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Annual Update 2003/2004 - Treatment of Psychiatric Disorders

Treatment of Psychiatric Disorders by Condition

Condition	Phase	Drug	Source
Agitation (associated with schizophrenia or bipolar I mania)	L-2004	Olanzapine[1,2]	Lilly
Anxiety	II	AP-521	Asahi Kasei
	II	AZD-8129	AstraZeneca
	II	R-673	Roche
	II	SL-65.1498	Sanofi-Aventis
	II	Vestipitant mesilate	GlaxoSmithKline
	I/II	SEP-174559	Sepracor
	I	679769	GlaxoSmithKline
	I	823296	GlaxoSmithKline
	I	AAG-561	Novartis
	I	BTG-1640	Abiogen/BTG
	I	ELB-139	elbion
	I	Emapunil	Dainippon Pharmaceutical/Novartis
	I	Itriglumide[2]	Rotta
	I	NBI-34041	Neurocrine Biosciences/ GlaxoSmithKline
	I	R-1204	Roche
	I	SSR-149415	Sanofi-Aventis
	I	XBD-173	Novartis
Anxiety, generalized	L-2004 (US)	Escitalopram oxalate[1,2]	Lundbeck/Forest
	Prereg.	Pregabalin[1,2]	Pfizer
	III (EU)	Escitalopram oxalate[1,2]	Lundbeck/Forest
	III	Pagoclone[2]	Indevus
	II/III	Ocinaplon[2]	DOV Pharmaceutical
	II/III	Tiagabine hydrochloride[2]	Cephalon
	II	Osemozotan hydrochloride[2]	MediciNova/Mitsubishi Pharma
	I	PRX-00023	Predix Pharmaceuticals
Attention deficit hyperactivity disorder	L-2003	Atomoxetine hydrochloride[2]	Lilly
	Prereg.	Methylphenidate hydrochloride (patch)	Noven/Shire Pharmaceuticals
	III	Modafinil[1,2]	Cephalon
	III	SPD-503	Shire Pharmaceuticals
	II/III	SPD-465	Shire Pharmaceuticals
	II	AFX-221	Afecta Pharmaceuticals
	II	NS-2359	GlaxoSmithKline/NeuroSearch
	II	TC-5231	Targacept
	I	PRX-00023	Predix Pharmaceuticals
	Discontinued	SPD-473 (BTS-74398)	Shire Pharmaceuticals
Attention deficit hyper-activity disorder (adults)	L-2004	SLI-381	Shire Pharmaceuticals
	III	Dexmethylphenidate hydrochloride	Novartis/Celgene

Continuation

Treatment of Psychiatric Disorders by Condition

Condition	Phase	Drug	Source
Autism	Prereg.	Risperidone[1,2]	Janssen
	III	RG-1068	Repligen
Bipolar disorder	L-2004	Lamotrigine[1,2]	GlaxoSmithKline
	L-2004	Olanzapine/fluoxetine hydrochloride	Lilly
	R-2004	Aripiprazole[1,2]	Otsuka/Bristol-Myers Squibb
	Prereg,	SPD-417	Shire Pharmaceuticals
	III	Asenapine maleate[2]	Organon/Pfizer
	II	Licarbazepine	Novartis
	I/II	RG-2133	Repligen
	I/II	Valrocemide	Acorda/Teva
	I	DP-VPA	D-Pharm
Depression	III	Lif-247	Enhance Lifesciences
	III	SR-58611	Sanofi-Aventis
	II	AZD-8129	AstraZeneca
	II	Org-34517	Organon
	II	R-673	Roche
	II	Radafaxine hydrochloride	GlaxoSmithKline
	II	Vestipitant mesilate	GlaxoSmithKline
	II	Vilazodone hydrochloride	Genaissance/Merck KGaA
	II	YKP-10A	SK Bio-Pharmaceuticals; Janssen
	I/II	PRX-00023	Predix Pharmaceuticals
	I	679769	GlaxoSmithKline
	I	823296	GlaxoSmithKline
	I	AAG-561	Novartis
	I	AEP-924	Novartis
	I	Delucemine hydrochloride	NPS Pharmaceuticals
	I	DOV-21947	DOV Pharmaceutical/Merck & Co.
	I	E-6006	Esteve
	I	Emapunil	Dainippon Pharmaceutical/Novartis
	I	Lu-AA-21004	Lundbeck
	I	NBI-34041	Neurocrine Biosciences/ GlaxoSmithKline
	I	ND-1251	Neuro3d
	I	R-1204	Roche
	I	SA-4503 (AGY-94806)	M's Science/AGY Therapeutics
	I	SSR-146977	Sanofi-Aventis
	I	SSR-149415	Sanofi-Aventis
Depression, major	L-2004 (US)	Duloxetine hydrochloride[2]	Boehringer Ingelheim/Lilly/Shionogi
	Prereg. (other markets)	Duloxetine hydrochloride[2]	Boehringer Ingelheim/Lilly/Shionogi
	Prereg.	Transdermal selegiline	Somerset Pharmaceuticals
	III	Agomelatine[2]	Servier
	III	Desvenlafaxine succinate	Wyeth
	III (JP)	Duloxetine hydrochloride[2]	Boehringer Ingelheim/Lilly/Shionogi
	II/III	L-759274	Merck & Co.
	II/III	Saredutant[2]	Sanofi-Aventis
	II	DOV-216303	DOV Pharmaceutical/Merck & Co.
	II	VPI-013 (OPC-14523)	Vela Pharmaceuticals/Otsuka
	I	RG-2133	Repligen
	Discontinued	Gepirone hydrochloride[2]	Organon
Depression, major (psychotic)	III	Mifepristone[1,2]	Corcept Therapeutics
Depression, treatment-unresponsive	II	LAX-101	Amarin/Laxdale
Impulse control disorders	II	Nalmefene[1,2]	BioTie Therapies/ SomaxonPharmaceuticals

Continuation

Treatment of Psychiatric Disorders by Condition

Condition	Phase	Drug	Source
Insomnia	Prereg.	Eszopiclone[2]	Sepracor
	III	Gaboxadol[2]	Lundbeck/Merck & Co.
	III	Indiplon[2]	Neurocrine Biosciences/Pfizer
	III (US, EU)	Ramelteon[2]	Takeda
	II	MDL-100907[2]	Aventis
	II	PD-200390	Pfizer
	II (JP)	Ramelteon[2]	Takeda
	II	Tiagabine hydrochloride	Cephalon
	I	NGD-96-3	Neurogen/Pfizer
Mania (acute)	L-2004	Ziprasidone hydrochloride[1,2]	Pfizer
	L-2003	Quetiapine fumarate[1,2]	AstraZeneca
Narcolepsy	III	Armodafinil	Cephalon
Narcolepsy (excessive daytime sleepiness)	III	Sodium oxybate[1]	Orphan Medical/Celltech Group (UCB Pharma)
Panic disorder	I	BTG-1640	Abiogen/BTG
	I	Itriglumide[2]	Rotta
Phobia, social	L-2003 (EU)	Escitalopram oxalate[1,2]	Lundbeck/Forest
	II	PH-94B	Pherin Pharmaceuticals
Premenstrual syndrome	II	PH-80	Pherin Pharmaceuticals
	Clinical	Drospirenone[2]	Schering AG
Psychiatric disorders	I	C-9054	Merck & Co.
Psychosis	I	Lu-31-130	Lundbeck
	Discontinued	Lu-35-138	Lundbeck
Schizophrenia	III	Asenapine maleate[2]	Organon/Pfizer
	III	Bifeprunox mesilate	Lundbeck/Solvay/Wyeth
	III (JP)	Blonanserin[2]	Almirall Prodesfarma/Dainippon Pharmaceutical
	III	Iloperidone[2]	Titan/Vanda Pharmaceuticals
	III	Paliperidone ER	Johnson & Johnson
	II	ACP-103	Acadia
	II (EU)	Blonanserin[2]	Almirall Prodesfarma/Dainippon Pharmaceutical
	II	Ocaperidone	Neuro3d/Janssen
	II	Org-24448	Organon/Cortex
	II	Osanetant	Sanofi-Aventis
	II	RG-1068	Repligen
	II	SLV-310	Solvay/Wyeth
	II	SLV-313	Solvay/Wyeth
	II	SM-13496	Sumitomo Pharmaceuticals
	II	Talnetant	GlaxoSmithKline
	I	644784	GlaxoSmithKline
	I	742457	GlaxoSmithKline
	I	773812	GlaxoSmithKline
	I	ACP-104	Acadia
	I	ACR-16	Carlsson Research/Merck & Co.
	I	EMR-62218	Merck KGaA
	I	SLV-314	Solvay/Wyeth
	I	SSR-125047	Sanofi-Aventis
	I	SSR-146977	Sanofi-Aventis
	I	SSR-181507	Sanofi-Aventis
	I	YKP-1358	SK Bio-Pharmaceuticals
Sleep apnea	III	Armodafinil	Cephalon
	I/II	SEP-226332	Sepracor

Continuation

Treatment of Psychiatric Disorders by Condition

Condition	Phase	Drug	Source
Sleep disorders	II	Eplivanserin	Sanofi-Aventis
	II	Org-50081	Organon
	II	PD-6735	Phase 2 Discovery
	II	Ramelteon[2]	Takeda
	I	EMR-62218	Merck KGaA
	Discontinued	Melatonin, controlled-release tablets	Paladin/Neurim

