KW-6002, which was dose-related and correlated with plasma levels. Concomitant administration with low doses of L-DOPA or dopamine D_2 receptor agonists provided additive or synergistic improvement in motor disability and increased motor activity, but KW-6002 did not exacerbate L-DOPA-induced dyskinesia in animals primed by prior exposure to L-DOPA. Thus, the use of KW-6002 may allow a reduction in the dose of L-DOPA in Parkinson's disease and may also be useful as monotherapy. Furthermore, it may have beneficial effects in all stages –from early to late– of Parkinson's disease (4, 5).

A study using a rat model of Parkinson's disease revealed that KW-6002 improved motor disability without inducing dyskinesia. A total of 35 rats with unilateral 6-OHDA lesions of the nigrostriatal pathway received KW-6002, L-DOPA combined with benserazide, a combination of L-DOPA and KW-6002, or vehicle for 21 days. KW-6002 induced significant motor improvement, especially when combined with L-DOPA, although this combination and L-DOPA alone both caused increasingly severe dyskinesia (6).

A double-blind, placebo-controlled study involving administration of either KW-6002 or placebo to 16 patients with moderate to advanced Parkinson's disease confirmed the drug's therapeutic benefits for patients simultaneously treated with levodopa (7).

Table III: Clinical studies of KW-6002 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Parkinson's disease	Randomized double-blind	KW-6002, 40 mg/d iv ± Levodopa x 6 wk KW-6002, 80 mg/d iv ± Levodopa x 6 wk Placebo	16	Adenosine A_{2A} receptor blockade with KW-6002 improved symptoms in patients with Parkinson's disease and motor complications associated with levodopa	7
Parkinson's disease	Randomized, double-blind, multicenter	KW-6002, 20 mg/d x 12 wk (n=26) KW-6002, 40 mg/d x 12 wk (n=28) Placebo (n=29)	83	Adenosine A_{2A} receptor blockade with KW-6002 was safe and effective in reducing "off" time without effects on dyskinesia in patients with Parkinson's disease and motor complications associated with levodopa	8

The efficacy and safety of KW-6002 were assessed in a placebo-controlled study conducted in 83 patients with advanced Parkinson's disease. KW-6002 was more effective than placebo and did not increase dyskinesia (8).

The results of these two clinical studies are summarized in Table III.

1. *KW-6002 completes phase IIa trials in Parkinson's disease*. DailyDrugNews.com (Daily Essentials) Feb 19, 2002.

2. Whawell, E., Upton, R., Mirza, N., Wyat, A., Weiss, S.M. *The effects of the adenosine A_{2A} receptor antagonist, KW-6002 on pre-pulse inhibition in the rat*. J Psychopharmacol 2001, 15(3, Suppl.): Abst H11.

3. Upton, R., Willoughby, A., Weiss, S.M. *The effects of adenosine A_{2A} receptor antagonist, KW-6002, in animal models of Parkinson's disease*. J Psychopharmacol 2001, 15(3, Suppl.): Abst I38.

4. Kanda, T., Jackson, M.J., Kamenosono, T. et al. *Adenosine A_{2A} antagonist: A novel antiparkinsonian agent that does not provoke dyskinesia in parkinsonian monkeys*. 5th Int Conf Prog Alzheimer Parkinson Dis (March 31-April 5, Kyoto) 2001, Abst IV-PD-34.

5. Jenner, P. *Adenosine receptor antagonists in the treatment of Parkinson's disease*. 5th Int Conf Prog Alzheimer Parkinson Dis (March 31-April 5, Kyoto) 2001, Abst P-15-1.

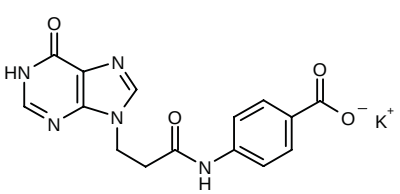
6. Lundblad, M., Vaudano, E., Cenci, M.A. *Adenosine A_{2A} receptor antagonist KW-6002 relieves motor disability without producing cellular and motor signs of dyskinesia in a rat model of Parkinson's disease*. 3rd Forum Eur Neurosci (July 13-17, Paris) 2002, Abst 186.2.

7. Sherzai, A., Bara-Jimenez, W., Gillespie, M., Favit, A., Bibbiani, F., Morris, M.J., Mouradian, M.M. *Adenosine A_{2a} antagonist treatment of Parkinson's disease*. 54th Annu Meet Am Acad Neurol (April 13-20, Denver) 2002, Abst P06.104.

8. Hubble, J.P. et al. *A novel adenosine antagonist (KW-6002) as a treatment for advanced Parkinson's disease (PD) with motor complications*. 54th Annu Meet Am Acad Neurol (April 13-20, Denver) 2002, Abst S21.001.

Original monograph - Drugs Fut 2001, 26(1): 21.

Leteprinim Potassium



Leteprinim potassium (AIT-082, Neotrofin™; NeoTherapeutics) is a *para*-aminobenzoic acid derivative of hypoxanthine proven to enhance cognition and improve memory impairment in a number of different animal models.

Neotrofin™ has been reported to turn on memory-related genes in the brain to produce various neurotrophic factors, and to reduce β-amyloid accumulation *in vitro*. In animal models, Neotrofin™ is biologically active in neuroprotection, the release of neurotrophic factors and stimulating stem cell proliferation. Safety, good tolerance and evidence of efficacy were demonstrated in phase I trials, as was the feasibility of once-daily dosing. Phase II studies of Neotrofin™ are ongoing in Parkinson's disease, spinal cord injury (SCI) and chemotherapy-induced neuropathy, with results expected by the end of this year. Two studies in chemotherapy-induced neuropathy were initiated in January 2002, and results are expected in 2003. NeoTherapeutics plans to seek a codevelopment partner for Neotrofin™ before initiating further clinical studies (1-14).

Data from a double-blind, dose-escalating (150-1000 mg) phase II clinical trial of Neotrofin™ in 19 patients diagnosed with Alzheimer's disease demonstrated that the compound facilitates brain activity in these patients, leading to statistically significant and dose-related improvements in memory, attention and judgment, as

demonstrated in a multifaceted battery of neurocognitive tests. Positron emission tomography (PET) scanning, which measures the metabolic activity of the brain, and electroencephalography (EEG), which measures brain waves, on the same patients were consistent with improvement following Neotrofin™ administration. These findings motivated the company to begin a 1-year pivotal clinical trial of Neotrofin™ at doses of 500 mg and 1000 mg in patients with moderate Alzheimer's disease. Preliminary analysis of this pivotal trial showed that while some patients experienced improvement in ADAS-cog scores and clinical global change ratings, not listed as primary endpoints of the trial, the results did not reach statistical significance and results fell short of the predetermined pivotal 12-week endpoints required for FDA approval. Based on these data, the company is no longer devoting resources to the clinical development of Neotrofin™ for Alzheimer's disease (1, 2, 7-10).

The potential of Neotrofin™ for the therapy of neurodegenerative disorders was demonstrated in a study of the drug's protective activity against long-term excitotoxicity of hippocampal neurons in rats with kainate-induced status epilepticus. Seizures and neurotoxicity were almost completely inhibited by diazepam (20 mg/kg i.p. 20 min before kainate injection), whereas Neotrofin™ treatment (60 mg/kg/day i.p. for 7 days beginning 20 min before kainate injection) had no effect on seizures but did decrease kainate-induced mortality, the reduction of glutamic acid decarboxylase activity and the loss of hippocampal neurons (15).

Rats with unilateral 6-OHDA lesions were used as a model of Parkinson's disease and administered Neotrofin™ (10 mg/kg s.c.) or vehicle 15 min before the induction of substantia nigra lesions and daily for 30 days. Treatment with the drug reduced apomorphine-induced rotations and delayed their onset compared to vehicle-treated animals, suggesting its ability to protect nigrostriatal dopaminergic neurons from the neurodegeneration typical of Parkinson's disease (16, 17). The acute effects of Neotrofin™ (i.p. or p.o.) were also evaluated in rats with unilateral 6-OHDA lesions. Single doses of the drug produced rotations in these animals and significantly increased hyperlocomotion induced by the NMDA antagonist MK-801, indicating acute modulation of dopaminergic function (18).

While Neotrofin™ did not alter the antitumor activity of paclitaxel, vincristine or cisplatin in human breast, lung and colon tumor cell lines, the agent did reduce the severity of vincristine-induced neuropathy and enhance recovery after vincristine treatment in rats (19).

Results from preclinical trials with Neotrofin™ indicated that the agent stimulated the proliferation of brain stem cells in adult mice. Stimulation of neurogenesis may be a means of repopulating the brain with new neurons and therefore provide a therapeutic approach to slowing and even reversing the damage done by disease or injury. In two blinded, dose-response studies, mice were given a single dose of Neotrofin™ and 24 h later the number of newly formed brain stem cells was counted. Analysis revealed that in animals treated with doses between 1 and 10 mg/kg, there was a significantly higher number of newly generated brain cells. Studies are currently ongoing to examine the effect of multiple doses and to determine whether the newly formed brain stem cells will mature to become neurons (20).

In a double-blind, placebo-controlled, dose-escalating phase I study, 8 healthy elderly volunteers received Neotrofin™ as a single oral dose each week starting with placebo and then increasing to 0.6, 2, 6 and 20 mg/kg at the end of week 5. The drug was safe and well tolerated and pharmacokinetic variables indicated that once-daily dosing was appropriate in this population (21).

Interim results from a pilot study of Neotrofin™ in early-stage Parkinson's disease indicated acute efficacy in the initial weeks of treatment. Data have been analyzed from the first 4 weeks of the 12-week study in which 20 patients received Neotrofin™ and 6 patients received placebo. Acute efficacy was observed in the first few weeks when patients received Neotrofin™ 250 mg twice a day. This was followed by a decrease in efficacy as patients were titrated first to 500 mg twice daily, then to 1000 mg twice daily. Neotrofin™ patients showed statistically significant improvement in motor examination scores from the Unified Parkinson's Disease Rating Scale (UPDRS) within 2 or 3 h of receiving their first 250-mg dose. Significant improvement was also noted before and 2-3 h after a second 250-mg morning dose, when patients were receiving a morning and evening dose for 2 weeks. However, the improvement was smaller and not statistically significant when patients received Neotrofin™ 500 mg twice a day for 2 weeks and were evaluated before and 2-3 h after a second morning dosing. Score changes among placebo patients were not statistically significant, although the small size of the placebo group limited the power of these analyses. Patients went on to receive Neotrofin™ 1000 mg twice daily for the remainder of the study, but analysis of the data has not yet been conducted. The results did not exclude a neurotrophic mechanism, but suggested that an additional acute action may also be implicated. The diminishing efficacy during the treatment period may be due to loss of response to continued treatment, or to lower efficacy with higher doses. The current protocol will be stopped, and a new study of maintained lower doses will be initiated in order to identify the reason for diminishing efficacy. A larger placebo group will also be used (22-24).

1. *Neotrofin fails to meet primary endpoint in Alzheimer's disease*. DailyDrugNews.com (Daily Essentials) April 30, 2002.

2. *New strategic focus announced by NeoTherapeutics*. DailyDrugNews.com (Daily Essentials) May 8, 2002.

3. Wieland, S., Huff, J. *The use of Neotrofin™ in the treatment of neurodegenerative diseases*. 5th Int Conf Prog Alzheimer Parkinson Dis (March 31-April 5, Kyoto) 2001, Abst V-AD-51.

4. Fleming, K., Carreon, D., Alva, G., Potkin, S. *The neurocognitive effects of AIT-082 (Neotrofin) in patients with Alzheimer's disease*. 8th Int Conf Alzheimer's Dis Relat Disord (July 20-25, Stockholm) 2002, Abst 325.

5. *Two phase II trials of Neotrofin initiated in chemotherapy-induced neuropathy*. DailyDrugNews.com (Daily Essentials) Jan 10, 2002.

6. *Two centers added to 12-week study of Neotrofin in spinal cord injury*. DailyDrugNews.com (Daily Essentials) Aug 28, 2001.

7. *Encouraging clinical data reported for Neotrofin in Alzheimer's disease*. DailyDrugNews.com (Daily Essentials) Jan 11, 2001.

8. *NeoTherapeutics begins pivotal trial of Neotrofin in Alzheimer's disease*. DailyDrugNews.com (Daily Essentials) Feb 7, 2001.

9. *Pivotal trial of Neotrofin for Alzheimer's disease begins enrolling patients*. DailyDrugNews.com (Daily Essentials) April 18, 2001.

10. *Enrollment completed in pivotal Alzheimer's disease trial of Neotrofin*. DailyDrugNews.com (Daily Essentials) Sept 17, 2001.

11. *Neotrofin protects against kainic acid-induced neuronal injury in rodent model*. DailyDrugNews.com (Daily Essentials) June 13, 2001.

12. *NeoTherapeutics adds site to Neotrofin SCI study*. DailyDrugNews.com (Daily Essentials) July 3, 2001.

13. *Neotrofin increases hippocampal stem cells in mice*. DailyDrugNews.com (Daily Essentials) July 31, 2001.

14. *NeoTherapeutics to evaluate Neotrofin in spinal cord injury patients*. DailyDrugNews.com (Daily Essentials) March 28, 2001.

15. DiIorio, P., Virgilio, A., Giuliani, P., Ballerini, P., Vianale, G., Mid-dlemiss, P.J., Rathbone, M.P., Ciccarelli, R. *AIT-082 is neuroprotective against kainate-induced neuronal injury in rats*. Exp Neurol 2001, 169(2): 392.

16. Huff, F.J., Hauptmann, N., Yan, M., Helton, D.R. *Neotrofin™ is neuroprotective in an animal model of Parkinson's disease*. 4th Annu Meet Am Soc Exp NeuroTher (March 14-16, Washington DC) 2002, Abst.

17. Glasky, A.J., Huff, F.J., Nauptmann, N., Yan, M., Helton, D.R. *Neuroprotective effects of Neotrofin™ on a model of Parkinson's disease in the rat*. Pharmacologist 2002, 44(2, Suppl. 1): Abst 68.7.

18. Fedulov, V., Helton, D.R. *Acute effects of Neotrofin™ in a model of Parkinson's disease in the rat*. 14th World Congr Pharmacol (July 7-12, San Francisco) 2002, Abst LB 46.

19. Foreman, M., Taylor, E.M., Jenkins, S., Lenaz, L., Poindron, P., Baillet, C., Callizot, N., Neshaw, K., Chen, S. *Effects of AIT-082 (Neotrofin™) on peripheral neuropathy induced by vincristine treatment in rats*. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Oct 29-Nov 2, Miami Beach) 2001, Abst 141.

20. *Neotrofin increases number of brain stem cells in preclinical models*. DailyDrugNews.com (Daily Essentials) Feb 5, 2001.

21. Grundman, M., Farlow, M., Peavy, G. et al. *A phase I study of AIT-082 in healthy elderly volunteers*. J Mol Neurosci 2002, 18(3): 283.

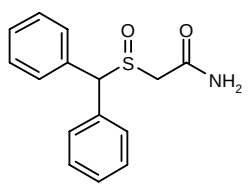
22. *Interim data announced from Neotrofin pilot study in Parkinson's disease*. DailyDrugNews.com (Daily Essentials) June 3, 2002.

23. *NeoTherapeutics begins phase II Parkinson's disease trial of Neotrofin*. DailyDrugNews.com (Daily Essentials) April 2, 2001.

24. *Four centers added to Neotrofin Parkinson's disease trial*. DailyDrugNews.com (Daily Essentials) Aug 30, 2001.

Original monograph - Drugs Fut 1997, 22(9): 945.

Modafinil



Modafinil (Provigil®, Modavigil®, Modasomil®) is marketed by Cephalon or licensees in over 20 countries for the treatment of excessive daytime sleepiness associated with narcolepsy. The product is also being evaluated in clinical trials for its potential in the treatment of other disorders, including attention deficit hyperactivity disorder (ADHD) (1-5).

In C57Bl/6 mice, modafinil 64 mg/kg significantly increased scores in tests of delayed spontaneous alternation, a measure of working memory. At this dose, the drug also enhanced alternation rates at long, but not short, intertrial intervals (6).

Aged rats (23 months old) were tested for cognitive function using a delayed alternation task before and after administration of modafinil. Modafinil 30 mg/kg improved performance on the test, and after 3 days of treatment correct responding in the aged rats was equal to that of 2-month-old control animals (7).