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

Treatment of Psychiatric Disorders by Source

Source	Condition	Drug	Phase
Abiogen	Anxiety	BTG-1640	I
	Panic disorder	BTG-1640	I
Acadia	Schizophrenia	ACP-103	II
		ACP-104	I
Acorda	Bipolar disorder	Valrocemide	I/II
Afecta Pharmaceuticals	Attention deficit hyperactivity disorder	AFX-221	II
AGY Therapeutics	Depression	SA-4503 (AGY-94806)	I
Almirall Prodesfarma	Schizophrenia	Blonanserin[2]	III (JP)
		Blonanserin[2]	II (EU)
Amarin	Depression, treatment-unresponsive	LAX-101	II
Asahi Kasei	Anxiety	AP-521	II
AstraZeneca	Anxiety	AZD-8129	II
	Depression	AZD-8129	II
	Mania (acute)	Quetiapine fumarate[1,2]	L-2003
Aventis	Insomnia	MDL-1009072	II
BioTie Therapies	Impulse control disorders	Nalmefene[1,2]	II
Celgene	Attention deficit hyperactivity disorder (adults)	Dexmethylphenidate hydrochloride	III
Celltech Group (UCB Pharma)	Narcolepsy (excessive daytime sleepiness)	Sodium oxybate[1]	III
Cephalon	Anxiety, generalized	Tiagabine hydrochloride[2]	II/III
	Attention deficit hyperactivity disorder	Modafinil[1,2]	III
	Insomnia	Tiagabine hydrochloride[2]	II
	Narcolepsy	Armodafinil	III
	Sleep apnea	Armodafinil	III
Corcept Therapeutics	Depression, major (psychotic)	Mifepristone[1,2]	III
Cortex	Schizophrenia	Org-24448	II
Dainippon Pharmaceutical	Anxiety	Emapunil	I
	Depression	Emapunil	I
	Schizophrenia	Blonanserin[2]	III (JP)
		Blonanserin[2]	II (EU)
DOV Pharmaceutical	Anxiety, generalized	Ocinaplon[2]	II/III
	Depression	DOV-21947	I
	Depression, major	DOV-216303	II
D-Pharm	Bipolar disorder	DP-VPA	I
elbion	Anxiety	ELB-139	I
Enhance Lifesciences	Depression	Lif-247	III
Esteve	Depression	E-6006	I
Forest	Anxiety, generalized	Escitalopram oxalate[1,2]	L-2004 (US)
		Escitalopram oxalate[1,2]	III (EU)
	Phobia, social	Escitalopram oxalate[1,2]	L-2003 (EU)
Genaissance	Depression	Vilazodone hydrochloride	II
GlaxoSmithKline	Anxiety	679769	I
		823296	I
		NBI-34041	I
		Vestipitant mesilate	II
	Attention deficit hyperactivity disorder	NS-2359	II
	Bipolar disorder	Lamotrigine[1,2]	L-2004
	Depression	679769	I
		823296	I
		NBI-34041	I
		Radafaxine hydrochloride	II
		Vestipitant mesilate	II
	Schizophrenia	644784	I
		742457	I
		773812	I
		Talnetant	II
Indevus	Anxiety, generalized	Pagoclone[2]	III
Janssen	Autism	Risperidone[1,2]	Prereg.
	Depression	YKP-10A	II
	Schizophrenia	Ocaperidone	II
Johnson & Johnson	Schizophrenia	Paliperidone ER	III

Continuation

Treatment of Psychiatric Disorders by Source

Source	Condition	Drug	Phase
Laxdale	Depression, treatment-unresponsive	LAX-101	II
Lilly	Agitation (associated with schizophrenia or bipolar I mania)	Olanzapine[1,2]	L-2004
	Attention deficit hyperactivity disorder	Atomoxetine hydrochloride[2]	L-2003
	Bipolar disorder	Olanzapine/fluoxetine hydrochloride	L-2004
	Depression, major	Duloxetine hydrochloride[2]	L-2004 (US)
		Duloxetine hydrochloride[2]	Prereg. (other markets)
		Duloxetine hydrochloride[2]	III (JP)
Lundbeck	Anxiety, generalized	Escitalopram oxalate[1,2]	L-2004 (US)
		Escitalopram oxalate[1,2]	III (EU)
	Depression	Lu-AA-21004	I
	Insomnia	Gaboxadol[2]	III
	Phobia, social	Escitalopram oxalate[1,2]	L-2003 (EU)
	Psychosis	Lu-31-130	I
		Lu-35-138	Discontinued
	Schizophrenia	Bifeprunox mesilate	III
MediciNova	Anxiety, generalized	Osemozotan hydrochloride[2]	II
Merck & Co.	Depression	DOV-21947	I
	Depression, major	DOV-216303	II
		L-759274	II/III
	Insomnia	Gaboxadol[2]	III
	Psychiatric disorders	C-9054	I
	Schizophrenia	ACR-16	I
Merck KGaA	Depression	Vilazodone hydrochloride	II
	Schizophrenia	EMR-62218	I
	Sleep disorders	EMR-62218	I
Mitsubishi Pharma	Anxiety, generalized	Osemozotan hydrochloride[2]	II
M's Science	Depression	SA-4503 (AGY-94806)	I
Neurim	Sleep disorders	Melatonin, controlled-release tablets	Discontinued
Neuro3d	Depression	ND-1251	I
	Schizophrenia	Ocaperidone	II
Neurocrine Biosciences	Anxiety	NBI-34041	I
	Depression	NBI-34041	I
	Insomnia	Indiplon[2]	III
Neurogen	Insomnia	NGD-96-3	I
NeuroSearch	Attention deficit hyperactivity disorder	NS-2359	II
Novartis	Anxiety	AAG-561	I
		Emapunil	I
		XBD-173	I
	Attention deficit hyperactivity disorder (adults)	Dexmethylphenidate hydrochloride	III
	Bipolar disorder	Licarbazepine	II
	Depression	AAG-561	I
		AEP-924	I
		Emapunil	I
Noven	Attention deficit hyperactivity disorder	Methylphenidate hydrochloride (patch)	Prereg.
NPS Pharmaceuticals	Depression	Delucemine hydrochloride	I
Organon	Bipolar disorder	Asenapine maleate[2]	III
	Depression	Org-34517	II
	Depression, major	Gepirone hydrochloride[2]	Discontinued
	Sleep disorders	Org-50081	II
	Schizophrenia	Asenapine maleate[2]	III
		Org-24448	II
Orphan Medical	Narcolepsy (excessive daytime sleepiness)	Sodium oxybate[1]	III
Otsuka	Bipolar disorder	Aripiprazole[1,2]	R-2004
	Depression, major	VPI-013 (OPC-14523)	II
Paladin	Sleep disorders	Melatonin, controlled-release tablets	Discontinued
Pfizer	Anxiety, generalized	Pregabalin[1,2]	Prereg.
	Bipolar disorder	Asenapine maleate[2]	III
	Insomnia	Indiplon[2]	III

Continuation

Treatment of Psychiatric Disorders by Source

Source	Condition	Drug	Phase
Pfizer		NGD-96-3	I
		PD-200390	II
	Mania (acute)	Ziprasidone hydrochloride[1,2]	L-2004
	Schizophrenia	Asenapine maleate[2]	III
Phase 2 Discovery	Sleep disorders	PD-6735	II
Pherin Pharmaceuticals	Phobia, social	PH-94B	II
	Premenstrual syndrome	PH-80	II
Predix Pharmaceuticals	Anxiety, generalized	PRX-00023	
	Attention deficit hyperactivity disorder	PRX-00023	
	Depression	PRX-00023	I/II
Repligen	Autism	RG-1068	III
	Bipolar disorder	RG-2133	I/II
	Depression, major	RG-2133	I
	Schizophrenia	RG-1068	II
Roche	Anxiety	R-1204	I
		R-673	II
	Depression	R-1204	I
		R-673	II
Rotta	Anxiety	Itriglumide[2]	I
	Panic disorder	Itriglumide[2]	I
Sanofi-Aventis	Anxiety	SL-65.1498	II
		SSR-149415	I
	Depression	SR-58611	III
		SSR-146977	I
		SSR-149415	I
	Depression, major	Saredutant(2)	II/III
	Schizophrenia	Osanetant	II
		SSR-125047	I
		SSR-146977	I
		SSR-181507	I
	Sleep disorders	Eplivanserin	II
Schering AG	Premenstrual syndrome	Drospirenone[2]	Clinical
Sepracor	Anxiety	SEP-174559	I/II
	Insomnia	Eszopiclone[2]	Prereg.
	Sleep apnea	SEP-226332	I/II
Servier	Depression, major	Agomelatine[2]	III
Shionogi	Depression, major	Duloxetine hydrochloride[2]	L-2004 (US)
		Duloxetine hydrochloride[2]	Prereg. (other markets)
		Duloxetine hydrochloride[2]	III (JP)
Shire Pharmaceuticals	Attention deficit hyperactivity disorder	Methylphenidate hydrochloride (patch)	Prereg.
		SPD-465	II/III
		SPD-473 (BTS-74398)	Discontinued
		SPD-503	III
	Attention deficit hyperactivity disorder (adults)	SLI-381	L-2004
	Bipolar disorder	SPD-417	Prereg,
SK Bio-Pharmaceuticals	Depression	YKP-10A	II
	Schizophrenia	YKP-1358	I
Solvay	Schizophrenia	Bifeprunox mesilate	III
		SLV-310	II
		SLV-314	I
		SLV-313	II
Somaxon Pharmaceuticals	Impulse control disorders	Nalmefene[1,2]	II
Somerset Pharmaceuticals	Depression, major	Transdermal selegiline	Prereg.
Sumitomo Pharmaceuticals	Schizophrenia	SM-13496	II
Takeda	Insomnia	Ramelteon[2]	III (US, EU)
		Ramelteon[2]	II (JP)
	Sleep disorders	Ramelteon[2]	II

Continuation

Treatment of Psychiatric Disorders by Source

Source	Condition	Drug	Phase
Targacept	Attention deficit hyperactivity disorder	TC-5231	II
Teva	Bipolar disorder	Valrocemide	I/II
Titan	Schizophrenia	Iloperidone[2]	III
Vanda Pharmaceuticals	Schizophrenia	Iloperidone[2]	III
Vela Pharmaceuticals	Depression, major	VPI-013 (OPC-14523)	II
Wyeth	Depression, major	Desvenlafaxine succinate	III
	Schizophrenia	Bifeprunox mesilate	III
		SLV-310	II
		SLV-313	II
		SLV-314	I

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

Treatment of Psychiatrc Disorders

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644784/742457/773812

GlaxoSmithKline has three compounds in phase I clinical development for the treatment of schizophrenia. 644784 is a cyclooxygenase type 2 (COX-2) inhibitor which is also being tested for acute and chronic pain conditions including neuropathic pain; 742457 is a 5-HT_6 receptor antagonist which is also in early clinical evaluation for Alzheimer's disease; and 773812 is a mixed 5-HT/dopamine antagonist.

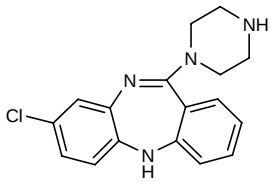
679769/823296

Early clinical evaluation is being conducted at GlaxoSmithKline with the NK_1 receptor antagonists 679769 (GW-679769) and 823296, compounds with potential in depression and anxiety.

AAG-561

Novartis is conducting phase I clinical trials with AAG-561, a CRF_1 receptor antagonist, as a potential new therapy for anxiety and depression.

ACP-103/ACP-104



ACP-104

ACP-103, a 5-HT_{2A} receptor inverse agonist, was discovered at Acadia and is being developed as an adjunctive therapy for schizophrenia and for treatment-induced dysfunction in Parkinson's disease. When combined with available antipsychotic agents, ACP-103 may reduce the side effects associated with these drugs, as well as expand their range of efficacy. Recently reported phase II clinical results demonstrated that ACP-103 reduced both the motor disturbances and hyperprolactinemia caused by haloperidol in healthy volunteers. A multicenter phase II trial is also under way exploring ACP-103 for treatment-induced psychosis in Parkinson's disease (1, 2).

Acadia is also developing another small-molecule drug candidate for schizophrenia. ACP-104 (*N*-desmethylclozapine, norclozapine), the major metabolite of clozapine, is a potent muscarinic M_1 receptor agonist in phase I development, with phase II trials expected to begin shortly. The compound appears to have additional beneficial cognitive effects.

1. *Favorable results for ACP-103 for use in Parkinson's patients*. DailyDrugNews.com (Daily Essentials) July 2, 2004.

2. *ACP-103 reduces side effects of haloperidol*. DailyDrugNews.com (Daily Essentials) Sept 17, 2004.

ACR-16

The dopaminergic stabilizer ACR-16 is a candidate for the treatment of schizophrenia and other neuropsychiatric disorders, including Parkinson's disease and Huntington's disease. Carlsson Research has completed phase Ib clinical trials indicating a good safety and pharmacokinetic profile, as well as efficacy in the treatment of these disorders, with beneficial effects on psychotic symptoms, cognitive, emotional and motor functions, and sleep. Preclinical studies indicate its utility in treating the full range of symptoms of schizophrenia, including both positive and negative symptoms and impaired cognitive and

social functions, paired with a low likelihood for extrapyramidal symptoms. The company entered into a licensing agreement with Merck & Co. in 2003 granting the latter rights to develop and market ACR-16, as well as back-up and follow-up compounds.

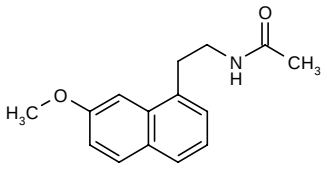
AEP-924

A potential new antidepressant, AEP-924, is undergoing phase I trials at Novartis.

AFX-221

Afecta Pharmaceuticals' AFX-221 (NGI-221) is a new nonstimulant treatment for attention deficit hyperactivity disorder (ADHD) and Tourette syndrome. The compound targets multiple neurotransmitters and is designed for once-daily administration at low doses. It was last reported to be in phase II evaluation for ADHD.

Agomelatine



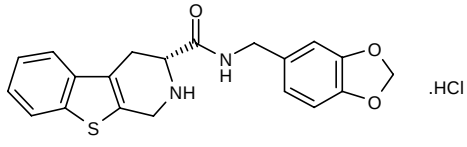
The first and only dual melatonin agonist/5-HT_{2C} receptor antagonist, Servier's agomelatine (S-20098, Valdoxan) apparently continues in late-stage clinical evaluation for major depressive disorders.

Original monograph – Drugs Fut 2003, 28(1): 7.

Additional References

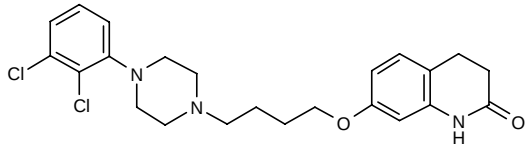
Montgomery, S.A., Kennedy, S.H., Burrows, G.D., Lejoyeux, M., Hindmarch, I. *Absence of discontinuation symptoms with agomelatine and occurrence of discontinuation symptoms with paroxetine: A randomized, double-blind, placebo-controlled discontinuation study*. Int Clin Psychopharmacol 2004, 19(5): 271.

AP-521



Phase II clinical evaluation of AP-521, a benzothienopyridine derivative that binds to 5-HT_{1A} receptors, for anxiety continues at Asahi Kasei.

Aripiprazole



Aripiprazole (Abilify®) has been available from Otsuka and Bristol-Myers Squibb for several years in the U.S. for the treatment of schizophrenia and was cleared for marketing in the E.U. for this indication earlier this year (1, 2). The product was just recently approved by the U.S. FDA for use in the treatment of acute bipolar mania, including manic and mixed episodes associated with bipolar disorder (3).

In a multicenter, double-blind, randomized, placebo-controlled study, 262 patients with acute mania associated with bipolar disorder were given aripiprazole (30 mg, optionally reduced to 15 mg) for a period of 3 weeks. Compared to placebo, the drug was well tolerated and effective, as reflected by improved total Young Mania Rating Scale scores (4).

Patients with bipolar I disorder undergoing an acute manic or mixed episode (n=272) received aripiprazole (30 mg, optionally reduced to 15 mg) for 3 weeks in a multicenter, double-blind, placebo-controlled phase III study. The drug again proved effective and safe (5).

A 26-week, double-blind, randomized, placebo-controlled study evaluated the efficacy of aripiprazole (30 mg/day, optionally reduced to 15 mg/day) in preventing relapse in 161 bipolar I patients experiencing acute mania following a stabilization period with open-label drug over 6-18 weeks. Aripiprazole was more effective and induced a significantly lower rate of and delayed time to relapse as compared to placebo (6).

1. *Positive opinion in Europe for Abilify*. DailyDrugNews.com (Daily Essentials) March 2, 2004.

2. *European approval for Abilify for schizophrenia*. DailyDrugNews.com (Daily Essentials) June 9, 2004.

3. *FDA approves Abilify® (aripiprazole) for treatment of acute bipolar mania, including manic and mixed episodes.* Bristol-Myers Squibb Press Release 2004, Oct 1.

4. Van Peborgh, P. et al. *Aripiprazole versus placebo in the treatment of acute mania*. 12th Assoc Eur Psychiatr Congr (April 14-18, Geneva) 2004, Abst.

5. Scott, K. et al. *Aripiprazole in acute mania: Results from a second placebo-controlled study*. 12th Assoc Eur Psychiatr Congr (April 14-18, Geneva) 2004, Abst.

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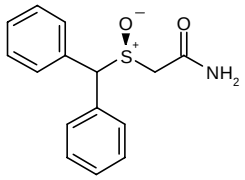
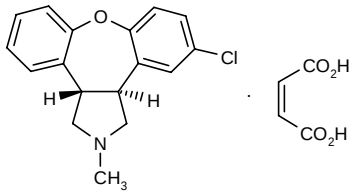
Armodafinil



Cephalon has updated the status of its phase III program for (*R*)-modafinil (armodafinil), a single isomer of the active pharmaceutical ingredient contained in Provigil® (modafinil; see below). The program, initiated in December 2003, is evaluating the compound for the treatment of excessive sleepiness associated with narcolepsy and obstructive sleep apnea/hypopnea syndrome (OSA/HS). The efficacy portion of the phase III program consists of two 12-week, randomized, double-blind, placebo-controlled trials in patients with OSA/HS and one in patients with narcolepsy. The trials are expected to include some 800 patients. The primary outcome measures are the Maintenance of Wakefulness Test (MWT) and the Clinical Global Impression of Change-Clinician (CGI-C). The trials are being conducted concurrently at sites in the U.S., Europe, Canada and Australia. An NDA filing for armodafinil is scheduled for the fourth quarter of 2004. A new study of armodafinil in patients with shift work sleep disorder is also planned for early 2004, with a supplemental NDA for that indication to follow at a later stage (1).

1. *Phase III R-modafinil program progresses towards Q4 NDA filing*. DailyDrugNews.com (Daily Essentials) Jan 15, 2004.

Asenapine Maleate



Asenapine maleate (Org-5222), a serotonin/dopamine antagonist (SDA), is a potential new medication for the treatment of a variety of neurological/psychiatric disorders that is entering phase III trials for schizophrenia and bipolar disorder under a global agreement between Organon and Pfizer. The companies will collaborate on the clinical development and manufacturing of asenapine and copromote the product in the U.S., the E.U., Japan and other markets (1-5).

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2. *Pfizer and Akzo Nobel's Organon collaboration moves forward*. DailyDrugNews.com (Daily Essentials) Jan 12, 2004.

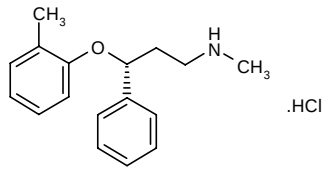
3. *Pfizer reports 2003 year-end R&D highlights*. Pfizer Press Release 2004, Jan 22.

4. *Pfizer reports Q1 R&D highlights*. Pfizer Press Release 2004, April 20.

5. *Pfizer reports Q2 R&D highlights*. Pfizer Press Release 2004, July 21.

Original monograph – Drugs Fut 1993, 18: 1117.