Healthy volunteers (n=28) received single oral doses of warfarin 5 mg followed by either placebo or modafinil 200 mg on days 8-14 and 400 mg on days 15-41 in an evaluation of the pharmacokinetic interaction between the drugs. On day 35, study subjects were given another 5 mg dose of warfarin. Compared with placebo, the pharmacokinetics of warfarin were not altered by modafinil administration (8).

Methylphenidate did not affect the steady-state pharmacokinetics of modafinil in a randomized, open trial in 32 healthy volunteers. Study subjects received modafinil 200 mg on days 1-7 and 400 mg on days 8-28; 16 subjects also received methyphenidate 20 mg on days 22-28 given 8 h after the dose of modafinil. The treatments were well tolerated (9).

Low-dose dextroamphetamine did not affect the steady-state pharmacokinetics of modafinil in a randomized, open-label study in 32 healthy volunteers. Modafinil was given once daily for 28 days at a dose of 200 mg on days 1-7 and 400 mg on days 8-28. Dextroamphetamine 20 mg was administered to half of the study subjects on days 22-28 after modafinil. Tolerability with concomitant drug administration was similar to that with modafinil alone (10).

An investigational, multicenter study of modafinil in 248 children aged 6-13 has shown the treatment to significantly improve the symptoms of ADHD in children. The

4-week, double-blind, placebo-controlled, parallel study randomized children and adolescents to 1 of 4 dose regimens of modafinil daily or placebo. The primary efficacy endpoint measure was the teacher-completed school version of the ADHD rating scale IV. All modafinil treatment groups demonstrated a reduction in symptoms of ADHD, with certain groups reaching statistical significance compared to placebo. The greatest significance was seen in the group receiving 300 mg once a day (11).

Modafinil (begun at 100 mg/day and increased to a maximum of 400 mg/day) was evaluated as treatment for ADHD in an open-label trial in 15 children. Once-daily modafinil treatment for an average of 4.6 weeks led to significant improvements in ADHD measures, more so in those concerning hyperactive/impulsive than inattentive features. Most side effects were mild in severity (12).

A double-blind, randomized, placebo-controlled, crossover trial in 22 adults meeting DSM-IV criteria for ADHD compared modafinil, dextroamphetamine and placebo. The study included three 2-week treatment periods separated by 4-day washout periods; the optimal doses of active drugs were selected over 4-7 days and maintained for the remainder of the treatment period. The mean optimal doses of modafinil and dextroamphetamine were 206.8 mg/day and 21.8 mg/day, respectively. Both active treatments were associated with significant improvement compared to placebo in ADHD symptoms on the DMS-IV ADHD scale; a nonsignificant trend for less severe symptoms was seen on modafinil compared to dextroamphetamine. A nonsignificant trend for improvement in cognitive test scores was also seen on active drugs, but no effect was seen on mood. Treatments were well tolerated and no significant differences were seen among groups in the frequency of adverse events. These preliminary results will require confirmation in larger trials, but suggest that modafinil has potential as a safe and effective alternative to stimulants in adult ADHD (13).

Following a report of marked improvement in spasticity in a patient with cerebral palsy treated with modafinil, 10 children with spastic cerebral palsy were entered in a pilot trial to further examine its potential benefit. Nine children completed treatment with 50 or 100 mg modafinil once daily in the morning for 1 month. Significant improvement in spasticity was obtained during treatment with modafinil in 7 patients according to modified Ashworth scores. Although no significant difference in ambulation was seen upon blinded review of videotapes of the patients, 6 of the 9 patients showed improvement in gait speed. A larger double-blind, placebo-controlled trial is planned to confirm these positive effects on spasticity (14, 15).

Treatment of a 56-year-old woman with amyotrophic lateral sclerosis (ALS) with modafinil at a maximum tolerated dose of 300 mg/day led to improvements in alertness, energy and daily function. Modafinil was prescribed in addition to other drugs for ALS and for depression (16).

Results from pilot studies indicated that modafinil tablets reduce fatigue and sleepiness in patients who are clinically depressed and who are partial responders to antidepressant therapy. Results from the first study indicated that patients receiving modafinil plus antidepressant treatment, as compared to patients on antidepressant treatment plus placebo, achieved statistically significant reductions in fatigue, as measured by the Fatigue Severity Scale, and in sleepiness, as measured by the Epworth Sleepiness Scale. Statistically significant improvements in energy and concentration, as measured by a subscale of the Hamilton Depression Scale (HAM-D retardation scale), were seen in patients taking modafinil and various antidepressants, including Prozac®, Zoloft® or Paxil®, but not in patients taking Celexa™, a compound with which modafinil has a known metabolic interaction. This trial was a 6-week pilot, double-blind, randomized study involving 136 patients with major depressive disorders who were partially responsive to their current antidepressant treatment. Study participants received between 100 mg and 400 mg of modafinil daily. A second study also showed significantly reduced fatigue in patients with depression. In this 4-week, prospective, open-label study in 24 adults with major depressive disorder who were being treated with antidepressant therapy, patients treated with modafinil demonstrated significant reductions in fatigue, as measured by the Fatigue Symptom Inventory and Fatigue Analog Scale. Improvements in cognition were also observed, particularly in concentration (17).

1. *MAA submitted for Provigil seeking label expansion in U.K.* DailyDrugNews.com (Daily Essentials) April 3, 2002.

2. *Modafinil approved in Australia, New Zealand and Korea*. DailyDrugNews.com (Daily Essentials) Sept 2, 2002.

3. *Cephalon announces agreement to acquire French pharmaceutical company*. DailyDrugNews.com (Daily Essentials) Dec 5, 2001.

4. *Cephalon completes acquisition of Lafon*. DailyDrugNews.com (Daily Essentials) Jan 2, 2002.

5. *Modafinil receives approval in Mexico*. DailyDrugNews.com (Daily Essentials) Jan 24, 2002.

6. Beracochea, D., Cagnard, B., Celerier, A., Le Merrer, J., Peres, M., Pierard, C. *First evidence of a delay-dependent working memory-enhancing effect of modafinil in mice*. NeuroReport 2001, 12(2): 375.

7. Miller, M., Roux, S., Porsolt, R. *Modafinil improves cognitive function in aged rats*. 17th World Congr Neurol (June 17-22, London) 2001, Abst P0322.

8. Robertson, P. Jr., Hellriegel, T., Arora, S., Nelson, M. *Effect of modafinil at steady state on the single-dose pharmacokinetic profile of warfarin in healthy volunteers*. J Clin Pharmacol 2002, 42(2): 205.

9. Hellriegel, E.T., Arora, S., Nelson, M., Robertson, P. Jr. *Steady-state pharmacokinetics and tolerability of modafinil given alone or in combination with methylphenidate in healthy volunteers*. J Clin Pharmacol 2001, 41(8): 895.

10. Hellriegel, E.T., Arora, S., Nelson, M., Robertson, P. Jr. *Steady-state pharmacokinetics and tolerability of modafinil administered alone or in combination with dextroamphetamine in healthy volunteers*. J Clin Pharmacol 2002, 42(4): 450.

11. *Provigil improves ADHD symptoms in children*. DailyDrugNews.com (Daily Essentials) Sept 18, 2002.

12. Rugino, T.A., Copley, T. *Effects of modafinil in children with attention-deficit/hyperactivity disorder: An open-label study*. J Am Acad Child Adolesc Psychiatry 2001, 40(2): 230.

13. Taylor, F.B., Russo, J. *Efficacy of modafinil compared to dextroamphetamine for the treatment of attention deficit hyperactivity disorder in adults*. J Child Adolesc Psychopharmacol 2000, 10(4): 311.

14. Hurst, D.L., Lajara-Nanson, W.A., Schiffer, R.B. *Modafinil use in spastic cerebral palsy: A pilot study*. 30th Annu Meet Child Neurol Soc (Oct 17-20, Victoria) 2001, Abst P65.

15. Hurst, D.L., Lajara-Nanson, W. *Use of modafinil in spastic cerebral palsy*. J Child Neurol 2002, 17(3): 169.

16. Sternbach, H. *Adjunctive modafinil in ALS*. J Neuropsychiatry Clin Neurosci 2002, 14(2): 239.

17. *Provigil has beneficial effects in depression; marketing and distribution agreement announced*. DailyDrugNews.com (Daily Essentials) May 31, 2001.

Original monograph - Drugs Fut 1990, 15(2): 130.

Natalizumab

Natalizumab (Antegren®) is a selective adhesion molecule (SAM) inhibitor discovered by Elan, a humanized monoclonal antibody and the first in a class of drugs known as α_4 integrin inhibitors that are designed to block immune cell adhesion to blood vessel walls and the subsequent migration of lymphocytes into tissue. Natalizumab binds to the cell-surface receptors known as $\alpha_4\beta_1$ (VLA-4) and $\alpha_4\beta_7$ (LPAM-1).

Biogen and Elan have established an exclusive worldwide collaboration to develop, manufacture and commercialize natalizumab and are currently conducting phase III clinical trials for multiple sclerosis (MS) and Crohn's disease (see *Drugs of the Future* 2002, 27(7): 707). The two companies are collaborating on two MS trials: the AFFIRM (Antegren safety and eFFicacy In Relapsing-remitting MS) trial, and the SENTINEL (Safety and Efficacy of NaTalizumab In combination with AvoNEx® [interferon β-1a; Serono] in subjects with reLapsing-remitting MS) trial. The AFFIRM trial is a 2-year, multicenter, double-blind, randomized, placebo-controlled study in approximately 900 patients. It will evaluate whether Antegren® is effective as monotherapy in slowing the rate of disability in MS and in reducing the rate of clinical relapses. The SENTINEL trial is a 2-year, multicenter, double-blind, randomized, placebo-controlled study in around 1200 patients. It will assess whether treatment of MS with Antegren® in combination with Avonex® is more effective than Avonex® treatment alone in slowing the rate of disability in MS and in reducing the rate of clinical relapses. In a previous phase II trial of Antegren®, 213 patients with relapsing forms of MS were studied. Treatment with Antegren® for 6 months led to fewer new gadolinium-enhanced lesions than treatment with placebo. In the placebo group, the cumulative mean number of new enhanced lesions during the treatment period was 9.6, while the Antegren® 3 mg/kg group had a mean of 0.6 new lesions and the Antegren® 6 mg/kg group had accumulated 1.2 new lesions in the same period. There were 34 relapses in the placebo group compared with 19 in the Antegren® 3 mg/kg group and 14 in the Antegren® 6 mg/kg group (1-6).

The optimal dose for natalizumab in terms of safety and efficacy was established using a population pharmacokinetic model with data obtained from phase II clinical trials. It was found that better and more consistent serum concentrations were achieved with a fixed dose of natalizumab administered once every 4 weeks compared to dosing on a mg/kg basis. Fixed monthly dosing is currently being used in phase III clinical trials of natalizumab in MS (7).

The effects of monthly intravenous administration of natalizumab on the brain activity of patients with relapsing MS were analyzed in a randomized, double-blind study. Natalizumab suppressed new brain lesions and clinical relapses during the treatment period of 6 months (8). The results of this study and the one that follows are summarized in Table IV.

The appearance of abnormalities in the blood-brain barrier (BBB) has been implicated in the development of MS lesions, and MRI studies have established an association between BBB leakage and relapse of MS. A recent study found that natalizumab reduced by 90% the frequency of new areas of BBB leakage, although it had no effect on preexisting leakage areas. Compared to placebo, patients treated with natalizumab showed increased well-being and a 50% lower relapse rate. Long-term studies are currently being conducted in order to determine the efficacy and safety of natalizumab and its effects on disability (9).

1. *Patient enrollment underway in Canadian phase III trials of Antegren in MS*. DailyDrugNews.com (Daily Essentials) May 2, 2002.

2. *Biogen updates advances in late-stage pipeline*. DailyDrugNews.com (Daily Essentials) July 23, 2002.

3. *Elan repositions business for long-term growth*. DailyDrugNews.com (Daily Essentials) Sept 10, 2002.

4. *Initiation of phase III trials of Antegren in multiple sclerosis and Crohn's disease*. DailyDrugNews.com (Daily Essentials) Dec 21, 2001.

5. *Promising phase II results reported for Antegren in both MS and Crohn's disease*. DailyDrugNews.com (Daily Essentials) Jan 23, 2001.

6. *Biogen expects product pipeline to double during 2001*. DailyDrugNews.com (Daily Essentials) Jan 17, 2001.

7. Bennett, D., Ludden, T., Shah, J., Floren, L., Beckman, E. *The use of pharmacokinetic (PK) modeling and efficacy data to establish optimal dosing of natalizumab (Antegren™)*. 18th Congr Eur Comm Treat Res Multiple Scler (Sept 18-21, Baltimore) 2002, Abst P130.

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

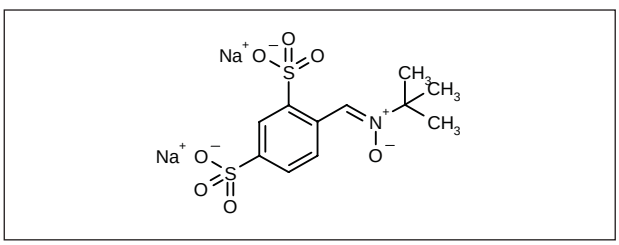
Indication	Design	Treatments	n	Conclusions	Ref.
Multiple sclerosis	Randomized, multicenter	Natalizumab, 3 mg/kg iv 1x/mo x 6 mo Natalizumab, 6 mg/kg iv 1x/mo x 6 mo Placebo	213	Natalizumab administered as a monthly iv injection during 6 months reduced new and enlarging T2 lesions, new T1 gadolinium-enhaced and T1 hypotense brain lesions and prevented clinical relapses, but posttreatment results after 6 months of follow-up were similar to those with placebo	8
Multiple sclerosis	Randomized	Natalizumab x 6 mo Placebo		Natalizumab decreased the frequency of new leakage lesions in the blood-brain barrier and the relapse rate of patients with multiple sclerosis. These changes were associated with improved well being	9

8. Dalton, C., O'Connor, P., Rice, G., Khan, O., Phillips, J.T., Barker, G., MacManus, D., Miszkiel, K., Miller, D. *Natalizumab treatment for relapsing MS: Further results of a randomized, double-blind, placebo-controlled trial*. 54th Annu Meet Am Acad Neurol (April 13-20, Denver) 2002, Abst S23.003.

9. Miller, D. *Clinical trials of agents targeting the blood brain barrier: Successes and failures*. 18th Congr Eur Comm Treat Res Multiple Scler (Sept 18-21, Baltimore) 2002, Abst 36.

Original monograph - Drugs Fut 2000, 25(9): 917.

NXY-059



NXY-059 is a novel nitrone-based spin trap agent in clinical development by AstraZeneca under license from Centaur as a neuroprotectant for cerebral ischemia and stroke.

The efficacy and safety of a generic form of NXY-059 (NXY-059G; 100 mg/kg infused i.v. starting 5 min postembolization) were examined alone and in combination with tPA (20% bolus/80% i.v. infusion over 30 min starting 60 min postembolization) in a study using a rabbit large-clot embolic stroke model. Hemorrhage rates for animals treated with tPA alone, NXY-059G alone and controls were 67%, 79% and 52%, respectively, as compared to 47% in animals treated with both tPA and NXY-059G. In addition, hemorrhage volume was decreased in animals receiving the combination as compared to controls and animals treated with either agent alone. NXY-059G alone or in combination had no effect on infarct size or volume and the agent did not affect other physiological parameters. Thus, NXY-059G, although detrimental to cerebral vasculature as monotherapy, improved the safety of thrombolytic therapy (1, 2).

In a rabbit small-clot embolic stroke model, NXY-059G 100 mg/kg was infused 5 min or 3 h after embolization, tPA 3.3 mg/kg was administered alone 1 or 3 h after embolization, or NXY-059G was administered 5 min after embolization and followed by tPA either 1 or 3 h after embolization. Behavioral analysis and measurement of the amount of microclots that produce neurological dysfunction in 50% of a group of animals showed that early administration of NXY-059G provided neuroprotection. Combination with tPA was without negative side effects and also provided neuroprotection, although in this study the combination was not superior to either drug administered alone (3, 4).