Atomoxetine Hydrochloride



The American Academy of Child and Adolescent Psychiatry (AACAP) has issued guidelines that highlight the importance of accurate diagnosis and appropriate treatment of attention deficit hyperactivity disorder (ADHD). The guidelines include new recommendations for treatment in which Lilly's atomoxetine hydrochloride (Strattera®) is a first-line therapy option, representing the first time the AACAP has listed a nonstimulant as a first-line therapy option for ADHD. Atomoxetine received FDA approval in November 2002 for the treatment of ADHD in children, adolescents and adults. The selective norepinephrine reuptake inhibitor works differently than other approved treatments for the disorder, all of which are stimulants. It is believed to work by blocking or slowing the reabsorption of norepinephrine, keeping more norepinephrine at work in the spaces between neurons in the brain. The drug received its first European approval in the U.K. just recently and became available there in July. It has also been approved in Australia, Mexico, Argentina and other Latin American countries (1, 2). Recent clinical studies with atomoxetine are summarized below.

Pediatric and adolescent patients with ADHD (n=412) were treated with atomoxetine (maximum dose of 1.8 mg/kg/day) for at least 2 years and a meta-analysis of data was undertaken to assess the long-term effects of the drug on growth. Atomoxetine did not induce any significant effect on growth and is not expected to unduly influence final stature status in the majority of patients (3).

The efficacy of atomoxetine (1.2-1.8 mg/kg/day for about 12 weeks) was assessed in a relapse prevention study in 604 pediatric patients with ADHD. Patients with diminished symptoms were randomized in a double-blind manner to continuation therapy with atomoxetine or placebo for a further 9 months. Compared with placebo, atomoxetine was more effective in reducing symptoms and enhancing psychological function (4, 5).

The addition of atomoxetine (40 mg/day) to ongoing antidepressant medication was assessed in a case series including 15 patients with an inadequate response to standard therapy. A positive categorical response was seen in 9 patients, and the additional treatment appeared to reduce symptoms and increase social and occupational functioning (6). The results of this and some of the following studies are depicted in Table I.

Open-label atomoxetine (up to 160 mg/day) was given to 384 adults with ADHD for up to 97 weeks in a study assessing the effects of dose on response. It was found that clinical responses to treatment were more likely to occur in patients taking higher total or higher weight-based doses of atomoxetine (7).

Parents' assessment of personality changes in children with ADHD (n=20) indicated that personality impairments associated with stimulant treatment were significantly greater than those associated with atomoxetine treatment (8).

Analysis of data from 5 clinical trials in patients with ADHD showed that atomoxetine was associated with significant improvement in 674 patients with moderate hyperactive symptoms, 815 with moderate inattentive symptoms, 339 with severe hyperactive symptoms and 444 with severe inattentive symptoms at baseline (9, 10).

Actigraphy, polysomnography, and parent and child diaries indicated that sleep was improved in children with ADHD treated with atomoxetine as compared with methylphenidate. In the randomized, double-blind, crossover trial, children given atomoxetine had a shorter time to sleep onset and less difficulty getting up than those given methylphenidate (11).

Analysis of data from double-blind, placebo-controlled trials in children with ADHD indicated that atomoxetine was well tolerated and effective in patients aged 6-7 years and in those aged 8-16 years, although greater efficacy was seen in the latter group (12).

Long-term treatment of adolescents with ADHD with atomoxetine was evaluated using data pooled from clinical trials including 414 patients treated for at least 1 year. The safety of the treatment was maintained and significant improvement in ADHD Rating Scale scores was sustained from 3 months to 2 years (13).

Responses to atomoxetine were not significantly different in children as compared to adolescents with ADHD in an analysis of data from randomized, double-blind, placebo-controlled trials (n=1,071). Adverse effects were also similar between the age groups (14).

An observational study in 482 pediatric patients with ADHD treated in the community found that therapy with atomoxetine significantly reduced ADHD severity. Improvements were seen in patients with comorbidities or previous stimulant treatment and few treatment discontinuations were observed (15).

Data gathered from 192 children aged 6-7 years with ADHD indicated that long-term treatment with atomoxetine (mean dose of 1.55 mg/kg/day) was well tolerated, with efficacy maintained for 1-2 years (16).

Mental health assessments improved significantly in adult patients with ADHD treated with atomoxetine 80 mg/day (n=172), and these changes were correlated with improvements in ADHD symptoms (17).

In a randomized, double-blind study, 148 children with ADHD and concurrent Tourette syndrome and/or chronic motor tic disorder were treated with atomoxetine 0.5-1.5 mg/kg/day or placebo for up to 18 weeks. In addition to reducing the severity of ADHD symptoms, atomoxetine reduced the severity of tics in these patients and was well tolerated (18-20).

The initiation of atomoxetine treatment at the target dose of 1.2 mg/kg/day b.i.d., without titration, was

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

Indication	Design	Treatments	n	Conclusions	Ref.
Depression		Standard therapy x 8 [min] weeks + Atomoxetine, 40 mg o.d. x 6 wks	15	The addition of atomoxetine to standard antidepressant therapy improved responses in patients with major depressive disorder	6
Attention deficit hyperactivity disorder	Open	Atomoxetine, 60-120 mg o.d. x 34 [mean] wks	384	The severity of the symptoms of attention deficit hyperactivity disorder in adult patients, measured using the Conner's Adult Attention Deficit/ Hyperactivity Disorder Rating Scale - Investigator and the Clinical Global Impression of Severity scale sores, decreased significantly after treatment with atomoxetine daily for an average of 34 weeks. Few patients discontinued the study because of adverse events	7
Attention deficit hyperactivity disorder	Retrospective	Atomoxetine Stimulants	20	Atomoxetine showed less effect on personality than stimulants in children with attention deficit hyperactivity disorder	8
Attention deficit hyperactivity disorder	Pooled/meta-analysis	Atomoxetine Placebo	2272	Atomoxetine improved attention deficit hyperactivity disorder in patients with moderate and severe hyperactive or inattentive symptoms	9, 10
Attention deficit hyperactivity disorder	Randomized Double-blind Crossover	Atomoxetine Methylphenidate		Sleep was improved in children with attention deficit hyperactivity disorder treated with atomoxetine as compared with methylphenidate	11
Attention deficit hyperactivity disorder	Pooled/meta-analysis	Atomoxetine (n=347) Placebo (n=274)	621	Atomoxetine was well tolerated and effective in attention deficit hyperactivity disorder patients aged 6-7 years and in those aged 8-16 years	12
Attention deficit hyperactivity disorder	Pooled/meta-analysis	Atomoxetine, 1.5 [mean] mg/kg/d x up to 2 y	414	Atomoxetine was safe and effective over the long term in patients with attention deficit hyperactivity disorder	13
Attention deficit hyperactivity disorder	Pooled/meta-analysis	Atomoxetine	1071	Responses to atomoxetine were similar in children and adolescents with attention deficit hyperactivity disorder	14
Attention deficit hyperactivity disorder	Open	Atomoxetine	482	Atomoxetine was well tolerated and effective in children and adolescents with attention deficit hyperactivity disorder	15
Attention deficit hyperactivity disorder	Pooled/meta-analysis	Atomoxetine, 1.55 [mean] mg/d x 1-2 y	192	Atomoxetine efficacy and tolerability were maintained over the long term in children with attention deficit hyperactivity disorder	16
Attention deficit hyperactivity disorder	Open	Atomoxetine, 80 mg/d x 6 wks	172	Atomoxetine improved the mental health of adults with attention deficit hyperactivity disorder	17

Continuation

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

Indication	Design	Treatments	n	Conclusions	Ref.
Attention deficit hyperactivity disorder, Tic, Tourette syndrome	Randomized Double-blind	Atomoxetine, 0.5-1.5 mg/kg/d x up to 18 wks (n=76) Placebo (n=72)	148	Atomoxetine reduced the severity of tics in patients with attention deficit hyperactivity disorder and comorbid tic disorders	18, 19
Attention deficit hyperactivity disorder	Open	Atomoxetine, 1.2 mg/kg/d b.i.d.	25	Side effects were acceptable in patients with attention deficit hyperactivity disorder given atomoxetine without titration	21

assessed in a case series of 25 adolescents with ADHD hospitalized for aggressive behavior. Side effects were more severe without titration but were acceptable in these patients, and no long-term effects of this dosing regimen were noted (21).

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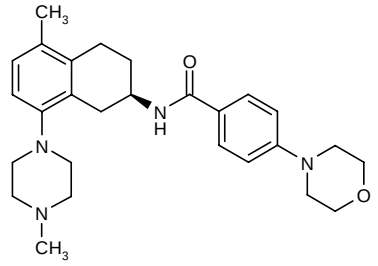
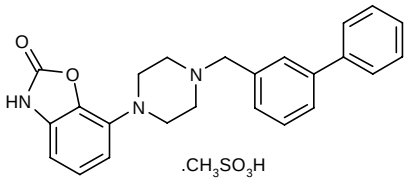
AZD-8129



AZD-8129 (AR-A2, AR-A000002) is a new 5-HT_{1B} receptor antagonist designed by AstraZeneca. Phase II trials are in progress evaluating its potential in the treatment of both anxiety and depression.

Bifeprunox Mesilate



Bifeprunox mesilate (DU-127090), a partial dopamine agonist developed jointly by Lundbeck and Solvay, is a putative new antipsychotic compound aimed at the treatment of both positive and negative symptoms of schizophrenia. Lundbeck has marketing rights to bifeprunox in Europe and a number of other markets, while Lundbeck and Solvay will jointly market the product in Brazil and Argentina. Solvay and Wyeth recently entered a development and marketing agreement in the U.S., Mexico, Japan and Canada. Phase II data have shown efficacy in patients with schizophrenia. It is expected to provide an improved safety profile with the advantages of no weight gain, increase in prolactin, glucose dysregulation or Q-T_c prolongation. In addition, it is expected to have a favorable lipid profile and extrapyramidal symptoms comparable to placebo. Phase III trials commenced in 2003 for the treatment of schizophrenia. Submissions are planned in a number of markets simultaneously in 2006, with expected market launch in 2007. Bifeprunox may also have potential in other disorders such as bipolar disorder (1-6).

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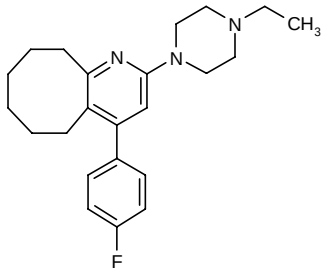
6. *Lundbeck reports Q1 R&D highlights*. Lundbeck Web Site 2004, May 10.

Blonanserin



Blonanserin (AD-5423, Lonasen®) is being codeveloped by Dainippon (Japan, China, Taiwan and South Korea) and Almirall Prodesfarma (worldwide) for the treatment of schizophrenia. A chemically novel antipsychotic agent, blonanserin acts as a dopamine D2/5-HT_2 receptor antagonist and is currently in phase III trials in Japan and phase II trials in Europe and the U.S.

Original monograph – Drugs Fut 1992, 17(1): 9.

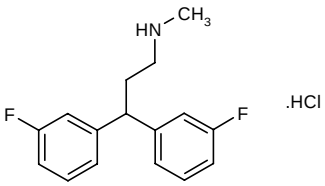
BTG-1640

The first in a new class of nonsedating, nonaddictive drugs for anxiety and depression, BTG-1640 is being developed at Abiogen under license from BTG, and recently entered phase I clinical trials for the treatment of anxiety states such as panic disorder.

C-9054

Merck & Co. has a compound designated C-9054 in early clinical development for psychiatric diseases.

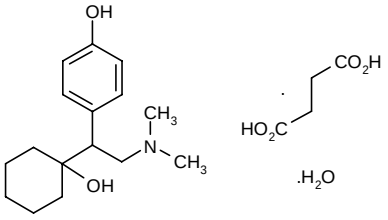
Delucemine Hydrochloride



Delucemine hydrochloride (NPS-1506) is a novel agent from NPS Pharmaceuticals that targets and blocks open NMDA receptor-operated calcium channels.

Originally developed as a neuroprotectant for the treatment of stroke, the compound may also be effective in treating acute depression and is now undergoing early clinical evaluation.

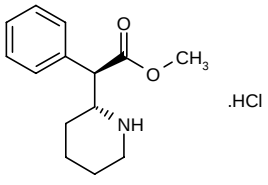
Desvenlafaxine Succinate



In a recent review of its R&D pipeline, Wyeth highlighted 11 new drug programs in late-stage clinical development that it anticipates filing with regulatory authorities from 2004 through 2007. Among late-stage R&D projects in early phase III development or beyond proof-of-concept and targeted for submission in 2006 is desvenlafaxine succinate (DVS-233), a metabolite of venlafaxine now in phase III for the treatment of major depressive disorder (MDD). Desvenlafaxine has a dual serotonin/norepinephrine reuptake inhibitor (SNRI) mechanism of action and is expected to achieve a different balance of serotonin and norepinephrine reuptake inhibition compared to other antidepressants. Submissions for the treatment of MDD are expected in early 2006. The drug is also in phase III evaluation as the first potential nonhormonal treatment for the relief of vasomotor symptoms associated with menopause (VMS). Desvenlafaxine is expected to provide significant relief of hot flushes by a direct thermoregulatory mechanism. Filing for the treatment of VMS is expected in mid-2006 (1).

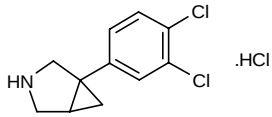
1. *Wyeth reviews R&D pipeline*. DailyDrugNews.com (Daily Essentials) June 7, 2004.

Dexmethylphenidate Hydrochloride



A long-acting, once-daily version of dexmethylphenidate hydrochloride (Focalin® LA) is in late-stage development at Novartis, under license from Celgene, for use in adults, in addition to children and adolescents, with ADHD. Dexmethylphenidate is the active D-isomer of methylphenidate (Ritalin®) and was introduced in 2001 for the treatment of ADHD in children and adolescents.

DOV-21947/DOV-216303



DOV-21947

Merck & Co. and DOV Pharmaceutical have entered into an agreement for the development and commercialization of DOV's novel triple uptake inhibitors being developed for depression and related psychiatric disorders. Merck has licensed exclusive worldwide rights to DOV-21947, which is in phase I, for all therapeutic indications. Merck has also licensed exclusive worldwide rights to DOV-216303, currently in phase II trials in patients with major depressive disorder, for the treatment of depression, anxiety and addiction, with DOV retaining rights to the compound for other indications. In preclinical studies to date, DOV's compounds have proven to be potent and highly efficacious compared to commonly used antidepressants. Merck will assume responsibility for the full development, manufacturing and commercialization of DOV-21947 and pay DOV royalties. DOV has an option to copromote in the U.S. to psychiatrists and other specialists in depression (1).

The safety and pharmacokinetics of DOV-216303 were evaluated in 2 double-blind, randomized clinical trials in which single doses (5, 10, 25, 50, 100 and 150 mg) and multiple doses (50, 75 and 100 mg/day for 10 days) of DOV-216303 or placebo were administered to healthy male volunteers aged 18-35 years. The serum levels of DOV-216303 increased with dose and significantly inhibited the reuptake of norepinephrine, serotonin and dopamine at doses of 10 mg and above. Both single and multiple doses of DOV-216303 were well tolerated and associated with a low incidence of adverse events (2) (see Table II).

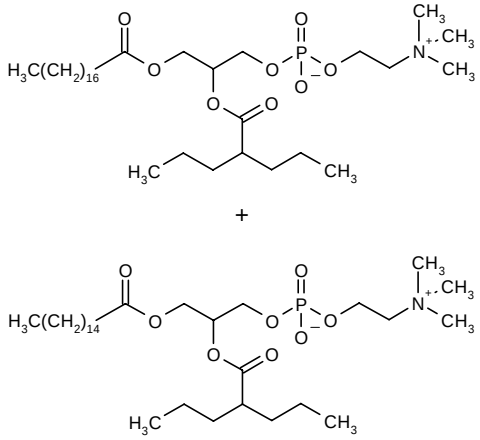
1. *Merck & Co. and DOV enter agreement for triple uptake inhibitor development*. DailyDrugNews.com (Daily Essentials) Aug 11, 2004.

2. Lippa, A., Beer, B., Stark, J., Krieter, P., Czobor, P., Skolnick, P. *DOV 216303, a triple reuptake inhibitor: First in human studies*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR393.

Table II: Clinical studies of DOV-216303 (from Prous Science Integrity®).

Indication	Design	Treatments	Conclusions	Ref.
Healthy volunteers	Randomized Double-blind	DOV-216303, 5 mg DOV-216303, 10 mg DOV-216303, 25 mg DOV-216303, 50 mg DOV-216303, 75 mg DOV-216303, 100 mg DOV-216303, 150 mg Placebo	Both single and multiple doses of DOV-216303 were well tolerated in healthy male volunteers	2

DP-VPA

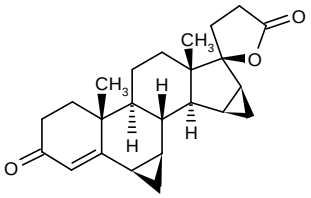


D-Pharm has completed a year-long restructuring process as part of its strategic refocusing on the development of its proprietary clinical-stage products, specifically the phase II products DP-b99 and DP-VPA. DP-VPA, a mixture of two phospholipid derivatives of valproic acid, is D-Pharm's proprietary prodrug of sodium valproate (VPA) designed using the company's Regulated Activation of Produgs (D-RAP™) technology that allows precise control of drug action at the site of pathology. DP-VPA is in development for the first-line treatment of epilepsy, bipolar disorder and migraine prophylaxis. In the first quarter of 2003, DP-VPA completed a phase II efficacy study in 67 patients with resistant complex partial epilepsy, significantly reducing the number of seizures relative to placebo. Follow-up analysis revealed long-lasting effects of the drug. The data also suggest that the no-drug washout period was insufficient to eliminate the drug effect in the first group of patients. This suggests a once-a-day treatment modality. D-Pharm reacquired full rights to DP-VPA from Shire earlier this year (1, 2).

1. *Restructuring at D-Pharm completed*. DailyDrugNews.com (Daily Essentials) Jan 9, 2004.

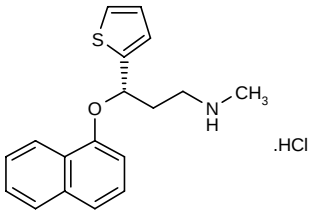
2. *D-Pharm reacquires rights to epilepsy drug DP-VPA*. DailyDrugNews.com (Daily Essentials) Jan 22, 2004.

Drospirenone



Drospirenone, a progestogen used in Schering AG's oral contraceptive Yasmin®, was reported by the company to be undergoing clinical evaluation for the treatment of premenstrual dysphoric disorder, a severe form of premenstrual syndrome, in late 2003.