The effects of NXY-059 on long-term functional disability and brain damage were examined in a primate model of stroke at doses tolerated in humans. Monkeys subjected to permanent right middle cerebral artery occlusion (MCAO) were administered either saline or NXY-059 (28 mg/kg) by i.v. infusion at 5 min after occlusion, followed by 48-h continuous infusion at a rate of 16 mg/kg/h

by s.c. minipump, and evaluated at 3 and 10 weeks. As compared to saline-treated controls, NXY-059 significantly reduced functional disability, measured by reaching with the contralesional arm and spatial perceptual neglect, as well as reducing the amount of brain damage measured histologically. Overall infarct size was reduced by 51%, and damage to cortex, white matter, caudate and putamen was reduced by 54%, 52%, 49% and 33%, respectively. The preclinical profile of NXY-059 emerging from these and other studies –ability to both reduce functional disability and protect gray and white matter, wide therapeutic window, neuroprotection at doses proven safe in humans, *etc.*– provides support for further clinical trials as an acute stroke therapy (5).

In a study in rats subjected to permanent MCAO, the neuroprotective effects of different doses and different times of administration of NXY-059 were assessed. In the dose-ranging experiments, animals were treated with vehicle or NXY-059 30, 50 or 70 mg/kg/h infused by minipump over 24 h following an i.v. bolus injection 5 min after occlusion. In other experiments, rats were treated with a loading dose of 50 mg/kg followed by 24-h infusion at 50 mg/kg/h starting at 5, 30, 60, 120 and 240 min after occlusion. Significant reductions in the volume of damage were seen after doses of 30, 50 and 70 mg/kg/h –23%, 57% and 81%, respectively– and treatment could be delayed up to 4 h after stroke onset, as demonstrated by reductions in the volume of cerebral damage of 52%, 45%, 50%, 43% and 35%, respectively, when treatment with NXY-059 was initiated at 5, 30, 60, 120 and 240 min (6).

Results from a study in rats suggest that the antiischemic effects of NXY-059 are a result of indirect actions on mitochondria. NXY-059 (5 min and 1 h i.v.) and ciclosporin (5 min i.v.) were administered following recirculation after occlusion of the middle cerebral artery for 2 h. Both compounds reduced cytochrome *c* release, infarct volumes to about 30% of control and mitochondrial respiratory decline during recirculation. However, *in vitro*, both agents failed to block the effect of calcium on mitochondrial swelling (7).

A recent study assessed the neuroprotective effects of NXY-059 in rats subjected to transient (2-h) MCAO and reperfusion. Examination of neuronal damage following MCAO revealed a reduction in the levels of the activated antiapoptotic kinase phosphorylated Akt (p-Akt) in the focus and penumbra of the infarct region, in addition to a consequent increase in cytosolic cytochrome *c* levels in cortical neurons in the infarct area. Treatment with NXY-059 (30 mg/kg by i.v. bolus followed by 30 mg/kg/h by infusion for up to 24 h starting 1 h after reperfusion) blocked the increase in cytosolic cytochrome *c* in the infarct area. It also attenuated the increases in neuronal cytosolic cytochrome *c* levels and the reductions in neuronal p-Akt seen postreperfusion. These results suggest that the neuroprotective effects of NXY-059 in focal cerebral ischemia are due to inhibition of mitochondrial cytochrome *c* release and maintenance of activation of the Akt pathway (8).

In rat models of transient MCAO, NXY-059 was found to provide significant protection (reduction in infarct volume) even when administered at 5 h after occlusion, and protection, although nonsignificant, was still seen when treatment was begun 8 h after MCAO. Using a rat model of permanent MCAO, dose-dependent reductions in infarct volume were also obtained. Maximum protection was reached when drug was administered 5 min after MCAO, but significant protection was still seen when treatment was delayed to 4 h postocclusion. Moreover, in a primate model of permanent MCAO, NXY-059 demonstrated long-term positive effects on motor and spatial deficits and protected white and gray matter at plasma levels reported to be well tolerated in stroke patients. Thus, NXY-059 appears to have a suitable therapeutic window of opportunity (at least 4 h) for evaluation in stroke patients (9).

The tolerability and pharmacokinetics of NXY-059 were assessed in a randomized, double-blind, placebo-controlled trial in patients with acute stroke. Within 24 h after stroke onset, 147 patients received placebo or NXY-059 as either 250 mg over 1 h followed by 85 mg/h for 71 h (low-dose regimen) or 500 mg over 1 h followed by 170 mg/h for 71 h (high-dose regimen). The proportions of patients with primary intracerebral hemorrhage were 6%, 16% and 8% in the placebo, low-dose and high-dose groups, respectively. Similarly, serious events occurred in 16%, 23% and 16% of patients in the respective groups during 30 days of follow-up, and the death rates for the respective groups were 0%, 10% and 4%. The incidences of hyperglycemia, headache and fever were comparable among the three study groups, and no significant difference in stroke outcome was observed among groups. The mean unbound steady-state plasma concentrations of NXY-059 were 25 μmol/l in the low-dose group and 45 μmol/l in the high-dose group. Estimated clearance was 4.6 l/h according to population pharmacokinetic analysis. Based on their results and on recent studies in animal models of permanent ischemia, the authors suggest that a higher dose of NXY-059 may be needed to achieve clinical efficacy (10).

Unbound plasma concentrations of NXY-059 associated with neuroprotection in rat models of cerebral ischemia (45 μM) have proven safe in humans with stroke, and the safety and tolerability of higher target concentrations were therefore evaluated in acute stroke patients. A total of 134 patients were treated within 24 h of stroke onset with placebo or NXY-059 at 420 or 844 mg/h over 71 h following a loading dose. The target concentration of 200 μM was exceeded in the patients given the higher dose. NXY-059 proved to be well tolerated in this study, with similar outcomes in all three groups (11).

1. Lapchak, P.A., Araujo, D.M., Song, D., Wei, J., Purdy, R., Zivin, J.A. *Effects of the spin trap agent disodium-[(tert-butylimino)methyl]benzene-1,3-disulfonate N-oxide (generic NXY-059) on intracerebral hemorrhage in a rabbit large clot embolic stroke model: Combination studies with tissue plasminogen activator*. Stroke 2002, 33(6): 1665.

2. Lapchak, P.A., Araujo, D.M., Song, D., Purdy, R., Zivin, J.A. *NXY-059 pharmacology part 2: The spin trap agent disodium-[(tert-butylimino)methyl]benzene-1,3-disulfonate N-oxide (NXY-059) increases hemorrhage incidence in a rabbit large clot embolic stroke model: Combination studies with tissue plasminogen activator (tPA).* Stroke 2002, 33(1): Abst P213.

3. Lapchak, P.A., Araujo, D.M., Song, D., Wei, J., Zivin, J.A. *Neuroprotective effects of the spin trap agent disodium-[(tert-butylimino)methyl]benzene-1,3-disulfonate N-oxide (generic NXY-059) in a rabbit small clot embolic stroke model: Combination studies with the thrombolytic tissue plasminogen activator.* Stroke 2002, 33(5): 1411.

4. Lapchak, P.A., Araujo, D.M., Song, D., Wei, J., Zivin, J.A. *NXY-059 pharmacology part 1: The spin trap agent disodium-[(tert-butylimino)methyl]benzene-1,3-disulfonate N-oxide (NXY-059) is neuroprotective in a rabbit small clot embolic stroke model: Combination studies with tissue plasminogen activator (tPA).* Stroke 2002, 33(1): Abst P223.

5. Marshall, J.W.B., Duffin, K.J., Green, A.R., Ridley, R.M. *NXY-059, the free radical trapping nitrone-based agent, reduces hemiparesis and reduces grey and white matter damage after focal cerebral ischemia in monkeys.* Stroke 2001, 32(1): Abst 60.

6. Sydserff, S.G., Borrelli, A.R., Cross, A.J. *The neuroprotective efficacy of NXY-059 in permanent MCAO in the rat: Dose response and therapeutic window.* Stroke 2001, 32(1): Abst P78.

7. Yoshimoto, T., Kristian, T., Hu, B.R., Ouyang, Y.B., Siesjo, B.K. *Effect of NXY-059 on secondary mitochondrial dysfunction after transient focal ischemia: Comparison with cyclosporin A.* Brain Res 2002, 932(1-2): 99.

8. Yoshimoto, T., Kanakaraj, P., Ma, J.Y., Cheng, M.S., Kerr, I., Malaiyandi, L., Watson, J.A., Siesjo, B.K., Maples, K.R: *NXY-059 maintains Akt activation and inhibits release of cytochrome c after focal cerebral ischemia*. Brain Res 2002, 947(2): 191.

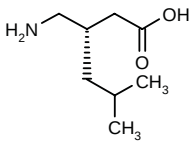
9. Green, A.R., Odergren, T., Ashwood, T. *Extending the time window: Studies with NXY-059 in animal models of stroke.* Eur Neuropsychopharmacol 2001, 11(Suppl. 3): Abst S.23.02.

10. Lees, K.R., Sharma, A.K., Barer, D., Ford, G.A., Kostulas, V., Cheng, Y.-F., Odergren, T. *Tolerability and pharmacokinetics of the nitrone NXY-059 in patients with acute stroke.* Stroke 2001, 32(3): 675.

11. Lees, K.R., Barer, D.H., Ford, G.A., Hacke, W., Kostulas, V., Sharma, A.K., Odergren, T. *Safety and tolerability of NXY-059 at higher target concentrations in acute stroke patients.* Stroke 2002, 33(1): Abst P267.

Original monograph - Drugs Fut 2002, 27(3): 240.

Pregabalin



Pfizer recently reported that it will delay seeking regulatory approval of the GABA analogue pregabalin (CI-1008, PD-144723) for use in adjunctive epilepsy, neuropathic pain (see *Drugs of the Future* 2002, 27(4): 426) and generalized anxiety disorders (*Drugs of the Future* 2002, 27(10): in preparation). The submission to the FDA was originally scheduled to be made by the end of this year. However, the company now expects to submit an application in Europe in March 2003, and subsequently in the U.S.

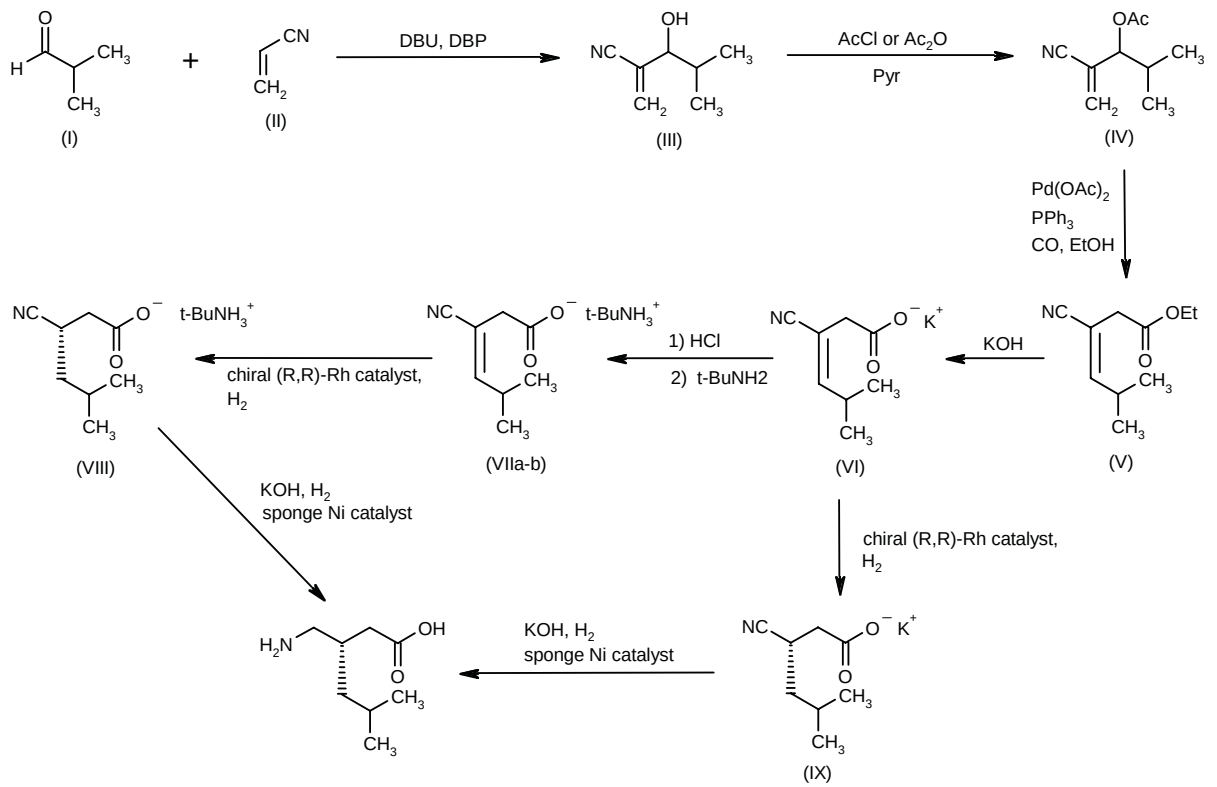
An asymmetric synthesis of pregabalin has been reported: Condensation of isobutyraldehyde (I) with acrylonitrile (II) by means of DBU and 2,6-di-*tert*-butyl-4-methylphenol (DBP) gives 3-hydroxy-4-methyl-2-methylenepentanenitrile (III), which is acylated with AcCl or Ac_2O and pyridine to yield the acetate (IV). The carboxylation of (IV) by means of $Pd(OAc)_2$, PPh_3, CO and EtOH affords 3-cyano-4-methyl-3-hexenoic acid ethyl ester (V), which is hydrolyzed with KOH in THF/water to provide the corresponding carboxylic acid potassium salt (VI). Acidification of (VI) with HCl, followed by reaction with *tert*-butylamine, gives the corresponding salt (VII), which is reduced with H_2 over a chiral (*R,R*)-rhodium catalyst [(*R,R*)-Rh] in THF/water to yield (*S*)-3-cyano-5-methylhexanoic acid butylammonium salt (VIII). Finally, the CN group of (VIII) is reduced with H_2 over a sponge-Ni catalyst in basic (KOH) ethanol (1). Scheme 1.

The delay in submission of pregabalin to the FDA will allow for the inclusion of requested toxicological mechanistic studies, following results from a lifetime mouse study showing an increased incidence of a specific tumor type. It is not known whether these results are applicable to humans, since pregabalin is not a chemical mutagen and not genotoxic in preclinical studies, and a similar lifetime dosing study in rats did not show increases in any tumor type, nor were negative results seen in any other toxicological screen or study. However, these findings led Pfizer to restrict the use of pregabalin for certain patients in clinical trials following discussions with the FDA (2-4).

A study using the rat conflict and elevated X-maze tests of anxiety demonstrated the efficacy of pregabalin. The agent was found to selectively bind with high affinity to the $alpha_2$delta subunit of voltage-dependent calcium channels (VDCC); its *R*-enantiomer, *R*-isobutyl-GABA, displayed approximately 10-fold weaker affinity. Pregabalin induced anxiolytic-like effects in both the rat conflict test (MED = 3 mg/kg) and elevated X-maze test (MED = 10 mg/kg), in contrast to *R*-isobutyl-GABA which only induced effects in the conflict test at a dose of 100 mg/kg (5).

The effects of gabapentin and pregabalin on the influx of calcium during epileptic-like activity were evaluated in anesthetized rats. Gabapentin 10, 30 and 100 mg/kg and pregabalin 30 mg/kg markedly reduced the duration and frequency of afterdischarges from stimulation of the contralateral CA3 hippocampus, which appeared to be a valid model of epileptiform activity (6).

Scheme 1: Syntheis of Pregabalin



The blood-brain barrier influx and efflux of pregabalin were determined by microdialysis after i.v. infusion of the drug in rats. It was found that pregabalin is able to penetrate the brain. Modeling of pharmacokinetic and pharmacodynamic data indicated that the anticonvulsant effect of the drug was not directly proportional to levels in brain extracellular fluid (7).

The single- and multiple-dose pharmacokinetics of pregabalin were assessed in 111 healthy volunteers given doses ranging from 1-900 mg/day with and without food. The drug demonstrated linear pharmacokinetics and systemic exposure was proportional to dose with either single or multiple dosing. Food decreased the rate, but not the extent, of pregabalin absorption, an effect deemed clinically insignificant. Steady state occurred after 1-2 days of repeated administration, and very little nonrenal clearance was found (8).