Duloxetine Hydrochloride



Lilly launched Cymbalta® (duloxetine hydrochloride, LY-248686), a balanced and potent selective serotonin and norepinephrine reuptake inhibitor (SSNRI), in the U.S. following its approval on August 3, 2004 for the treatment of major depression. The drug is being reviewed worldwide for major depressive disorder. Duloxetine helps treat both the emotional and physical symptoms of depression. More recently, duloxetine was approved by the FDA as the first and only therapy for the management of diabetic peripheral neuropathic pain. Although it does not change the underlying nerve damage caused by diabetic peripheral neuropathy, it does help relieve the pain often associated with the disorder by increasing levels of serotonin and norepinephrine, scientists believe. Furthermore, duloxetine (Yentreve®/Ariclaim®) has been approved in the E.U. for the indication of moderate to severe stress urinary incontinence in women. The drug increases neurotransmitter concentration, which is believed to

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

Indication	Design	Treatments	n	Conclusions	Ref.
Depression	Pooled/meta-analysis	Duloxetine, 20-60 mg b.i.d. x 8 wks (n=736) Duloxetine, 40 mg b.i.d. x 26 wks Duloxetine, 60 mg b.i.d. x 26 wks Paroxetine, 20 mg o.d. x 8 wks (n=499) Placebo (n=129)	1466	Duloxetine had fewer effects on sexual function than paroxetine in patients with depression	8
Depression	Pooled/meta-analysis	Duloxetine Placebo	1139	Duloxetine demonstrated efficacy in the acute treatment of major depressive disorder	11
Depression	Randomized Double-blind Pooled/meta-analysis	Duloxetine, 40-120 mg o.d. x 8 wks (n=888) Paroxetine, 20 mg o.d. x 8 wks (n=362) Fluoxetine, 20 mg o.d. x 8 wks (n=70) Placebo (n=513)	1833	Duloxetine was more effective than paroxetine, fluoxetine or placebo in improving both major depression and associated anxiety symptoms	12-14
Depression	Randomized Double-blind Pooled/meta-analysis	Duloxetine, 40-120 mg o.d. x 9 [max.] wks (n=1138) Placebo (n=775)	1913	Duloxetine was effective in improving depressive symptoms in patients with major depressive disorder with or without melancholic features	16
Depression	Open	Duloxetine, 60 mg o.d. x 1 wk → 90 mg o.d. x 1 wk → 120 mg o.d. x 4 wks	128	No additional adverse events were associated when the daily dose of duloxetine was increased from 60 to 120 mg in patients with major depressive disorder	17, 18
Depression	Randomized Double-blind Pooled/meta-analysis	Duloxetine, 60 mg o.d. x 9 wks (n=244) Placebo (n=251)	495	Compared with placebo, duloxetine significantly improved the Hamilton Rating Scale for Depression scores for depressed mood, guilt, suicidality, work/activities, anxiety and the symptoms of physical pain in patients with major depressive disorder	19
Depression	Randomized Double-blind Pooled/meta-analysis	Duloxetine, 60 mg o.d. x 9 wks Duloxetine, 20 mg b.i.d. x 9 wks Duloxetine, 40 mg b.i.d. x 9 wks Duloxetine, 60 mg b.i.d. x 9 wks Placebo	590	No significant differences were found in the efficacy and safety of duloxetine in the treatment of Hispanic, African and Caucasian patients with major depression	20
Depression	Open Multicenter	Duloxetine, 40-60 mg b.i.d. x up to 52 wks	520	Long-term administration of duloxetine was safe and effective in patients with major depressive disorder	21

increase the tone and contraction of the urethral sphincter, helping to prevent accidental urine leakage due to physical activities such as sneezing, coughing, laughing, lifting or exercising. Duloxetine will be jointly copromoted in the E.U. by Lilly and Boehringer Ingelheim under the brand name Yentreve®, except for Greece, Italy, and Spain, where it will be marketed under the brand name Yentreve® by Lilly and as Ariclaim® by Boehringer Ingelheim. The two companies entered into a long-term agreement in November 2002 to jointly develop and commercialize the drug in most countries worldwide with few exceptions; in the U.S., the collaboration excludes neuroscience indications (1-7). Licensee Shionogi is conducting phase III trials in Japan.

A comparative analytical study was undertaken using data from 2,032 patients with major depressive disorder treated with duloxetine (20-60 mg b.i.d.), paroxetine (20 mg once daily) or placebo over 8 weeks in acute-phase studies (n=1,466), and duloxetine (40 or 60 mg b.i.d.), paroxetine (20 mg once daily) or placebo given to responders over an additional 26 weeks in long-term studies (n=566). Results revealed that duloxetine across the 40-120 mg/day dose range significantly reduced acute-phase sexual dysfunction and improved overall sexual function as compared to paroxetine (8, 9) (see Table III). The acute safety of duloxetine was compared to that of paroxetine. Discontinuation rates were similar between both groups. Duloxetine was safe, well tolerated and showed comparable safety and tolerability to low-dose paroxetine over a wide dose range (10).

Duloxetine was superior to placebo in the acute treatment of major depressive disorder in a meta-analysis of 8 trials in a total of 1,139 patients. The difference in treatment results was seen in all performance measures

(11). The results from this and a number of the following clinical studies are summarized in Table III.

Duloxetine (40-120 mg/day) has been compared with serotonin reuptake inhibitors (SSRIs) in 6 randomized, double-blind, placebo-controlled trials in patients with depression, and the results of these trials have been pooled and analyzed. Overall, the rates of remission were 43%, 38% and 28% for duloxetine, SSRIs (paroxetine 20 mg/day or fluoxetine 20 mg/day) and placebo, respectively. Furthermore, the remission rate with duloxetine was significantly higher than that with SSRIs in patients with baseline 17-item Hamilton Rating Scale for Depression scores of 19 or more (12-15).

The influence of melancholic features on the efficacy of duloxetine as an antidepressant was evaluated using pooled data from 8 double-blind, placebo-controlled clinical trials. Patients with major depressive disorder were randomized to receive placebo or duloxetine (40-120 mg once daily) for up to 9 weeks. No significant differences between melancholic and nonmelancholic patients were found in the improvements induced by duloxetine in the HAMD-17 score, the Clinical Global Impression-Severity (CGI-S) score and the Patient Global Impression-Improvement (PGI-I) score (16).

The safety profile of duloxetine was evaluated in a clinical trial that successively treated 128 major depressive disorder patients with placebo for 1 week, followed by increasing doses of duloxetine (60 mg once daily for 1 week, 90 mg once daily for 1 week, and then 120 mg once daily for 4 weeks). The percentage of patients who withdrew from the study due to adverse events was similar to that found in previous controlled clinical trials. The most common adverse events were nausea, headache, dry mouth, dizziness and loss of appetite. The results suggested that dose escalation did not increase the incidence of adverse events associated with duloxetine therapy. After 4 weeks at the highest dose, significant improvements in depression measures were seen (17, 18).

Early response to duloxetine was evaluated using pooled data from 2 clinical trials that randomized major depressive disorder patients to receive placebo or duloxetine (60 mg/day) for 11 weeks. After 1 week, patients treated with duloxetine showed significant improvements in the Hamilton Depression (HAMD-17) scores for depressed mood, guilt, suicidality, work/activities and anxiety compared to placebo-treated patients. These improvements were maintained throughout the study (19).

Pooled data from 7 double-blind clinical trials showed no significant differences in the efficacy and safety of duloxetine (60 mg once daily, and 20, 40 and 60 mg twice daily) in major depressive disorder patients of Hispanic, African or Caucasian descent (20).

Long-term administration of duloxetine in patients with major depressive disorder was evaluated in a 1-year, open, multicenter trial in which 520 patients were treated for at least 360 days. Measures of disease severity and disability were significantly improved by doses of 80-120 mg/day and the drug was safe and well tolerated (21).

1. *Positive opinion handed down in Europe for duloxetine for SUI*. DailyDrugNews.com (Daily Essentials) March 30, 2004.

2. *Lilly reports 2003 year-end R&D highlights*. Eli Lilly and Co. Press Release 2004, Jan 29.

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

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

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

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

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

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9. Delgado, P.L. et al. *Comparison of sexual functioning in patients receiving duloxetine or paroxetine: Acute and long-term data*. 12th Assoc Eur Psychiatr Congr (April 14-18, Geneva) 2004, Abst.

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13. Swindle, R.W., Mallinckrodt, C.H., Rosenbaum, J., Lu, Y., Watkin, J.G., Detke, M.J. *Efficacy of duloxetine treatment: Analysis of pooled data from six placebo- and SSRI-controlled clinical trials*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR722.

14. Thase, M.E., Lu, Y., Joliat, M., Detke, M.J. *Remission in placebo-controlled trials of duloxetine with an SSRI comparator*. 59th Annu Meet Soc Biol Psychiatry (April 29-May 1, New York) 2004, Abst 127.

15. Thase, M.E. et al. *Remission in placebo-controlled trials of duloxetine with an SSRI comparator*. 12th Assoc Eur Psychiatr Congr (April 14-18, Geneva) 2004, Abst.

16. Mallinckrodt, C.H., Watkin, J.G., Liu, C., Wohlreich, M.M., Raskin, J. *Duloxetine in the treatment of MDD: A comparison of efficacy in patients with and without melancholic features*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR719.

17. Wohlreich, M.M., Mallinckrodt, C.H., Watkin, J.G., Prakash, A. *Duloxetine treatment of MDD: Safety and efficacy*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR712.

18. Wohlreich, M., Mallinckrodt, C., Watkin, J., Prakash, A. *Duloxetine for the treatment of major depressive disorder: Safety and efficacy associated with rapid dose escalation (60-120 mg QD)*. 59th Annu Meet Soc Biol Psychiatry (April 29-May 1, New York) 2004, Abst 659.

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20. Plewes, J.M. II., Bailey, R.K., Mallinckrodt, C.H., Watkin, J.G., Wohlreich, M.M., Lewis-Fernandez, R. *Duloxetine treatment of MDD in Hispanic and African-American patients*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR820.

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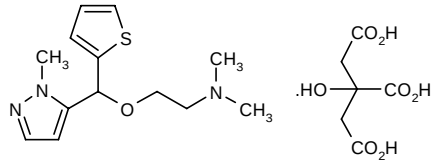
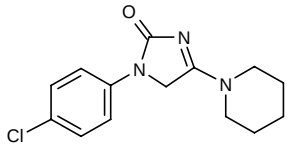
E-6006



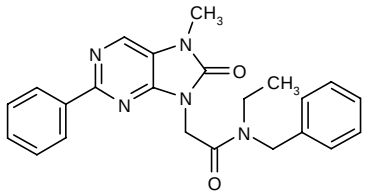
Esteve's E-6006 is a modulator of substance P release in the CNS and is in phase I clinical evaluation as an antidepressant. It has demonstrated a good tolerance and safety profile in healthy volunteers and reportedly lacks addictive potential.