Determination of the population pharmacokinetics of pregabalin based on data from phase I and phase II/III studies in patients with refractory partial seizures showed that oral clearance of the drug was related to creatinine clearance, but not gender, race, age, menopausal status, daily dose or dosing regimen. Antiepileptics such as carbamazepine, lamotrigine, phenobarbital, phenytoin, tiagabine, topiramate and valproate also had no effect on pregabalin clearance or pharmacokinetics (9-12).

A randomized, double-blind, crossover study in 24 healthy volunteers with normal and stageable sleep was conducted to compare the effects of pregabalin, alprazolam and placebo on sleep and daytime activity. A significantly smaller increase in REM latency was seen with pregabalin versus alprazolam, and pregabalin significantly increased slow-wave sleep compared to alprazolam and placebo (13). The cognitive and psychomotor effects of pregabalin, alprazolam and placebo were also compared. Compared with alprazolam, pregabalin-treated subjects had significantly less impairment on the following tests: Hicks Choice Reaction Time, the Compensatory Tracking Task, the Sternberg Short-Term Memory Task, the Rapid Visual Information Processing Task and Brake Reaction Time. Compared with placebo, pregabalin significantly improved Brake Reaction Time (14). The results of this study and some that follow are summarized in Table V.

According to data from a large dose-response efficacy trial in 453 patients, pregabalin exposure and prega-

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

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized, double-blind, crossover	Pregabalin Alprazolam Placebo	24	Pregabalin and alprazolam significantly decreased the time to sleep onset and improved sleep efficiency compared to placebo. Pregabalin appeared to have an effect on sleep architecture that distinguished it from benzodiazepines	13, 14
Epilepsy, partial seizures	Randomized, double-blind	Pregabalin, 50 mg/d x 12 wk Pregabalin, 150 mg/d x 12 wk Pregabalin, 300 mg/d x 12 wk Pregabalin, 600 mg/d x 12 wk Placebo	453	Pregabalin exposure and dose were equally good predictors of the drug's efficacy	15
Epilepsy	Pooled/meta-analysis	Pregabalin, 25-600 mg/d Placebo	19	Of 19 patients with epilepsy enrolled in a randomized, double-blind trial and/or an open add-on study of pregabalin therapy, 4 developed focal myoclonus	17
Epilepsy, partial seizures	Pooled/meta-analysis	Pregabalin, 50-600 mg/d x 12 wk Placebo	1052	Pregabalin 600 mg/d was safe and well tolerated and increased the percentage of seizure-free patients, the response rate and the number of patients with improvements greater than 75% compared with placebo	18, 21, 22

balin dose were equally good predictors of the drug's efficacy as an anticonvulsant in patients with refractory partial seizures (15).

A study evaluated pregabalin as add-on therapy in the treatment of partial-onset seizures. Data from 16 patients completing at least 8 months of an open-label phase of a multicenter, double-blind, placebo-controlled trial of pregabalin titrated up to a maximum daily dose of 600 mg were analyzed. Significant reductions in the seizure frequency were obtained in the first 8 weeks of the open-label phase and maintained to the end of the study, with reductions of 47% and 51% during the first and last 8 weeks, respectively. Dizziness, somnolence and ataxia, mostly transient and mild to moderate in severity, were the most frequent adverse events (16).

A review of the records of 19 patients with focal epilepsy who were treated with pregabalin (50-600 mg/day) in a randomized, double-blind trial, an open extension study or in both studies revealed that 4 of the patients developed focal myoclonus. In the studies, other antiepileptics were also taken (17).

Data from 3 multicenter, randomized, double-blind, placebo-controlled studies of add-on pregabalin therapy in a total of 1052 patients with partial seizures showed that the drug was effective, safe and well tolerated. In the trials, patients received placebo or pregabalin 50-600 mg/day b.i.d. or t.i.d. for 12 weeks. The primary efficacy parameter –symmetrized percent change in partial seizure frequency– and the secondary efficacy parameter of responder rate (patients with at least a 50% reduction in seizure frequency) showed significant changes in favor of pregabalin during the first week of treatment. Pharmacokinetics were proportional to dose and predictable. Adverse events were mainly mild to moderate, transient CNS-related effects. Over 84% of all patients opted to enter open-label extension studies of pregabalin (18-20).

Three double-blind, parallel-group studies in a total of 1042 patients with refractory partial seizures determined the relationship between pregabalin exposure and response over 3 months following multiple dosing (50-600 mg/day). Data were best described by a mixed-effect model. A dose-dependent and asymptotic reduction in seizure frequency was observed in 75% of patients: the maximum decrease was 100% in women and 80% in men. In responsive patients, the expected decrease in the baseline seizure rate was 50% of maximum following

administration of 180 mg. The dose-response relationship seen was not influenced by age, race or menopausal status of women (21).

Patients with partial seizures enrolled in 1 of 3 multicenter, randomized, double-blind, placebo-controlled studies received pregabalin up to 600 mg/day for 12 weeks. Of patients taking pregabalin 600 mg/day, the percentage of seizure-free patients was 17% in one group. The pregabalin-treated patients had responder rates of 43-51% compared to 6-14% for placebo, and 75% or greater improvement rates in 21-33% compared to 2-3% for placebo (22).

1. Burk, M.J. et al. (Pfizer Inc.). *Asymmetric synthesis of pregabalin*. WO 0155090.

2. *Pfizer's pregabalin regulatory submission delayed*. DailyDrugNews.com (Daily Essentials) Sept 10, 2002.

3. *Industry leader Pfizer expects growth driven by broad and deep pipeline*. DailyDrugNews.com (Daily Essentials) Jan 21, 2002.

4. *Use of pregabalin restricted in certain clinical trial patients*. DailyDrugNews.com (Daily Essentials) Feb 13, 2001.

5. Field, M.J., Oles, R.J., Singh, L. *Pregabalin may represent a novel class of anxiolytic agents with a broad spectrum of activity*. Br J Pharmacol 2001, 132(1): 1.

6. Davis, M.D. *Gabapentin and pregabalin modulate a calcium component of epileptiform afterdischarges in the rat dentate gyrus as measured with in vivo fluorescence and fiber optics*. Soc Neurosci Abst 2001, 27: Abst 753.8.

7. Feng, M.R., Turluck, D., Burleigh, J., Lister, R., Fan, C., Middlebrook, A., Tayor, C., Su, T. *Brain microdialysis and PK/PD correlation of pregabalin in rats*. Eur J Drug Metab Pharmacokinet 2001, 26(1-2): 123.

8. Alvey, C.W. et al. *Clinical pharmacokinetics of pregabalin in healthy volunteers*. 10th World Congr Pain (Aug 17-22, San Diego) 2002, Abst 609-P243.

9. Bockbrader, H., Burger, P., Kugler, A., Knap, L., Garofalo, E. *The oral clearance (CL/F) of commonly prescribed antiepileptic drugs (AEDs) is unaffected by concomitant administration of pregabalin in adult patients with refractory partial seizures*. Epilepsia 2002, 43(Suppl. 8): Abst P453.

10. Corrigan, B. et al. *Pregabalin population pharmacokinetics in patients with refractory partial seizures*. Epilepsia 2002, 43(Suppl. 8): Abst P452.

11. Wilson, E. et al. *Pregabalin drug interaction studies in patients with epilepsy maintained on either valproate (VPA), lamotrigine (LTG), phenytoin (PHY), or carbamazepine (CBZ)*. Epilepsia 2002, 43(Suppl. 8): Abst P451.

12. Brockbrader, H.N., Strand, J.C., Wesche, D.L. et al. *Drug interaction studies of pregabalin (CI-1008, PGB) in patients with epilepsy maintained on either valproate (VA), lamotrigine (LMG), phenytoin (PHY), or carbamazepine (CBZ)*. Epilepsia 2001, 42(Suppl. 7): Abst 1.272.

13. Hindmarch, I. et al. *Evaluation of the sleep activity profile of pregabalin compared to alprazolam in normal volunteers*. Annu Meet Am Psychiatr Assoc (May 18-23, Philadelphia) 2002, Abst NR415.

14. Hindmarch, I., Dawson, J., Stanley, N. *Evaluation of cognitive and psychomotor profile of pregabalin compared to alprazolam in normal volunteers*. Annu Meet Am Psychiatr Assoc (May 18-23, Philadelphia) 2002, Abst NR206.

15. Kugler, A.R., Robbins, J.L. *Pregabalin exposure and pregabalin dose are equivalent predictors of seizures reduction*. 54th Annu Meet Am Acad Neurol (April 13-20, Denver) 2002, Abst P04.093.

16. Minecan, D.N., Passaro, E.A., Murugaiyan, P., Milling, C.J., Kutluay, E., Beydoun, A. *Long-term efficacy and safety of pregabalin for the treatment of partial onset seizures*. Epilepsia 2001, 42(Suppl. 7): Abst 2.258.

17. Huppertz, H.J., Feuerstein, T.J., Schulze-Bonhage, A. *Myoclonus in epilepsy patients with anticonvulsive add-on therapy with pregabalin*. Epilepsia 2001, 42(6): 790.

18. Stefan, H. et al. *Pregabalin adjunctive therapy in patients with partial seizures*. Epilepsia 2002, 43(Suppl. 8): Abst P378.

19. Ramsay, R.E., Kugler, A.R., Anhut, H. et al. *Pregabalin adjunctive therapy in patients with partial seizures*. Epilepsia 2001, 42(Suppl. 7): Abst F.02.

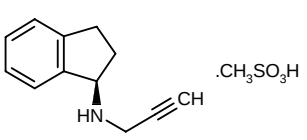
20. Arroyo, S., Anhut, H., Messmer, S., Mathé, H. *Pregabalin double-blind add-on study in patients with partial seizures*. Epilepsia 2001, 42(Suppl. 7): Abst 1.263.

21. Miller, R., Frame, B., Corrigan, B.W., Burger, P., Blockbrader, H., Garofalo, E., Lalonde, R. *Mixed effects modeling of pregabalin response in patients with refractory partial seizures*. Clin Pharmacol Ther 2001, 69(2): Abst PIII-55.

22. Brodie, M.J. et al. *Pregabalin adjunctive therapy in patients with partial seizures: Additional efficacy analysis*. Epilepsia 2002, 43(Suppl. 8): Abst 047.

Original monograph - Drugs Fut 1999, 24(3): 862.

Rasagiline Mesilate



The monoamine oxidase type B (MAO-B) inhibitor rasagiline mesilate (TVP-1012) is in phase III clinical trials for the treatment of Parkinson's disease. The drug is the subject of a global development and European marketing alliance between Teva and Lundbeck (1, 2).

In nerve growth factor (NGF)-differentiated pheochromocytoma PC-12 cells, selegiline reduced cell death induced by oxygen/glucose deprivation by 30%, while rasagiline reduced cell death by 45-55%. The major metabolite of selegiline (L-methamphetamine) enhanced oxygen/glucose deprivation-induced cell death, whereas the major metabolite of rasagiline, 1-(*R*)-aminoindan, did not (3).

The effects of rasagiline mesilate, its (*S*)-(–)-enantiomer TVP-1022, the racemic compound AGN-1135 and selegiline on monoamine oxidase (MAO-A and MAO-B) have been examined in a series of *in vitro, ex vivo* and *in vivo* experiments. The investigational antiparkinsonian drug rasagiline is an analogue of selegiline but is

associated with a reduced liability for amphetamine-like effects compared to the latter due to its metabolism to aminoindan instead of 1-methamphetamine. Both rasagiline and the racemate displayed highly potent, selective and irreversible inhibition of MAO-B *in vitro* and *in vivo*, whereas TVP-1022 showed little activity. Against rat brain MAO-B and MAO-A, rasagiline gave respective IC_{50} values of 4.43 ± 0.92 and 412 ± 123 nM, and against human brain enzymes respective IC_{50}s were 14 ± 3.5 and 710 ± 93 nM; similar potency was seen for selegiline (IC_{50} = 3.63 ± 0.59, 944 ± 52, 6.8 ± 1.4 and 1700 ± 444 nM, respectively, against rat brain MAO-B, rat brain MAO-A, human brain MAO-B and human brain MAO-A). As evaluated *ex vivo* following single oral doses, rasagiline inhibited brain and liver MAO-B with ED_{50} values of 0.1 and 0.042 mg/kg, respectively, and MAO-A in these tissues was inhibited with respective ED_{50} values of 6.48 and 2.38 mg/kg. Moreover, the compound selectively inhibited MAO-B in liver and brain in rats treated orally for 21 days, with respective ED_{50} values of 0.014 and 0.013 mg/kg. Although rasagiline had similar potency to selegiline *in vitro* for inhibition of MAO-B, it was at least 3 times more potent than selegiline *in vivo* against rat brain and liver MAO-B, and it maintained the selectivity of selegiline for MAO-B *versus* MAO-A. Based on these and other data, including reports of neuroprotective and antiapoptotic properties, it is suggested that rasagiline may have advantages over selegiline in the treatment of Parkinson's disease (4).

Salt-loaded, stroke-prone spontaneously hypertensive rats were administered rasagiline (1 or 3 mg/kg/day) or the (*S*)-enantiomer (3 or 6 mg/kg/day). Rasagiline 3 mg and the (*S*)-enantiomer 6 mg increased cumulative survival, delayed stroke and decreased the incidence and severity of stroke (5).

In a double-blind follow-up study, early Parkinson's disease patients taking 1 or 2 mg/day rasagiline continued treatment while those randomized to placebo switched to rasagiline 2 mg/day. Rasagiline demonstrated a possible disease-modifying effect as those patients treated for a longer period had smaller declines in Unified Parkinson's Disease Rating Scale (UPDRS) scores (6).

A 12-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled trial has evaluated the efficacy, safety and tolerability of rasagiline mesilate (0.5, 1 and 2 mg/day) as adjunctive treatment to levodopa in 70 Parkinson's disease patients. A decrease of 23% in the total UPDRS score was achieved in fluctuating patients as compared to an 8.5% decrease in the placebo patients. The treatment effect of all doses lasted at least 6 weeks after discontinuation. The drug was well tolerated and safe, with adverse events similar to those in the placebo group. All doses induced almost complete platelet MAO-B inhibition (7).

1. *Neurological drugs in Lundbeck's pipeline*. DailyDrugNews.com (Daily Essentials) Sept 20, 2001.

2. *Teva finalizes separate agreements with Aventis and Lundbeck*. DailyDrugNews.com (Daily Essentials) Feb 16, 2001.

3. Abu-Raya, S., Tabakman, R., Blaugrund, E., Trembovler, V., Lazarovici, P. *Neuroprotective and neurotoxic effects of monoamine oxidase-B inhibitors and derived metabolites under ischemia in PC12 cells*. Eur J Pharmacol 2002, 434(3): 109.

4. Youdim, M.B.H., Gross, A., Finberg, J.P.M. *Rasagiline [N-propargyl-1R(+)-aminoindan], a selective and potent inhibitor of mitochondrial monoamine oxidase B*. Br J Pharmacol 2001, 132(2): 500.

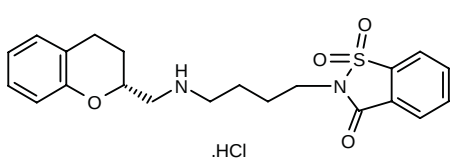
5. Eliash, S., Speiser, Z., Cohen, S. *Rasagiline and its (S)-enantiomer increase survival and prevent stroke in salt-loaded stroke-prone spontaneously hypertensive rats*. J Neural Transm - Gen Sect 2001, 108(8-9): 909.

6. Lang, A.E. *Earlier treatment with rasagiline may attenuate (UP-DRS) progression of PD*. Mov Disord 2001, 16(5): 981.

7. Rabey, J.M., Sagi, I., Huberman, M., Melamed, E., Korczyn, A., Giladi, N., Inzelberg, R., Djaldetti, R., Klein, C., Berecz, G. *Rasagiline mesylate, a new MAO-B inhibitor for the treatment of Parkinson's disease: A double-blind study as adjunctive therapy to levodopa*. Clin Neuropharmacol 2000, 23(6): 324.

Original monograph - Drugs Fut 1996, 21(9): 903.

Repinotan Hydrochoride



Bayer is evaluating repinotan hydrochloride (Bay-x-3702), a selective 5-HT_{1A} receptor agonist, in phase III trials for the treatment of stroke (1).

The efficacy of repinotan (10 μg/kg/h i.v. 5 min-4 h postinjury) in attenuating neuronal loss and enhancing cognitive performance was demonstrated in rats with controlled cortical impact injury. Neither repinotan nor MK-801 affected motor function although both significantly improved spatial learning and memory. Repinotan decreased neuronal loss in the CA1 and CA3 regions and significantly decreased cortical tissue loss compared to untreated controls (2).

Results from *in vitro* and *in vivo* experiments demonstrated that the neuroprotective activity of repinotan may involve inhibition of glutamate release. *In vitro* experiments using rat hippocampal slices showed that the agent concentration-dependently inhibited evoked

glutamate release (IC_{50} = 1 μM); this effect was blocked by WAY-100635, indicating the involvement of 5-HT_{1A} receptors. Microdialysis studies in rats subjected to permanent MCAO showed that the agent (1 or 10 μg/kg i.v. immediately after occlusion) attenuated the increase in and total release of cortical extracellular glutamate by about 50% as compared to controls; aspartate levels were not altered by treatment (3).

In a contusion model of traumatic brain injury in rats, repinotan (10 μg/kg/h by 4-h continuous i.v. infusion) significantly attenuated spatial learning and memory deficits in a water maze task (4).

Rats administered repinotan after transient focal ischemia had increased levels of the B-cell lymphoma protein BCL-2 in the ipsilateral cerebral cortex. An effect was seen at 6 h of reperfusion and was greater at 24 h of reperfusion. BCL-2-associated protein X (BAX) levels were not affected (5).

The Traumatic Brain Injury Study Group conducted a multicenter, double-blind, randomized, placebo-controlled trial to examine the safety and tolerability of repinotan hydrochloride in 60 patients with severe traumatic brain injury. The patients in this study were randomized within 24 h of injury to receive repinotan at doses of 0.5, 1.25 or 2.50 mg/day or placebo by continuous i.v. infusion over 7 days, and were then followed for 3 months. No seizures, no deleterious effects on intracranial pressure, hemodynamics or laboratory parameters and no serious drug-related adverse events were seen during or after treatment with repinotan. Preliminary assessment of efficacy showed that 60% of patients in the repinotan groups had a good clinical outcome, assessed using the Glasgow Outcome Scale, compared to 50% of those in the placebo group. The low and high doses of repinotan were associated with more favorable outcomes, while the intermediate dose was similar to placebo. Further studies appear to be warranted (6).

1. *Bayer presents pipeline overview at Goldman Sachs Healthcare Conference*. DailyDrugNews.com (Daily Essentials) June 15, 2001.

2. Kline, A.E., Yu, J., Yan, H.Q., Marion, D.W., Dixon, C.E. *The 5-HT_{1A} agonist, repinotan (BAYx3702), attenuates histopathology and enhances cognitive performance in traumatically brain injured rats*. J Neurotrauma 2000, 17(10): Abst E14.

3. Mauler, F., Fahrig, T., Horvath, E., Jork, R. *Inhibition of evoked glutamate release by the neuroprotective 5-HT_{1A} receptor agonist BAY x 3702 in vitro and in vivo*. Brain Res 2001, 888(1): 150.

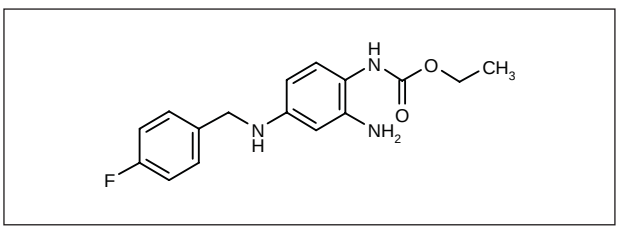
4. Kline, A.E., Yu, J., Horvath, E., Marion, D.W., Dixon, C.E. *The selective 5-HT_{1A} receptor agonist repinotan HCl attenuates histopathology and spatial learning deficits following traumatic brain injury in rats*. Neuroscience 2001, 106(3): 547.

5. Kukley, M., Schaper, C., Becker, A., Rose, K., Krieglstein, J. *Effect of 5-hydroxytryptamine 1A receptor agonist BAY X 3702 on BCL-2 and BAX proteins level in the ipsilateral cerebral cortex of rats after transient focal ischaemia*. Neuroscience 2001, 107(3): 405.

6. Ohman, J., Braakman, R., Legout, V. *Repinotan (BAY x 3702): A 5-HT_{1A} agonist in traumatically brain injured patients*. J Neurotrauma 2001, 18(12): 1313.

Original monograph - Drugs Fut 1997, 22(4): 341.

Retigabine



The antiepileptic drug retigabine, discovered by the former Asta Medica (now Viatris), has a unique mode of action, primarily acting as a selective neuronal potassium channel opener, leading to stabilization of depolarized neuronal cells. It is currently in pivotal clinical trials.

Researchers evaluated the effects of retigabine on the electroresponsive properties of individual neurons and on synaptic transmission between pairs of cultured mouse cortical neurons. Retigabine was found to hyperpolarize the resting membrane potentials of the neurons, decrease input resistance and decrease the amount of action potentials generated by direct current injection. Inhibitory postsynaptic currents were also potentiated by retigabine (1).

Retigabine and BMS-204352 (0.1-10 μM) reversibly and concentration-dependently activated KCNQ4 channels expressed in HEK293 cells. Both compounds also concentration-dependently increased the maximal current at large positive voltages (2). Retigabine (0.1-10 μM) was shown to enhance current through KCNQ2/Q3 potassium channels expressed in CHO cells, suggesting that these channels play a role in the anticonvulsant activity of retigabine and are a molecular target for the drug (3).

In DBA/2 mice, retigabine 0.5 mg/kg i.p. enhanced the efficacy of carbamazepine, diazepam, felbamate, lamotrigine, phenytoin, phenobarbital and valproate against sound-induced seizures (4).

Single doses of retigabine were found to significantly reduce glutamate and glutamine concentrations in the brains of mice, while 5-day treatment significantly reduced the activity of gamma-aminobutyric acid (GABA)-transaminase. This indicates that retigabine may function in part by blocking GABA metabolism and lowering concentrations of excitatory neurotransmitters in the brain (5).

The pharmacokinetic interactions between retigabine and valproic acid, topiramate, phenytoin and carbamazepine were investigated in 60 epileptic patients. Retigabine was administered as add-on therapy at doses of 100 or 200 mg b.i.d. or t.i.d., increased by 200 mg every 1 or 2 weeks until the maximum tolerated dose was reached. At this point, the other antiepileptic therapy was titrated down by 25% per week until only retigabine was administered. It was found that retigabine did not alter the pharmacokinetics of the other antiepileptic drugs, and that phenytoin and carbamazepine increased the clearance of retigabine (6).

Women taking ethinylestradiol/norgestrel were found to be exposed to efficacious concentrations of the contraceptive when taking retigabine concomitantly. In the study, 18 women were given ethinylestradiol 0.03 mg/norgestrel 0.3 mg for 2 menstrual cycles and retigabine 150 mg was administered 3 times daily on days 10-13 of the second cycle. Coadministration of retigabine did not significantly alter the pharmacokinetics of either ethinylestradiol or norgestrel. No clinically important alterations in laboratory values, vital signs or ECGs were seen and adverse events were mild (headache, nausea, sleepiness and vaginitis) (7, 8).

A total of 45 healthy volunteers enrolled in a randomized, placebo-controlled study of the safety and pharmacokinetics of retigabine received a single dose of the drug on day 1 and doses every 12 h for the following 14 days. Subjects were given retigabine in fixed doses of 200, 400, 500 and 600 mg/day or titrated doses given in 100-mg increments every 4 days, leading up to 700 mg/day on day 15. Linear, dose-proportional pharmacokinetics were noted and were not modified by multiple administration (9).

Results from a study conducted in 15 healthy male volunteers showed good tolerability and no pharmacokinetic interaction between phenobarbital and retigabine. Following a single oral dose of retigabine (200 mg), the mean AUC and $t_{1/2}$ values were 4050 ng·h/ml and 6.5 h, respectively. When increasing doses of retigabine (100-200 mg every 8 h for 6 days) were administered with phenobarbital (90 mg p.o. every 8 h for 28 days), there were no changes in the AUC and $t_{1/2}$ values of retigabine. The exposure to phenobarbital was also unchanged when given in combination with retigabine (303 mg·h/ml *vs*. 299 mg·h/ml) (10).

1. Otto, J.F., Kimball, M.M., Wilcox, K.S. *Effects of the anticonvulsant retigabine on cultured cortical neurons: Changes in electroresponsive properties and synaptic transmission*. Mol Pharmacol 2002, 61(4): 921.

2. Schroder, R.L., Jespersen, T., Christophersen, P., Strobaek, D., Jensen, B.S., Olesen, S.P. *KCNQ4 channel activation by BMS-204352 and retigabine*. Neuropharmacology 2001, 40(7): 888.

3. Wickenden, A.D., Yu, W., Zou, A., Jegla, T., Wagoner, P.K. *Retigabine, a novel anti-convulsant, enhances activation of KCNQ2/Q3 potassium channels*. Mol Pharmacol 2000, 58(3): 591.

4. De Sarro, G., Di Paola, E., Conte, G., Pasculli, M.P., De Sarro, A. *Influence of retigabine on the anticonvulsant activity of some antiepileptic drugs against audiogenic seizures in DBA/2 mice*. Naunyn-Schmied Arch Pharmacol 2001, 363(3): 330.

5. Sills, G.J., Rundfeldt, C., Buthler, E., Forrest, G., Thompson, G.G., Brodie, M.J. *A neurochemical study of the novel antepileptic drug retigabine in mouse brain*. Pharmacol Res 2000, 42(6): 553.

6. Sachdeo, R.C., Ferron, G.M., Partiot, A.M. et al. *An early determination of drug-drug interaction between valproic acid, phenytoin, carbamazepine or topiramate and retigabine in epileptic patients*. Epilepsia 2001, 42(Suppl. 7): Abst J.07.

7. Paul, J., Ferron, G.M., Richards, L., Getsy, J., Troy, S.M. *Retigabine does not alter the pharmacokinetics of a low-dose oral contraceptive in women*. Neurology 2001, 56(8, Suppl. 3): Abst P05.052.

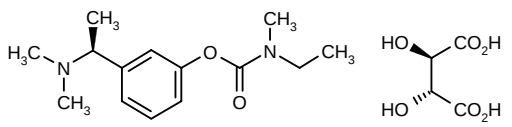
8. Paul, J., Ferron, G. *Retigabine does not alter the pharmacokinetics of a low dose oral contraceptive in women*. Epilepsia 2001, 42(Suppl. 7): Abst 3.128.

9. Ferron, G.M., Paul, J., Fruncillo, R., Richards, L., Knebel, N., Getsy, J., Troy, S. *Multiple-dose, linear, dose-proportional pharmacokinetics of retigabine in healthy volunteers*. J Clin Pharmacol 2002, 42(2): 175.

10. Ferron, G.M., Patat, A., Parks, V., Rolan, P., Troy, S. *Lack of pharmacokinetic interaction between retigabine and phenobarbital at steady-state in healthy subjects*. Clin Pharmacol Ther 2001, 69(2): Abst PII-64.

Original monograph - Drugs Fut 1995, 20(11): 1112.

Rivastigmine Tartrate



Rivastigmine tartrate (Exelon®), a dual acetylcholinesterase and butyrylcholinesterase inhibitor, is currently marketed by Novartis for the treatment of mild to moderate Alzheimer's disease and is now under clinical evaluation for the treatment of vascular dementia, Lewy body dementia and dementia in Parkinson's disease.

A 71-year-old female Parkinson's disease patient with mild dementia experienced a severe parkinsonian "off" state, low mood and high anxiety 90 min after a single 3-mg dose of rivastigmine. These results suggest that caution should be used when prescribing the drug in Parkinson's disease patients (1).

Study results indicate that rivastigmine tartrate is associated with significant improvement in behavioral disturbances in patients with dementia with Lewy bodies (DLB). Dementia with Lewy bodies is the second most common form of dementia after Alzheimer's disease –accounting for 15-25% of cases– and is differentiated from AD by the presence of large numbers of Lewy

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

Indication	Design	Treatments	n	Conclusions	Ref.
Parkinson's disease	Open, multicenter	Rivastigmine tartrate, 6 mg bid (titrated from 1.5 mg bid over 8 wk if tolerated) x 14 wk (n=15)	15	Rivastigmine tartrate appeared to improve psychotic symptoms and cognitive function in patients with Parkinson's disease	5
Hallucinations, Parkinson's disease	Open	Rivastigmine, maximum tolerated dose x 6 wk	12	Rivastigmine reduced neuropsychiatric complications, epecially hallucinations and sleep disturbances, and improved cognitive performance without affecting motor control	6
Vascular dementia	Open, multicenter	Rivastigmine,1.5 mg od x 4 d → 1.5 mg bid x 1 mo → 1.5 mg morning + 3 mg evening x 4 d → 3 mg bid x 4 d (following uptitration to 9-12 mg/d during 5 mo) x 8 mo (total)	82	Rivastigmine was effective in patients with vascular dementia and evidence of cortical infarct and was associated with a high level of family satisfaction	10

bodies, a relative lack of neurofibrillary tangles and a more marked deficit of acetylcholine. The disease is characterized clinically by fluctuating cognitive impairment, attention deficits, behavioral symptoms such as visual hallucinations, delusions, apathy and anxiety, and the presence of parkinsonian features. Based on the cholinergic deficit characterizing the disease, a multicenter, double-blind, placebo-controlled trial in Europe explored the use of rivastigmine in 120 patients with DLB. The patients were given either placebo or rivastigmine up to 12 mg/day for 20 weeks, followed by a 3-week drug-free period. Approximately twice as many patients (63%) taking rivastigmine showed at least a 30% improvement in psychiatric symptoms (apathy, anxiety, delusions; assessed on the Neuropsychiatric Inventory) compared to those receiving placebo (30%). Significant improvement was also seen on objective measures of cognitive functioning, particularly as regards attention. During the 3-week drug-free follow-up period, the differences between rivastigmine and placebo tended to disappear. The treatment was considered acceptable as regards safety and tolerability, drug-related side effects being mostly cholinergic in nature, *i.e.*, nausea and vomiting, anorexia and somnolence. The investigators concluded that cholinesterase inhibitors such as rivastigmine may represent a more rational treatment option for DLB than neuroleptics in terms of both efficacy and safety (2).

Quantitative EEG recordings were taken in Parkinson's disease patients with dementia before and after 12 weeks of treatment with rivastigmine at a mean dose of 8 ± 3 mg/day. Increased arousal or enhanced cognition were indicated by increased faster frequencies and decreased slower frequencies (3). In this study in a total of 21 patients, rivastigmine significantly improved the UPDRS score and the Alzheimer's Disease Asessment Scale total, commands, constructional, ideational, recognition and word finding scores (4).

Patients with advanced Parkinson's disease and recurrent hallucinations (n=15) were treated with rivastigmine (1.5 mg b.i.d. titrated up every 2 weeks to 6 mg b.i.d. or the maximum tolerated dose) in an open study. Treatment was given for a total of 14 weeks and was found to improve neuropsychiatric disturbances, including hallucinations and sleep disturbances. Rivastigmine treatment was also associated with reduced caregiver distress (5). The results of this study and some that follow are summarized in Table VI.

Rivastigmine was given at the maximum tolerated dose for 6 weeks to 12 patients with Parkinson's disease and hallucinations in an open study. The drug improved cognitive performance and neuropsychiatric symptoms, which worsened after rivastigmine withdrawal (6).

Rivastigmine was given to 10 patients with Parkinson's disease and dopaminomimetic psychosis in a 6-week, open-label trial. Rivastigmine doses were increased up to 6 mg b.i.d. Rivastigmine significantly improved psychosis in most patients without diminishing motor control. Mild adverse events were observed (7).

In an open pilot study, patients with subcortical vascular dementia (n=16) were treated with rivastigmine 3-6 mg/day or aspirin 100 mg/day for 22 months. Rivastigmine treatment was well tolerated and improved the characteristic symptoms of subcortical vascular dementia (8).

In a randomized, open-label trial, 65 patients with Alzheimer's disease, 10 with vascular dementia and 15 with both Alzheimer's disease and vascular dementia were treated with risperidone 0.5-2 mg/day and/or rivastigmine 3-12 mg/day for 20 weeks. Coadministration of the two agents was safe, with no clinically relevant adverse events seen (9).

Rivastigmine was evaluated in 82 patients with vascular dementia and evidence of cortical infarct on CAT head (formally known as multi-infarct dementia). Rivastigmine was started at a dose of 1.5 mg once daily and titrated up to a target dose of 12 mg/day. Cognitive improvement was seen in 81.7% of patients and there was a high degree of caregiver and family satisfaction with the treatment (10).