ELB-139



ELB-139 (elbion) is a low-affinity α3-selective partial benzodiazepine agonist with potential as an anxiolytic, exhibiting many of the favorable effects of benzodiazepines without their potential for the development of tolerance or low-dose dependency. Phase I trials are under way.

Emapunil

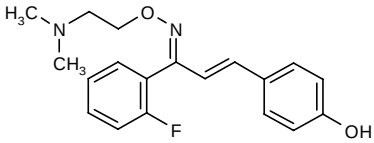


The potential anxiolytic and antidepressant emapunil (AC-5216) is a mitochondrial benzodiazepine receptor ligand discovered at Dainippon Pharmaceutical and licensed worldwide (except for Japan, South Korea, Taiwan and China) to Novartis. It is in phase I trials.

EMR-62218

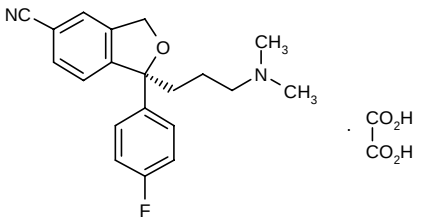
Phase I clinical trials are under way at Merck KGaA evaluating EMR-62218, a 5-HT_{2A} antagonist, in the treatment of schizophrenia and sleep disorders.

Eplivanserin



A phase IIb compound in the Sanofi-Aventis pipeline, eplivanserin (SR-46349) is a 5-HT_2 receptor antagonist being evaluated for its potential in sleep disorders.

Escitalopram Oxalate



Escitalopram oxalate, a selective serotonin reuptake inhibitor (SSRI) and the active (*S*)-isomer of the antidepressant citalopram, was first introduced by Lundbeck in Europe in 2002 under the trade name Cipralex® for the treatment of major depressive disorder and panic disorder. Late last year the product was also approved in several European countries for social anxiety disorder (SAD), and it is now available in 4 of the 5 major European markets. A filing is expected this year in Europe for its use in generalized anxiety disorder (GAD). Licensee Forest received FDA approval for the drug, known as Lexapro™, in August 2002 for the treatment of major depressive disorder in adults and in December 2003 for the treatment of GAD in adults. In the U.S., supplemental NDAs are under review at the FDA for panic disorder and SAD. Forest recently submitted a complete response to issues raised at the agency in its review of the sNDA for use in panic disorder. The company also plans to seek approval of escitalopram for use in pediatric patients with major depressive disorder (1-5). Escitalopram (MDL-55) is licensed to Mochida for development in Japan, where phase I trials have been completed in depression.

Results of a recently completed multicenter, double-blind, randomized, placebo-controlled, flexible-dose study of escitalopram in children and adolescents show that patients receiving the drug did not demonstrate a statistically significant difference compared to placebo in the primary efficacy measure, the mean change from baseline in the Children's Depression Rating Scale-Revised (CDRS-R) score. In the study, 264 patients aged 6-17 with major depressive disorder and a CDRS-R score of 40 or greater received either escitalopram (10-20 mg/day) or placebo for up to 8 weeks. In terms of the secondary efficacy measures of Children's Global Assessment Scale (CGAS) and the Clinical Global Impression-Severity (CGI-S) scale, the change from baseline in scores appeared greater for the escitalopram group compared to the placebo group, although the differences did not quite achieve statistical significance. When these same efficacy measures were analyzed for those subjects who remained in the study through the 8-week assessment, statistically significant improvements were seen in the escitalopram group for both these assessments in comparison to placebo. Escitalopram was well tolerated in both children and adolescents, with no significant difference in withdrawal rates due to adverse events. Two placebo-treated patients reported suicide-related events and 1 placebo patient reported worsening of depression, whereas only 1 escitalopram-treated patient reported a suicide-related event and no escitalopram-treated patient reported worsening of depression. Forest believes the results of this trial, in addition to the pediatric depression trials of citalopram, show that there is no added risk of suicidal behavior or worsening of depression due to the use of these products in pediatric patients. The safety data have now been reported to the FDA. In a European trial of citalopram, the drug did not show any improvement of depressive symptoms *versus* placebo, while the U.S. pediatric depression trial of citalopram showed a reduction of symptoms of depression to a significantly greater extent than placebo (5).

A recent review of the preclinical and clinical studies with escitalopram focused on its therapeutic profile of action and tolerability. It has been proposed that the *S*-enantiomer of the SSRI citalopram is the isomer that exerts antidepressant efficacy, and that the *R*-enantiomer is clinically inactive; preclinical and clinical data support this. Based on *in vitro* radioligand binding data, escitalopram is the most selective SSRI available. Hypotheses that escitalopram has a more rapid onset of action or fewer adverse effects than citalopram have not yet been fully documented in published studies, although its profile is at least comparable to citalopram. Escitalopram is more effective than placebo in the treatment of major depression and as effective as other SSRIs, including citalopram. Comparable to other SSRIs, it is well tolerated, safe in overdose and has a low incidence of adverse effects or drug interactions (6).

New data from a clinical study show that escitalopram is as effective and well tolerated as sertraline (Zoloft®). The double-blind study in 212 patients with major depressive disorder evaluated whether the starting dose of escitalopram (10 mg/day) could provide comparable efficacy to the full dosing range of sertraline (50-200 mg/day). The primary efficacy variable was the change in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from baseline to week 8. Results showed that patients receiving escitalopram experienced similar efficacy compared to patients receiving a median dose of sertraline of 150 mg/day. At week 4, 46% of sertraline-treated patients received 150 mg/day or more, and at week 8, 65% received 150 mg/day or more. Escitalopram and sertraline demonstrated comparable efficacy in reducing symptoms of depression and anxiety in patients with major depressive disorder. At week 8, 75% of escitalopram-treated patients and 70% of sertraline-treated patients had a 50% or greater reduction from baseline in their MADRS scores. Mean changes in MADRS scores from baseline to endpoint were –19.1 and –18.4 for the escitalopram and sertraline groups, respectively. For patients who were severely depressed at baseline, mean changes in MADRS scores from baseline to endpoint were –22.4 and –20.4 for the escitalopram and sertraline groups, respectively. Both treatment groups experienced improvement in anxiety symptoms associated with

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

Indication	Design	Treatments	n	Conclusions	Ref.
Anxiety, generalized	Open	Escitalopram, 10-20 mg/d x 24 wks	299	Escitalopram was safe and effective over the long term in patients with generalized anxiety disorder	10
Anxiety, social	Randomized Double-blind	Escitalopram, 20 mg x 24 wks (n=170) Paroxetine, 20 mg x 24 wks (n=169) Placebo (n=166)	505	Escitalopram was more effective than paroxetine in paients with social anxiety disorder	11

depression, according to the Hamilton Rating Scale for Depression (HAM-D) Anxiety Subscale total score (7).

Escitalopram 10-20 mg/day was given to 7 children and 5 adolescents with major depressive disorder in an 8-week open study. Changes in the CDRS-R scores (mean = –32.4) indicated that the treatment was equally effective in children and adolescents. Escitalopram was also well tolerated (8).

A 6-month study has found that escitalopram is as effective as paroxetine hydrochloride (Paxil®) in patients with GAD. In the randomized, double-blind, flexible-dose study, 123 patients with GAD (HAM-A score of at least 18) underwent a 1-week, single-blind, placebo lead-in period, after which they were randomized to receive either 10 mg/day of escitalopram or 20 mg/day of paroxetine. If clinically indicated, the escitalopram dose could be increased to 20 mg after 4 weeks of treatment, and the paroxetine dose could be escalated in 10-mg increments at biweekly intervals to a maximum dose of 50 mg/day. The primary efficacy variable was the mean change from baseline to week 24 in the HAM-A total score. At the end of the 6-month study, both escitalopram and paroxetine were associated with improvement in anxiety symptoms. Mean changes in the Hamilton Rating Scale for Anxiety (HAM-A) scores from baseline to endpoint were –15.3 and –3.3, respectively. At endpoint, the overall mean daily doses of escitalopram and paroxetine were 14.4 mg and 29.9 mg, respectively. Significantly fewer escitalopram-treated patients withdrew from the study due to adverse events compared to patients treated with paroxetine (6.6% *vs*. 22.6%). Escitalopram-treated patients also had a lower incidence of clinically significant weight increase (9).

Escitalopram 10-20 mg/day was administered for 24 weeks to 299 patients with GAD in an open-label extension study. Measurements of anxiety and quality of life improved over the course of treatment, with 92% of patients responding and tolerability maintained over the long term (10) (see Table IV).

Data from a randomized, double-blind, 24-week trial in 505 patients with SAD were analyzed to compare the efficacy of escitalopram to that of paroxetine and placebo. It was found that escitalopram 20 mg was significantly superior to paroxetine 20 mg for the Liebowitz Social Anxiety Scale factors of strangers, eat/drink small group, work and party and numerically superior for the factor of public space (11) (see Table IV).

1. *Cipralex approved in select European countries for social anxiety disorder*. DailyDrugNews.com (Daily Essentials) Dec 9, 2003.

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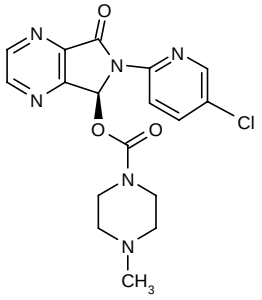
Eszopiclone



The FDA has accepted the resubmission of Sepracor's NDA for eszopiclone (Estorra™) for the treatment of insomnia as a complete response and has begun its review of the resubmission. The FDA has classified the resubmission as Class 2, giving a 6-month review period beginning on the date that the resubmission was received. The NDA was resubmitted after receipt of an approvable letter in February 2004 for the treatment of insomnia characterized by difficulty falling asleep and/or difficulty maintaining sleep during the night and early morning. Upon approval, Sepracor would expect the recommended dosing to achieve sleep onset and maintenance to be 2 and 3 mg for adult patients, 2 mg for elderly patients with sleep maintenance difficulties, and 1 mg for sleep onset in elderly patients whose primary complaint is difficulty falling asleep. The FDA has not requested additional clinical or preclinical trials for approval. The NDA contains a total of 24 clinical trials, which included more than 2,700 adult and elderly subjects, and more than 60 preclinical studies. A total of 6 randomized, placebo-controlled phase III studies for the treatment of chronic or transient insomnia were conducted in both adult and elderly patients. A comprehensive phase IIIb clinical program for Estorra™ commenced in the fourth quarter of 2003. The program includes a series of 4 double-blind, placebo-controlled studies designed to gather further clinical information on the compound's effect in the treatment of insomnia in specific patient groups. The first is an 8-week study for the treatment of insomnia in patients suffering from depression. The second is a 4-week study for the treatment of insomnia in patients suffering from rheumatoid arthritis. The third is a 4-week study for the treatment of insomnia in women experiencing perimenopause, and the fourth is a 6-month safety and efficacy study for the treatment of chronic insomnia (1-8).