The safety of a combination of memantine and cholinesterase inhibitors in the treatment of dementia and Alzheimer's disease was assessed in an open-label, observational postmarketing surveillance study in 158 patients suffering from dementia. Memantine was combined with donepezil, rivastigmine or tacrine, and the tolerability of the treatment was generally good or very good. The combination of memantine and other drugs was safe, with only 6 patients reporting adverse events and all of these resolved without sequelae and without discontinuation of treatment. The combination was also effective, as physicians considered that the condition of the patients had improved or remained stable in 93% of the cases. These were the first results to suggest a good clinical tolerability of the combination of an uncompetitive NMDA antagonist such as memantine with cholinesterase inhibitors such as rivastigmine in the treatment of Alzheimer's disease and vascular dementia (11).

1. Richard, I.H., Justus, A.W., Greig, N., Marshall, F., Kurlan, R. *Rivastigmine-induced worsening of motor function and mood in a patient with Parkinson's disease*. Mov Disord 2001, 16(Suppl. 1): Abst 104.

2. McKeith, I. et al. *Efficacy of rivastigmine in dementia with Lewy bodies: A randomised, double-blind, placebo-controlled international study*. Lancet 2000, 356(9247): 2031.

3. Neufeld, M.Y., Fogelson, M.Y., Kogan, E., Giladi, N., Shabtai, H., Korczyn, A.D. *The effect of rivastigmine on the quantitative EEG in Parkinson's disease patients with dementia*. 5th Int Conf Prog Alzheimer Parkinson Dis (March 31-April 5, Kyoto) 2001, Abst IV-PD-32.

4. Giladi, N., Shabtai, H., Benbunan, B., Gurevich, T., Anca, M., Sidis, S., Koreczyn, A.D. *The effect of treatment with rivastigmin (Exelon) on cognitive functions of patients with dementia and Parkinson's disease*. 5th Int Conf Prog Alzheimer Parkinson Dis (March 31-April 5, Kyoto) 2001, Abst IV-PD-33.

5. Reading, P.J., Luce, A.K., McKeith, I.G. *Rivastigmine in the treatment of parkinsonian psychosis and cognitive impairment: Preliminary findings from an open trial*. Mov Disord 2001, 16(6): 1171.

6. Reading, P.J., Luce, A.K., McKeith, I.G. *Rivastigmine in the treatment of parkinsonian hallucinosis*. 54th Annu Meet Am Acad Neurol (April 13-20, Denver) 2002, Abst P05.110.

7. Van Laar, T., de Vires, J.J., Nakhosteen, A., Leenders, K.L. *Rivastigmine as anti-psychotic treatment in patients with Parkinson's disease*. Parkinsonism Relat Disord 2001, 7(Suppl. 1): Abst P-TU-248.

8. Moretti, R., Torre, P., Antonello, R.M., Cazzato, G., Griggio, S., Bava, A. *An open-label pilot study comparing rivastigmine and low-dose aspirin for the treatment of symptoms specific to patients with subcortical vascular dementia*. Curr Ther Res 2002, 63(7): 443.

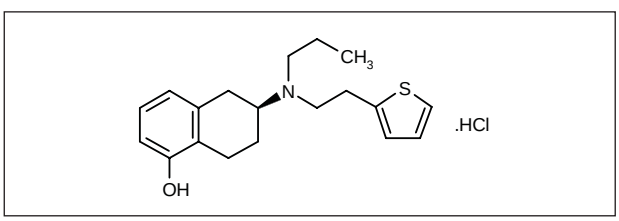
9. Weiser, M., Davidson, M., Rotmensch, H., Korczyn, A., Hartman, R., Anad, R., Cicin-Sain, A. *A pilot, randomized, open-label trial assessing safety and pharmacokinetic parameters of co-administration of rivastigmine with risperidone in demential patients with behavioral disturbances*. 8th Int Conf Alzheimer's Dis Relat Disord (July 20-25, Stockholm) 2002, Abst 633.

10. Amin, S., Shua-Haim, J., Smith, J. *Rivastigmine (Exelon) for patients with vascular dementia: The clinical and caregivers' voice*. 8th Int Conf Alzheimer's Dis Relat Disord (July 20-25, Stockholm) 2002, Abst 220.

11. Hartmann, S., Möbius, H.-J. *Tolerability of memantine in combination with cholinesterase inhibitors in Alzheimer's disease and vascular dementia*. 8th Int Conf Alzheimer's Dis Relat Disord (July 20-25, *treatment with rivastigmin (Exelon) on cognitive functions of patients with dementia and Parkinson's disease*. 5th Int Conf Prog Alzheimer Parkinson Dis (March 31-April 5, Kyoto) 2001, Abst IV-PD-33.

Original monograph - Drugs Fut 1994, 19(7): 656.

Rotigotine Hydrochloride



Rotigotine hydrochloride (N-0923, SPM-962) is a selective nonergot dopamine D_2 receptor agonist which has been developed for transdermal delivery as a patch and is currently in phase III clinical trials for the treatment of Parkinson's disease (1).

Rotigotine CDS™ (Constant Delivery System™), which delivers the drug transdermally over 24 h, was developed by the former Discovery Therapeutics, now Aderis Pharmaceuticals, and is partnered with Schwarz. The Parkinson's patch was designed to test the hypothesis that delivery of dopamine in a nonpulsatile manner is beneficial in patients with early and advanced Parkinson's disease. The Parkinson's patch is applied once a day to the skin and is replaced by a new patch after 24 h (2).

In a multicenter, double-blind, randomized study, 242 patients with early Parkinson's disease received placebo or transdermal rotigotine at doses of 4.5, 9.0, 13.5 or 18.0 mg/day. The study protocol included a 4-week dose-titration period, a 7-week dose-maintenance period, a 1-week dose-deescalation period and a 2-week safety follow-up period. At week 11, patients randomized to the 13.5- and 18-mg doses showed significant improvements in the Activities of Daily Living and Motor components of the UPDRS II/III, the primary study endpoint. The changes in UPDRS II/III scores between baseline and week 11 as compared to placebo were 1.4 units (4.5 mg), 2.6 units (9.0 mg), 5.1 units (13.5 mg) and 5.2 units (18.0 mg). In patients given rotigotine 4.5, 9.0, 13.5 and 18.0 mg/day, a 30% improvement in the UPDRS II/III was seen in 12%, 24%, 40% and 44%, respectively, compared to 18% in the placebo group. A dose-response relationship was found. Rotigotine was generally well tolerated, with nau-

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

Indication	Design	Treatments	n	Conclusions	Ref.
Parkinson's disease	Randomized, double-blind	Rotigotine, 4.5 mg/d x 11 wk Rotigotine, 9 mg/d x 11 wk Rotigotine, 13.5 mg/d x 11 wk Rotigotine, 18 mg/d x 11 wk Placebo	242	Rotigotine was effective and a dose-response relationship was seen with transdermal delivery of the drug to patients with early Parkinson's disease	4
Parkinson's disease	Randomized, double-blind	Rotigotine transdermal delivery system, 9 mg/patch (up to 20 cm^2 by wk 5) x 12 wk Rotigotine transdermal delivery system, 18 mg/patch (up to 40 cm^2 by wk 5] x 12 wk Rotigotine transdermal delivery system, 27 mg/patch (up to 60 cm^2 by wk 5] x 12 wk Placebo	383	No signficant difference was seen in efficacy (time spent "off") between rotigotine and placebo in patients with advanced Parkinson's disease	5
Parkinson's disease	Randomized, double-blind, multicenter	Rotigotine, 4.5 mg transdermal delivery system od x 12 wk Rotigotine, 9 mg transdermal delivery system od x 12 wk Rotigotine, 13.5 mg transdermal delivery system od x 12 wk Rotigotine, 18 mg transdermal delivery system od x 12 wk Placebo	316	Transdermal rotigotine administered as a constant delivery system was safe, well tolerated and effective in early idiopathic Parkinson's disease, especially at doses of 13.5 and 18 mg/day	7
Parkinson's disease	Open	Rotigotine transdermal patches, 20 cm^2 (up to 10 cm^2 q 2-3 d to MTD up to 80 cm^2) d 1-16 → MTD d 17-29 + L-DOPA/Carbidopa (minimum doses)	10	The rotigotine patch allowed levodopa doses to be reduced by over 50% without loss of motor efficacy, and less "off" time was reported by all but 1 of the evaluable patients	8
Parkinson's disease	Randomized, double-blind, multicenter	Rotigotine transdermal delivery system, 8.4 mg/patch (5 cm^2) x 21 d Rotigotine transdermal delivery system, 16.8 mg/patch (10 cm^2) x 21 d Rotigotine transdermal delivery system, 33.5 mg/patch (20 cm^2) x 21 d Rotigotine transdermal delivery system, 67 mg/patch (40 cm^2) x 21 d Placebo	85	Transdermal administration of rotigotine was safe, well tolerated and, at the highest doses tested, led to significantly greater reductions in levodopa doses	9

sea, vomiting, fatigue and somnolence being the main adverse effects. Application site skin reactions were also more common in the higher dose groups (3, 4). The results of this study and some that follow are summarized in Table VII.

The efficacy and safety of rotigotine as an adjunctive therapy to L-DOPA were assessed in patients with advanced Parkinson's disease and L-DOPA-induced motor fluctuations. In a multicenter, double-blind, placebo-controlled trial, 324 patients were randomized to placebo or rotigotine at a dose of 9, 18 or 27 mg/day. Following a 5-week dose-titration period, patients were maintained at target doses for 7 weeks, then followed for safety for 2 additional weeks. No significant differences in the change from baseline to end of treatment in absolute time spent "off", the primary efficacy endpoint, were observed between the placebo and rotigotine groups, possibly due to a large placebo effect. However, the magnitude of decrease in time spent "off" was greatest in the 27-mg rotigotine group (2.44 h), as compared to 1.72, 2.12 and 1.81 h for the 18-mg and 9-mg rotigotine groups and placebo, respectively. In the subgroup of patients with Hoehn and Yahr stage 4 and 5 disease and no major protocol violations, the reduction in "off" time was even greater: 2.88 (27 mg), 2.74 (18 mg), 2.49 (9 mg) and 1.96 h (placebo). The rotigotine transdermal delivery system was well tolerated and most patients rated patch handling as good or excellent. Given the clinical improvement observed with rotigotine, and in spite of the lack of a significant difference as compared to placebo, these researchers consider that further clinical trials of the product are warranted (5).

In a multicenter, randomized, placebo-controlled phase IIb trial in 316 patients, rotigotine CDS™ was associated with dose-dependent improvement on the UPDRS Parts II and III, defined as an improvement in patient symptoms including the ability to undertake activities associated with daily life. Rotigotine CDS™ significantly improved patients' motor function and was well tolerated (6, 7).

Continuous dopaminergic stimulation with the rotigotine TDS was assessed in 10 advanced Parkinson's disease patients in a 4-week study. Use of the rotigotine patch allowed levodopa doses to be reduced by over 50% without loss of motor efficacy. Less "off" time was reported by 6 of 7 patients and 5 of 7 had more "on without dyskinesia" time (8).

A double-blind, randomized, placebo-controlled phase II trial examined the efficacy of rotigotine TDS for replacing levodopa in 85 Parkinson's disease patients. The patients were randomized to placebo or rotigotine at doses of 8.4, 16.8, 33.5 or 67 mg over 21 days. The primary efficacy endpoint was achieved on the two higher doses. Doses of 33.5 and 67 mg rotigotine produced significant reductions in levodopa use of 26% and 28%, respectively, compared to 7% on placebo. The transdermal therapy was well tolerated, with mostly mild adverse events typical of dopaminergic agonists or transdermal patches (9).

1. *Schwarz updates clinical trial programs*. DailyDrugNews.com (Daily Essentials) Aug 23, 2001.

2. *Discovery Therapeutics changes name to Aderis*. DailyDrugNews.com (Daily Essentials) Feb 15, 2002.

3. Fahn, S. *Rotigotine transdermal system (SPM-962) is safe and effective as monotherapy in early Parkinson's disease (PD)*. Parkinsonism Relat Disord 2001, 7(Suppl. 1): Abst P-TU-181.

4. Blindauer, K.A. *Defining responder status in a clinical trial of the rotigotine transdermal system (SPM-962) in early Parkinson's disease*. Mov Disord 2001, 16(5): 981.

5. Quinn, N. *Rotigotine transdermal delivery system (TDS) (SPM 962) - A multicenter, double-blind, randomized, placebo-controlled trial to assess the safety and efficacy of rotigotine TDS in patients with advanced Parkinson's disease*. Parkinsonism Relat Disord 2001, 7(Suppl. 1): Abst P-TU-223.

6. *Dose-dependent improvement on rotigotine CDS in Parkinson's patients*. DailyDrugNews.com (Daily Essentials) April 22, 2002.

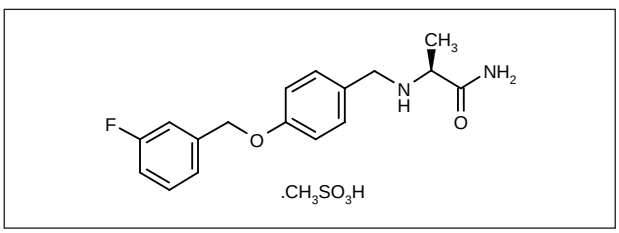
7. Bianchine, J. et al. *Efficacy and dose response of the novel transdermally applied dopamine agonist rotigotine CDS in early Parkinson's disease*. 54th Annu Meet Am Acad Neurol (April 13-20, Denver) 2002, Abst S21.002.

8. Metman, L., Gillespie, M., Farmer, C. et al. *Continuous transdermal dopaminergic stimulation in advanced Parkinson's disease*. Clin Neuropharmacol 2001, 24(3): 163.

9. Hutton, J.T., Metman, L.V., Chase, T.N. et al. *Transdermal dopaminergic D_2 receptor agonist therapy in Parkinson's disease with N-0923 TDS: A double-blind, placebo-controlled study*. Mov Disord 2001, 16(3): 459.

Original monograph - Drugs Fut 1993, 18(11): 1005.

Safinamide Mesilate



Newron's safinamide mesilate (NW-1015, formerly PNU-151774E), a selective and reversible inhibitor of MAO-B and glutamate release, as well as a potent Na^+ and Ca^{2+} channel blocker, has significant potential in the treatment of Parkinson's disease and epilepsy, and is currently in phase II clinical development.

The Na^+ channel blockade is characterized by frequency- and use-dependency, selectively affecting neurons with abnormal firing patterns and leaving normal activity unaltered. When administered by injection prior to systemic MPTP in mice, safinamide (10-40 mg/kg) completely prevented the loss in forebrain dopaminergic neurons, and even posttreatment (4 h after MPTP administration) with safinamide was associated with significant sparing of dopaminergic neurons in the substantia nigra pars compacta. In another model, safinamide at a dose of 20 mg/kg i.p. restored the reduced efficacy of L-DOPA in 6-OHDA-lesioned rats treated with L-DOPA daily for 4 weeks. In primates treated with the drug for 12 weeks at oral doses of 10 and 20 mg/kg/day, significant plasma levels were detected at 24 h after the last dose, as were significant increases in dopamine levels in the putamen and significant decreases in DOPAC levels compared to controls. Significant brain MAO inhibition was also detected at this time (1, 2).

The first clinical results for safinamide administered as single ascending oral doses of 2-10 mg/kg to healthy volunteers demonstrated good tolerance at all dose levels, transient lightheadedness and moderate headache being reported at higher doses. Peak plasma levels were reached rapidly and a long elimination half-life of over 24 h was seen. Pharmacokinetics were linear with dose. MAO-B activity in platelet-rich plasma was inhibited by over 90% for up to 48 h after all doses, whereas no effect was seen on MAO-A. In another study, subjects received single oral doses of 25-600 μg/kg and a significant, progressive and long-lasting inhibition of MAO-B activity was again detected. Together with findings in primates, these

results indicate that the levels of MAO-B inhibition seen in the clinic should result in enhanced nigrostriatal dopaminergic function, which in turn should provide symptomatic relief from the symptoms of Parkinson's disease, and dose-finding studies in patients are under way (3).

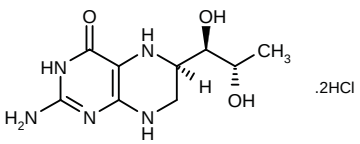
1. Maj, R., Caccia, C., Laberti, E., Calabresi, M., Benatti, L., Salvati, P., Fariello, R.G. *Safinamide (NW-1015): Experimental evidence of preventive and therapeutic antiparkinson properties*. 5th Int Conf Prog Alzheimer Parkinson Dis (March 31-April 5, Kyoto) 2001, Abst V-PD-50.

2. *Company Profile: Newron Pharmaceuticals*. DailyDrugNews.com (Daily Essentials) April 27, 2001.

3. Caccia, C., Tocchetti, P., Del Bo, L., Lamberti, E., Marzo, A., Salvati, P., Fariello, R.G. *Safinamide (NW-1015): Effects on platelets MAO-B activity in healthy volunteers*. 5th Int Conf Prog Alzheimer Parkinson Dis (March 31-April 5, Kyoto) 2001, Abst V-PD-51.

Original monograph - Drugs Fut 2001, 26(8): 745.

Sapropterin Dihydrochloride



Sapropterin dihydrochloride (6R-BH4, dapropterin dihydrochloride, SUN-0588; Suntory) is a natural cofactor for rate-limiting enzymes involved in dopamine and 5-HT biosynthesis, as well as for nitric oxide synthase (NOS). Sapropterin was introduced a number of years ago in Japan by Suntory as Biopten® as a treatment for hyperphenylalaninemia. Sapropterin has been reported to improve clinical symptoms in certain neurological disorders, including Parkinson's disease, depression and infantile autism.

The therapeutic effects of sapropterin were examined in rats with abnormal behavior induced by 6-OHDA or 5,7-DHT. Locomotor activities increased in the 6-OHDA-treated rats and decreased in 5,7-DHT-treated rats. Repeated administration of sapropterin suppressed these effects, suggesting potential in the treatment of infantile autism and developmental disorders associated with monoamine dysfunction (1).

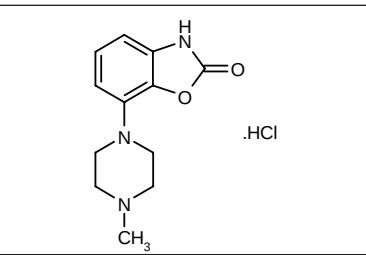
In a PET study, sapropterin was administered orally (3 mg/kg/day) for 6 months to 18 autistic children in a double-blind, crossover manner and was shown to significantly increase dopamine turnover in the anterior cingulate gyrus and occipital cortex, as well as to decrease *N*-[^{11}C]-methylspiperone binding in the thalamus. Dopamine turnover in the amygdala was negatively correlated with score on the Childhood Autism Rating Scale (2).

1. Mizuma, H., Nakata, R., Nozaki, S., Takashimo, S., Iizuka, H., Nishimura, N., Watanabe, Y., Kohashi, R. *Improvement of the monoamine depletion-induced abnormal behaviors by repeated administration of 6R-L-tetrahydrobiopterin*. Soc Neurosci Abst 2001, 27: Abst 447.21.

2. Takahashi, K., Torstenson, R., Danfors, T. et al. *Dysfunction of the dopaminergic system in pervasive developmental disorder: A PET study with drug treatment*. Soc Neurosci Abst 2001, 27: Abst 447.2.

Original monograph - Drugs Fut 1991, 16(1): 30.

SLV-308



A potential new Parkinson's disease therapeutic, SLV-308 (SME-308) is a dual partial dopamine D_2 receptor agonist and 5-HT_{1A} receptor agonist which is being codeveloped by Meiji Seika and Solvay and is currently in phase II trials (1).

SLV-308 0.01-0.3 mg/kg was administered to MPTP-treated marmosets to assess the agent's antiparkinsonian effects. Compared to vehicle, the 0.3 mg/kg dose resulted in a 663% increase in total locomotor counts 11 h after i.p. administration; the same dose induced an 855% increase in total locomotor counts 8 h after p.o. administration. Treatment produced qualitative results similar to those observed with other treatments for Parkinson's disease (2).

The effect of SLV-308 on motor deficits induced by MPTP was evaluated in adult marmosets. SLV-308 (0.003-0.3 mg/kg i.p.) was administered 40 min after treatment with domperidone (2 mg/kg p.o.). The treatment reversed akinesia and disability, demonstrating

the potential of SLV-308 as an adjunct for late-stage levodopa therapy in patients with Parkinson's disease (3).

Neurochemical analyses of SLV-308 *in vitro* and *in vivo* indicated that the agent is likely to have clinical utility in the treatment of Parkinson's disease. SLV-308 demonstrated potent partial agonism at cloned dopamine D_2 receptors and full agonism at cloned human 5-HT_{1A} receptors (4).

SLV-308 was tested in models of D_2 and 5-HT_{1A} receptor function, Parkinson's disease, depression, anxiety and psychosis. The drug appeared to act as a partial dopamine D_2 receptor agonist and a 5-HT_{1A} receptor agonist *in vivo*. Antidepressant activity and anxiolytic-like effects were also seen in various tests and SLV-308 was active in a model of psychosis (5).

1. *Codevelopment agreement reached by Meiji Seika and Solvay for new PD agent*. DailyDrugNews.com (Daily Essentials) June 14, 2001.

2. Johnston, L.C., Smith, L., McCreary, A.C., Jenner, P., Ronken, E. *SLV308: Antiparkinsonian effects in the MPTP-treated common marmoset (Calluthrix jacchus)*. Soc Neurosci Abst 2001, 27: Abst 200.3.

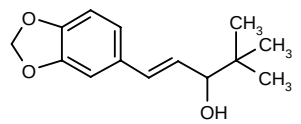
3. Johnston, L.C., Smith, L., Rose, S., Jenner, P. *The novel dopamine D_2 receptor partial agonist, SLV-308, reverses motor disability in MPTP-lesioned common marmosets (Callithrix jacchus)*. Br J Pharmacol 2001, 133(Suppl.): Abst 134P.

4. Hesselink, M., Siarey, R., Glennon, J., Onken, E., Scharrenburg, G., McCreary, A., Long, S. *SLV308, a molecule combining potent dopamine D_2 receptor agonism with serotonin 5-HT_{1A} receptor agonism: In vitro and in vivo neurochemistry*. Soc Neurosci Abst 2001, 27: Abst 200.4.

5. McCreary, A.C., Ronken, E., Herremans, A., van de Heyden, J., Tuinstra, T., von Scharrenburg, G., Hesselink, M., Long, S. *SLV308: A novel antiparkinsonian agent with antidepressant and anxiolytic efficacy*. Soc Neurosci Abst 2001, 27: Abst 200.5.

Original monograph - Drugs Fut 2001, 26(2): 128.

Stiripentol



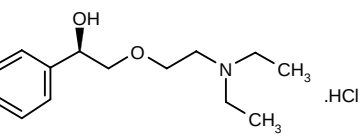
Stiripentol is an investigational anticonvulsant agent from Biocodex.

Researchers used human liver microsomes and cDNA-expressed CYP to evaluate the effect of stiripentol on the metabolism of carbamazepine and saquinavir. For *in vivo* investigation, data from pediatric epileptic patients and healthy adult volunteers was analyzed. *In vitro* and in epileptic patients, stiripentol potently inhibited the metabolism of carbamazepine to carbamazepine-10,11-epoxide. Regarding saquinavir metabolism, stiripentol demonstrated poor inhibitory activity *in vitro* and *in vivo* (1).

1. Tran, A., Cazali, N., Tréluyer, j., Rey, E., Vincent, J., Pons, G. *Variable inhibitory effect of stiripentol on CYP3A-dependent metabolism of different drugs in human*. Clin Pharmacol Ther 2002, 71(2): Abst MPI-108.

Original monograph - Drugs Fut 1980, 5(8): 413.

T-588



T-588 (Toyama), a cholinergic agent, is undergoing clinical testing in Japan and the U.K. as a potential therapy for Alzheimer's disease and is also being evaluated for use in amyotrophic lateral sclerosis (ALS).

T-588 was evaluated for its effects on the induction and maintenance of long-term potentiation and on the responses to paired-pulse stimulation in freely moving rats. The results suggested that the alleviation of learning and memory deficits in animal models of dementia may be due to the drug's facilitation of long-term synaptic plasticity in the dentate gyrus (1).

T-588 concentration-dependently increased astrocytic mitochondrial dehydrogenase activity in cultured astrocytes, thereby affecting cell vulnerability and protecting astrocytes from cell death after exposure to sodium nitroprusside (2).

An *in vitro* study using PC-12 cells showed that T-588 stimulated noradrenaline release in a concentration-dependent and extracellular calcium-independent manner. Release of [^{3}H]-noradrenaline was observed at concentrations as low as 10 μM. T-588 (30 μM) enhanced the calcium-dependent release of [^{3}H]-noradrenaline induced by ionomycin (10 μM), ATPγS (300 μM) and forskolin (10 μM). T-588 also concentration-dependently increased

cytosolic synaptophysin and 25-kDa synaptosome-associated protein immunoreactivity and induced translocation of synaptic vesicle in a calcium-dependent manner (3).

After induction of Purkinje cell long-term depression (LTD) in mouse cerebellar slices, it was found that preincubation of the slices with T-588 (< 1 μM) completely suppressed LTD (4).

The effect of T-588 on neurite outgrowth and choline acetyltransferase activity was examined in primary explant cultures of fetal rat ventral spinal cord. T-588 treatment (10 nM-10 μM) for 1 week demonstrated a significant neurite-promoting effect, and increased choline acetyltransferase activity 1.5 times over that of control at 1-10 μM. This neurotrophic action suggests the potential use of T-588 in treating diseases involving degeneration and death of spinal motor neurons, such as motor neuropathy and motor neuron disease (5).

T-588 has been evaluated in the Wobbler mouse model of ALS and was reported to improve the function of the motor tracts of the peripheral and central nervous systems following oral administration at doses of 3 or 30 mg/kg/day for 4 weeks (6).

1. Yamaguchi, H., Tamuta, R., Kuriwaki, J., Eifuku, S., Ono, T. *Effects of T-588, a cognitive enhancer compound, on synaptic plasticity in the dentate gyrus of freely moving rats*. J Pharmacol Exp Ther 2001, 298(1): 354.

2. Phuagphong, P., Wakamatsu, D., Kozaki, R., Matsuda, T., Baba, A. *Effect of T-588 on mitochondrial function and cell death of cultured astrocytes*. Jpn J Pharmacol 2001, 85(Suppl. I): Abst P-710.

3. Maekawa, M. et al. *Stimulation of noradrenaline release by T-588, a cognitive enhancer, in PC12 cells*. Jpn J Pharmacol 2000, 82(1): 59.

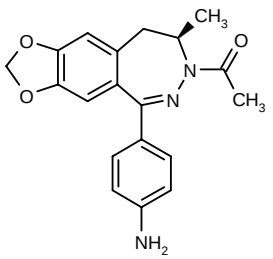
4. Kimura, T., Hirata, K., Sugimori, M., Llinas, R. *The effect of T-588, a neuroprotective agent, on the mouse cerebellar long-term depression*. Soc Neurosci Abst 2001, 27: Abst 389.6.

5. Iwasaki, Y., Ikeda, K., Ichikawa, Y., Igarashi, O., Kinoshita, M., Marubuchi, S., Ono, S. *T-588 enhances neurite outgrowth and choline acetyltransferase in cultured rat spinal ventral horn neurons*. Neurochem Res 2002, 27(3): 225.

6. Ikeda, K., Iwasaki, Y., Ichikawa, Y., Kinoshita, M., Marubuchi, S., Ono, S. *The effects of T-588 on the central and peripheral motor nervous system in the Wobbler mouse model of ALS*. 42nd Annu Meet Societas Neurologica Japonica (May 11-13, Tokyo) 2001, Abst P-3-0-6.

Original monograph - Drugs Fut 1997, 22(4): 386.

Talampanel



Ivax has entered into an exclusive agreement with Lilly to develop and market talampanel (GYKI-53773, LY-300164, IDR-53773), a noncompetitive AMPA receptor antagonist, on a worldwide basis. Phase II trials of the drug in patients with severe epilepsy not responsive to other drugs have shown efficacy, and phase III studies are planned to confirm and expand these results. Talampanel was initially discovered at the Institute for Drug Research in Hungary, now a wholly owned subsidiary of Ivax (1).

Single and multiple doses of talampanel (9-12.5 mg/kg i.p.) were evaluated in a rat model of epilepsy. Long-lasting antiepileptic effects were observed; significantly fewer animals treated with the highest dose and for the longest duration and beginning 3 h after induction of status epilepticus developed spontaneous recurrent seizures compared to control animals (2).

When administered to rats 30 min, but not 3 h, after traumatic brain injury, talampanel (4 mg/kg by i.v. bolus followed by 4 mg/kg/h by 72-h infusion) reduced the total contusion area and significantly attenuated neuronal damage in all 3 subsectors of the hippocampal CA1 sector (3).

Talampanel was investigated in 49 patients with refractory partial seizures enrolled in a multicenter, randomized, double-blind, placebo-controlled, crossover clinical study. Depending on concomitant antiepileptic therapy, patients were given talampanel in oral doses of 25, 60 or 75 mg t.i.d. during two 14-week treatment periods separated by a 4-week washout period. The treatment effectively reduced seizures (median reduction of 21%) in most patients compared with placebo. Dizziness, generally mild to moderate, and ataxia were common adverse events (4).

1. *Ivax acquires Lilly's talampanel, an advanced-stage antiepileptic*. DailyDrugNews.com (Daily Essentials) Feb 9, 2001.

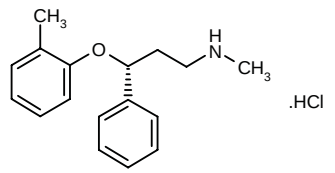
2. Loducca, R.D.S., Mello, L.E.A. *LY300164, an AMPA antagonist, prevents epileptogenesis in the pilocarpine model of epilepsy*. Soc Neurosci Abst 2001, 27: Abst 556.2.

3. Belayev, L., Alonso, O.F., Liu, Y.T., Chappell, A.S., Zhao, W.H., Ginsberg, M.D., Busto, R. *Talampanel, a novel noncompetitive AMPA antagonist, is neuroprotective after traumatic brain injury in rats*. J Neurotrauma 2001, 18(10): 1031.

4. Chappel, A.S., Sander, J.W., Brodie, M.J., Chadwick, D., Lledo, A., Zhang, D., Bjerke, J., Kiesler, G.M., Arroyo, S. *A crossover, add-on trial of talampanel in patients with refractory partial seizures*. Neurology 2002, 58(11): 1680.

Original monograph - Drugs Fut 2001, 26(8): 754.

Tomoxetine Hydrochloride



Lilly filed an NDA with the FDA last year for the use of tomoxetine hydrochloride (atomoxetine, LY-139603, Strattera™), a highly specific noradrenaline reuptake inhibitor, as a treatment for attention deficit hyperactivity disorder (ADHD) in children, adolescents and adults. An approvable letter was issued this summer and the company plans to launch this novel product before the end of the year (1).

Researchers found that CYP2D6 is the primary cytochrome P-450 enzyme responsible for the biotransformation of tomoxetine to its major metabolite 4-hydroxyatomoxetine. In patients with compromised CYP2D6 activity, multiple P-450 enzymes are capable of forming 4-hydroxyatomoxetine and such individuals would not be expected to have lower tomoxetine clearance when given P-450 inhibitors (2).

Evidence from a study investigating the potential mechanism of action of tomoxetine in ADHD suggests that the drug produces its beneficial effects through an increase in extracellular levels of dopamine and noradrenaline in the prefrontal cortex (3).

The pharmacokinetics of tomoxetine (20 mg p.o. s.d.) were determined in 10 patients with hepatic impairment and in 10 healthy controls. Patients with hepatic impairment had significant alterations in tomoxetine metabolites. Tomoxetine clearance was correlated with sorbitol clearance in these patients and with the debrisoquine metabolic ratio (a measure of CYP2D6 activity) in these patients and in controls (4).

Twelve healthy subjects received 5 days of tomoxetine 60 mg b.i.d., methylphenidate 60 mg once daily or placebo, with the other drug added on days 3-5. Methylphenidate was associated with greater maximal changes in heart rate than tomoxetine and the combination of the two drugs produced a maximum increase in heart rate similar to that seen with methylphenidate alone and greater than that for tomoxetine alone. Only methylphenidate increased blood pressure after multiple doses and combination of the drugs was associated with a similar increase to methylphenidate alone. Methylphenidate, but not tomoxetine, increased plasma adrenaline levels. Adverse events such as tachycardia and dry mouth were more common on methylphenidate and the combination of methylphenidate + tomoxetine showed a similar incidence of side effects to methylphenidate alone. Thus, at apparently therapeutic doses, tomoxetine produces fewer cardiovascular effects compared to methylphenidate and their combination does not appear to produce an additive effect (5). The results of this study and many that follow are summarized in Table VIII.

In similar clinical trials, 12 healthy individuals received 5 days of oral tomoxetine 50 mg b.i.d. or placebo with i.v. salbutamol 5 mcg/min for 2 h or placebo added on days 1, 3 and 5. Salbutamol (maximum mean increase of 20.5 bpm) increased heart rate to a significantly greater extent than tomoxetine (maximum mean increase of 7.0 bpm) and combination of the drugs produced a more or less additive effect and prolonged the increase in heart rate. The decrease in systemic vascular resistance observed on salbutamol was not altered by tomoxetine and salbutamol infusion did not influence the pharmacokinetics of tomoxetine. According to these results, the combination of the two drugs is not likely to be associated with clinically relevant hemodynamic effects compared to i.v. salbutamol alone. Moreover, the clinical impact on the cardiovascular system may be even less when tomoxetine is combined with inhaled β_2-agonists (6).

Healthy volunteers who had used recreational drugs were examined for their perception of drug effects following administration of tomoxetine 20, 45 or 90 mg, methylphenidate 20 or 40 mg and placebo. The results demonstrated a different profile for tomoxetine compared to the stimulant methylphenidate suggesting no significant abuse liability (7).

Safety data from several large open-label and controlled studies of tomoxetine in children and adolescents with ADHD have been analyzed. A total of 1500 children were treated with tomoxetine at doses up to 3.5 mg/kg/day, although most received 1.5 mg/kg/day. Few serious adverse events, none attributable to drug, were reported. The only adverse event reported more frequently on tomoxetine compared to placebo, but less frequently compared to methylphenidate, was mildly decreased appetite (7-22%, 5-7% and 15-32%, respectively). In contrast to methylphenidate, tomoxetine was not associated with insomnia. Furthermore, adverse events tended to decline with long-term therapy and discontinuation of therapy was not associated with adverse events. Mild tachycardia and a slight increase in diastolic blood pressure were observed on tomoxetine but were not considered clinically relevant, and no significant laboratory abnormalities were detected. Moreover, poor and extensive metabolizers showed no difference in tolerability (8-10). In terms of efficacy, treatment of children and adolescents with ADHD with tomoxetine 1.2-1.8 mg/kg/day significantly improved outcome compared to placebo on several rating scales, including the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version:Investigator (ADHDRS-IV-Parent:Inv) and the

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

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized, double-blind	Tomoxetine, 60 mg bid x 5 d + Methylphenidate, 60 mg qd on d 3-5 Methylphenidate, 60 mg qd x 5 d + Tomoxetine, 60 mg bid on d 3-5 Placebo x 5 d + Methylphenidate, 60 mg qd on d 3-5 Placebo x 5 d + Tomoxetine, 60 mg bid on d 3-5 Placebo x 5 d	12	Methylphenidate had greater cardiovascular effects than tomoxetine, and these effects were not increased when tomoxetine was added to methylphenidate	5
Healthy volunteers	Randomized, double-blind	Tomoxetine, 60 mg bid po x 5 d + Salbutamol, 5 µg/min iv x 2 h on d 1, 3, 5 Tomoxetine, 60 mg bid po x 5 d + Placebo iv on d 1, 3, 5 Placebo po x 5 d + Salbutamol, 5 µg/min iv x 2 h on d 1, 3, 5 Placebo po x 5 d + Placebo iv on d 1, 3, 5	12	Salbutamol alone had greater hemodynamic effects than tomoxetine alone, and the cardiovascular effects of salbutamol were only slightly increased by the addition of tomoxetine	6
Healthy volunteers	Randomized, double-blind, crossover	Tomoxetine, 20, 45 and 90 mg Methylphenidate, 20 and 40 mg Placebo		Tomoxetine differed from methylphenidate in subjective stimulant scores, with higher scores for nonpleasurable measures, indicating that the drug is not likely to be abused	7
ADHD	Pooled/meta-analysis	Tomoxetine, up to 3.5 mg/kg/d		Tomoxetine was well tolerated in open-label studies and 4 controlled trials. Increases in diastolic blood pressure, diminished appetite and mild tachycardia seen with tomoxetine treatment were deemed clinically insignificant	8
ADHD	Open	Tomoxetine, titration x 10 wk → x 1 y	325	Tomoxetine was well tolerated by children and adolescents with attention deficit hyperactivity disorder over a study period of 1 y	9
ADHD	Pooled/meta-analysis	Tomoxetine, 0.5, 1.2 or 1.8 mg/kg/d x 8-9 wk Placebo		Tomoxetine was more effective than placebo in improving attention deficit hyperactivity disorder in children	11
ADHD	Randomized	Tomoxetine, 0.5 mg/kg/d x 8 wk (n=44) Tomoxetine, 1.2 mg/kg/d x 8 wk (n=84) Tomoxetine, 1.8 mg/kg/d x 8 wk (n=85) Placebo (n=84)	297	Tomoxetine was well tolerated and significantly better than placebo in improving symptoms. The higher doses were the most beneficial and were similarly effective	12, 13
ADHD	Open	Tomoxetine, 10-20 mg/d (increased q wk up to 90 mg over 11 wk, mean dose 1.9 mg/kg/d)	30	Scores for symptoms of attention deficit hyperactivity disorder were significantly reduced by tomoxetine, which was not associated with clinically relevant adverse effects	14
ADHD	Randomized, double-blind	Tomoxetine, 0.5 mg/kg od x 8 wk Tomoxetine, 1.2 mg/kg od x 8 wk Tomoxetine, 1.8 mg/kg od x 8 wk Placebo	249	The attention deficit hyperactivity disorder symptoms (evaluated using the ADHD rating scale), the social and family functioning (measured using the Childhood Health Questionnaire) and the quality of life of children and adolescents with attention deficit hyperactivity disorder significantly improved after treatment with tomoxetine	15
ADHD	Pooled/meta-analysis	Tomoxetine bid Tomoxetine od Placebo		Compared to placebo, tomoxetine significantly improved the attention deficit hyperactivity disorder rating scale scores in children and adolescents	16

Continued

Table VIII Cont.: Clinical studies of tomoxetine (from Prous Science Integrity®).

ADHD	Double-blind, pooled/meta-analysis	Tomoxetine x 6-8 wk (n=250) Placebo (n=166)	416	Tomoxetine was effective in treating children and adolescents with attention deficit hyperactivity disorder	17
ADHD	Randomized, open	Tomoxetine x 10 wk (n=184) Methylphenidate x 10 wk (n=44)	228	The tolerability, safety and efficacy (improvement of inattentive and hyperactive/impulsive symptom clusters) of tomoxetine were similar to those of methylphenidate	18
ADHD	Open	Tomoxetine (dose-titrated according to tolerability and response)	10	Tomoxetine significantly improved symptoms according to both parents and investigators. Appetite suppression was the most common adverse event, although body weight was not affected	19

Conners' Parent Rating Scale-Revised:Short Form (CPRS-R:S). Tomoxetine significantly reduced ADHDRS total scores, as well as the inattentive and hyperactive/impsulsive subscales. Tomoxetine is thus associated with significant improvement in social and family functioning, thereby reducing the burden of illness on the patients and their parents (11-19).

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

2. Ring, B.J., Gillespie, J.S., Eckstein, J.A., Wrighton, S.A. *Identification of the human cytochromes P450 responsible for atomoxetine metabolism*. Drug Metab Dispos 2002, 30(3): 319.

3. Bymaster, F.P., Gehlert, D., Nelson, D. et al. *Atomoxetine increases cortical levels of norepinephrine and dopamine: A proposed mechanism of action in ADHD*. Eur Neuropsychopharmacol 2002, 12(Suppl. 3): Abst P.6.035.

4. Desager, J, et al. *Pharmacokinetics (PK) of atomoxetine (ATM) in hepatically impaired (HI) patients*. Clin Pharmacol Ther 2002, 71(2): Abst WPIII-85.

5. Yeo, K.P., Kelly, R., Lowe, S.L., Smith, B., Soon, D.K.W., Teng, C.H., Thomasson, H., Wise, S.D. *Haemodynamic effects of atomoxetine are less pronounced than methylphenidate, and not additive in combination*. J Clin Pharmacol 2001, 41(9): Abst 39.

6. Lowe, S.L., Lim, M., Smith, B., Sathirakul, K., Thomasson, H., Yasuda, M., Yeo, K.P., Wise, S.D. *Haemodynamic effects of IV salbutamol and oral atomoxetine, alone and in combination*. J Clin Pharmacol 2001, 41(9): Abst 49.

7. Laws, H.F., Heil, S.H., Bickel, W.K., Higgins, S.T., Faries, D.E., Badger, G. *Subjective responses to LY139603 (atomoxetine) and methylphenidate*. Eur Neuropsychopharmacol 2001, 11(Suppl. 3): Abst P.4.005.

8. Wernicke, J.F., Fouche, D.S., Spencer, T., Dunn, D., Faries, D.E., Kelsey, D.K., Heiligenstein, J.H., Michelson, D. *Safety of atomoxetine in pediatric patients treated for ADHD*. Eur Neuropsychopharmacol 2001, 11(Suppl. 3): Abst P.4.007.

9. Wernicke, J.F. et al. *Long-term safety of atomoxetine in children and adolescents with ADHD*. Annu Meet Am Psychiatr Assoc (May 18-23, Philadelphia) 2002, Abst NR338.

10. Wernicke, J.F., Dunn, D., Faries, D.E., Heligenstein, J.H., Kelsey, D.K., Kendrick, K.L., Michelson, D. *Safety of atomoxetine in placebo-controlled pediatric attention-deficit hyperactivity disorder trials*. 30th Annu Meet Child Neurol Soc (Oct 17-20, Victoria) 2001, Abst P84.

11. Dunn, D.W., Vernicke, J.F., Faries, D., Heligenstein, J.H., Allen, A.J., Laws, H., Michelson, D. *Efficacy of atomexetine in placebo-controlled pediatric attention-deficit hyperactivity disorder trials*. 30th Annu Meet Child Neurol Soc (Oct 17-20, Victoria) 2001, Abst 15.

12. Michelson, D., Faries, D.E., Wernicke, J.F., Spencer, T. *Atomoxetine in the treatment of children with ADHD: A randomized, placebo-controlled dose-response study*. Eur Neuropsychopharmacol 2001, 11(Suppl. 3): Abst P.4.008.

13. Michelson, D., Faries, D., Wernicke, J., Kelsey, D., Kendrick, K., Sallee, F.R., Spencer, T. *Atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: A randomized, placebo-controlled, dose-response study*. Pediatrics 2001, 108(5): E83.

14. Spencer, T., Biederman, J., Heilligenstein, J., Willens, T., Farias, D., Prince, J., Faraone, S.V., Rea, J., Witcher, J., Zervas, S. *An open-label, dose-ranging study of atomoxetine in children with attention deficit hyperactivity disorder*. J Child Adolesc Psychopharmacol 2001, 11(3): 251.

15. Donnelly, C., Faries, D., Swensen, A., Ruff, D., Michelson, D., Matza, L., Barker, C., Rentz, A., Revicki, D. *The effect of atomoxetine on the social and family functioning of children and adolescents with attention-deficit/hyperactivity disorder (ADHD)*. Eur Neuropsychopharmacol 2002, 12(Suppl. 3): Abst P.6.080.

16. Brown, W.J., Biederman, J., Spencer, T., Heiligenstein, J., Wernicke, J., Allen, A.J., Faries, D., Michelson, D. *Efficacy and safety of atomoxetine in the treatment of attention deficit/hyperactivity disorder in children and adolescents*. Eur Neuropsychopharmacol 2002, 12(Suppl. 3): Abst P.6.019.

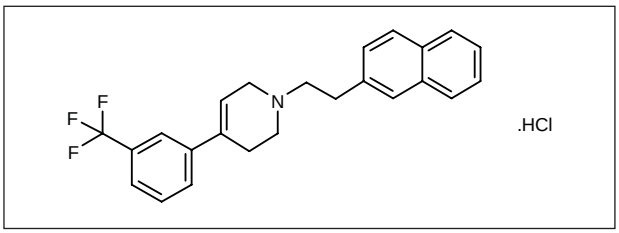
17. Allen, A.J. et al. *Efficacy of atomoxetine in children an adolescents with ADHD*. Annu Meet Am Psychiatr Assoc (May 18-23, Philadelphia) 2002, Abst NR348.

18. Dittmann, R.W., Fouche, D.S., Kratochvil, C., Heiligenstein, J.H., Spencer, T., Biederman, J. *Atomoxetine and methylphenidate treatment in children with ADHD: A prospective, randomized, open-label trial*. Eur Neuropsychopharmacol 2001, 11(Suppl. 3): Abst P.4.006.

19. Kratochvil, C.J., Bohac, D., Harringhton, M., Baker, N., May, D., Burke, W.J. *An open-label trial of tomoxetine in pediatric attention deficit hyperactivity disorder*. J Child Adolesc Psychopharmacol 2001, 11(2): 167.

Original monograph - Drugs Fut 1986, 11(2): 134.

Xaliproden Hydrochloride



Xaliproden hydrochloride (SR-57746A) is a non-peptide, orally active neurotrophic and neuroprotective agent developed at Sanofi-Synthélabo. It is in late-stage clinical trials for ALS.

Magnetic resonance imaging (MRI) was concluded to be useful for quantitatively analyzing the neuroprotective effects of xaliproden in rats with vincristine-induced (10 mg/kg/day p.o.) brain lesions. Increases in the MR signal and intensity in the septum on T2-weighted images appeared at day 3 and were maximal 10 days postinjection. In the presence of xaliproden, the appearance of increased signals was delayed until day 7 (1).

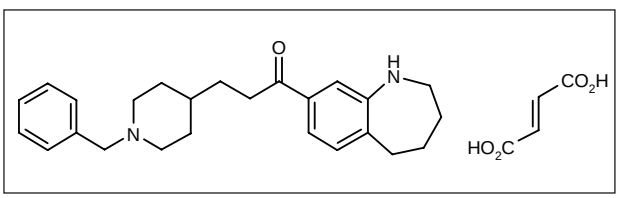
The results from a phase II clinical trial of xaliproden hydrochloride in Japanese patients with ALS were reported. This open trial enrolled 26 patients who received xaliproden at a dose of 1 or 2 mg/day for 24 weeks. The higher dose was significantly more effective in inhibiting disease progression according to the Modified Norris Bulbar scale, but both doses were similar as regards other efficacy parameters. Adverse events were few and minor, and steady state was reached after 4 weeks of drug treatment (2).

1. Lemaire, L., Fournier, J., Ponthus, C., LeFur, Y., Confort Gouny, S., Vion Dury, J., Keane, P, Cozzone, P.J. *Magnetic resonance imaging of the neuroprotective effect of xaliproden in rats*. Invest Radiol 2002, 37(6): 321.

2. Tashiro, K., Ikeda, S., Iwasaki, Y. et al. *Japanese phase II clinical study of SR57746A (xaliproden) in amyotrophic lateral sclerosis*. 126th Annu Meet Am Neurol Assoc (Sept 30-Oct 3, Chicago) 2001, 48.

Original monograph - Drugs Fut 1998, 23(6): 616.

Zanapezil Fumarate



A new acetylcholinesterase inhibitor from Takeda, zanapezil fumarate (TAK-147), is undergoing late-stage clinical trials in Japan for Alzheimer's disease.

The effect of zanapezil fumarate on spatial memory was investigated in rats using the Morris water maze test. TAK-147 and donepezil ameliorated scopolamine-induced deficits related to the memory acquisition process and significantly reversed deficits in the memory retrieval process. In additional experiments in an open-field test, TAK-147, scopolamine or donepezil did not alter locomotor activities (1).

1. Chen, Z., Xu, A.-J., Li, R., Wei, E.-Q. *Reversal of scopolamine-induced spatial memory deficits in rats by TAK-1471*. Acta Pharmacol Sin 2002, 23(4): 355.

Original monograph - Drugs Fut 1995, 20(3): 248.