Prior to the successful completion of the business combination between Aventis and Sanofi-Synthélabo to form Sanofi-Aventis, Sepracor and Aventis agreed to amend their collaboration relating to eszopiclone. Under the conditional amended agreement, Sepracor would have the right to read and reference Aventis's regulatory filings related to zopiclone outside the U.S. for the purpose of development and regulatory registration of eszopiclone outside the U.S., and Aventis would assign to Sepracor the foreign counterparts to the U.S. patent covering eszopiclone and its therapeutic use. Sepracor would permit Aventis to assign Sepracor's obligation to pay a royalty on sales of eszopiclone in the U.S. to a third party. Under terms of the original 1999 agreement, Sepracor exclusively licensed Aventis's preclinical, clinical and postmarketing surveillance data package relating to zopiclone, its isomers and metabolites, to develop, make, use and sell eszopiclone in the U.S. Zopiclone is marketed by Aventis in approximately 80 countries under the brand names Imovane® and Amoban® (9).

A trajectory analysis was carried out to determine whether distinct patterns of treatment response could be observed among eszopiclone- or placebo-treated patients with insomnia who took part in a 6-month, double-blind study. Unlike similar analyses in disorders like depression, where distinct treatment response profiles are easily determined, results did not show distinct treatment response trajectories in these patients, suggesting that 6 months of treatment with eszopiclone is associated with rapid and sustained response, with no signs of tolerance even among different patient subgroups (10).

The pharmacokinetic interaction between eszopiclone and digoxin, a drug commonly used in the adult population in whom insomnia medications are used, was evaluated in 12 healthy volunteers who received digoxin 0.25 once daily for 7 days, with a 3-mg dose of eszopiclone administered with digoxin on day 7. Results showed that this single dose of eszopiclone did not affect the steady-state pharmacokinetics of digoxin (11).

Pharmacokinetic and pharmacodynamic interactions were evaluated when eszopiclone was administered with warfarin in 12 healthy volunteers. In one treatment period, patients received eszopiclone 3 mg for 5 days, with a single dose of warfarin 25 mg given on the last day, while in a second treatment period patients received a single dose of warfarin 25 mg. No pharmacokinetic or pharmacodynamic interactions were observed between the two drugs, and eszopiclone did not affect the anticoagulant effect of warfarin (12).

Two multicenter, randomized, double-blind, placebo-controlled studies assessing the pharmacokinetics/pharmacodynamics of eszopiclone were carried out in healthy volunteers. One study was a parallel-group study in nonelderly adults aged 18-45 years who received 1, 3 or 6 mg once daily for 7 days or placebo, and a second study was a sequential-panel design in elderly adults 65-79 years of age who received 1, 2, 3 or 5 mg once daily for 7 days or placebo. Both groups reached steady state by 48 h. Based on the data, 3 mg is the targeted dose for nonelderly adults and 2 mg is the targeted dose for elderly adults in the treatment of insomnia (13).

The long-term efficacy and safety of eszopiclone were evaluated in a multicenter, double-blind, randomized,

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

Indication	Design	Treatments	n	Conclusions	Ref.
Insomnia	Randomized Double-blind Multicenter	Eszopiclone, 3 mg o.d. x 6 mo (n=593) Placebo (n=195)	791	Eszopiclone was well tolerated and significantly improved sleep duration and quality in patients with primary insomnia. These effects were reflected in a 40% improvement in daytime ability to function and a 20% improvement in daytime alertness and sense of physical well-being compared to placebo	14
Insomnia	Randomized Double-blind Multicenter	Eszopiclone, 2 mg o.d. [nighttime] x 2 wks Placebo	159	Compared with placebo, eszopiclone significantly improved sleep onset, wake time after sleep onset, total sleep time and quality and depth of sleep in elderly patients with primary insomnia. These effects were associated with significant improvements in next-day function	20

placebo-controlled clinical trial. Overall, 791 men and women aged 21-65 years who suffered from primary insomnia, slept less than 6.5 h every night and/or had a usual sleep latency of more than 30 min every night for at least 1 month before inclusion were randomized to receive eszopiclone (3 mg) or placebo every night for 6 months. Significant differences between study groups were found after only 1 week of treatment, when patients receiving eszopiclone showed a shorter median sleep latency per night (30 min *vs*. 60 min) and a shorter wake time after sleep onset (20 min *vs.* 45 min) compared to placebo-treated patients. These differences were maintained throughout the study. At the end of the treatment, eszopiclone was also associated with a lower median number of awakenings (1.6 *vs*. 2.0 per night). The overall result of these effects was that patients treated with eszopiclone slept longer and better, which in turn was reflected in a 40% improvement in daytime ability to function and a 20% improvement in daytime alertness and sense of physical well-being compared to placebo-treated patients. No significant differences were found between the safety profiles of the two study groups, although more patients treated with eszopiclone discontinued due to adverse events (12.8% *vs*. 7.1%). Most adverse events were mild or moderate, and the most common were unpleasant taste, headache, infection, pain, nausea and pharyngitis (14) (see Table V).

A randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of eszopiclone in 264 elderly patients with chronic insomnia. Results demonstrated that eszopiclone 2 mg provided consistent, statistically significant improvements in polysomnographic and patient-reported measures of sleep, including sleep onset and maintenance, and improved some domains of quality of life (15).

Data from 3 randomized, double-blind, placebo-controlled studies of eszopiclone in patients with primary insomnia were compared to determine whether efficacy and daytime effects were consistent across patients and studies. In all 3 studies, both elderly and nonelderly patients showed significant improvements in patient reports of sleep latency, wake after sleep onset and total sleep time. Consistent improvements in patient ratings of daytime functioning were also reported (16).

A 6-month open-label extension study designed to evaluate the continued efficacy and safety of eszopiclone treatment was carried out in patients with chronic insomnia who previously participated in a 6-month, double-blind study of eszopiclone *versus* placebo. A total of 471 patients entered this extension phase and received eszopiclone 3 mg nightly at bedtime. Results showed that eszopiclone was associated with sustained improvements in patient-related sleep and daytime functioning over 12 months of therapy. Treatment was well tolerated and there was no evidence of withdrawal or tolerance (17).

A pooled analysis of 2 studies conducted in elderly patients with insomnia was carried out in order to determine if improvements in sleep and daytime function were similar to the results found in a large 6-month study of adults with chronic insomnia. Both studies were randomized, double-blind, placebo-controlled evaluations in patients aged 64-85 years. Two weeks of nightly treatment with eszopiclone 2 mg improved sleep onset, maintenance, quality and daytime functioning, and was well tolerated (18).

Analysis of a subgroup of patients with substantial sleep maintenance problems from an earlier 6-month placebo-controlled trial that demonstrated the efficacy of eszopiclone in all aspects of sleep was carried out to estimate the effects of eszopiclone in patients selected for difficulty in staying asleep. Results showed that eszopiclone 3 mg was effective at reducing both high and low baseline wake after sleep onset, an effect that was maintained throughout the study period, suggesting that the

drug may be effective in patients with sleep maintenance insomnia (19).

A double-blind, randomized, placebo-controlled clinical trial evaluated the efficacy and safety of eszopiclone in 159 patients aged 65-85 years with primary insomnia. Compared with placebo, eszopiclone (2 mg every night) given for 2 weeks significantly improved sleep onset, wake time after sleep onset, total sleep time, quality of sleep and depth of sleep, These effects were associated with significant improvements in the next-day function of the patients, increasing daytime alertness, sense of well-being and daytime ability to function, and reducing daytime napping. Both treatments were well tolerated (20) (see Table V).

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6. *Estorra NDA resubmission accepted by FDA*. DailyDrugNews.com (Daily Essentials) July 20, 2004.

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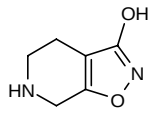
Gaboxadol



Lundbeck and Merck & Co. have entered into an agreement for the exclusive U.S. development and commercialization of gaboxadol (Lu-02-030, MK-0928, THP), a phase III hypnotic agent for the treatment of sleep disorders. The companies will jointly complete the ongoing phase III program, with Merck funding the majority of the remaining development activities. Following Merck's filing of an NDA, anticipated between late 2006 and mid-2007, the companies will copromote gaboxadol in the U.S. Lundbeck will receive a share of gaboxadol sales in the U.S. The agreement also includes an option for Lundbeck to copromote a Merck product prior to the launch of gaboxadol. Subsequently, the companies extended their agreement to Japan, whereby they will jointly conduct the clinical program required for filing an NDA in Japan, with Merck funding the majority of the development activities. Following approval, the companies plan to copromote gaboxadol in Japan and Lundbeck will receive a share of Japanese gaboxadol sales. Gaboxadol, a direct-acting $GABA_A$ receptor agonist, has a novel mode of action. It interacts directly with the GABA receptor recognition site and mediates its effects via a GABA receptor population that is different from that modulated by benzodiazepine ligands. In clinical trials, gaboxadol has shown sleep-inducing as well as sleep-maintaining properties, resulting in improvements in sleep architecture. The compound's novel mode of action is expected to result in minimal risk of abuse (1-4).

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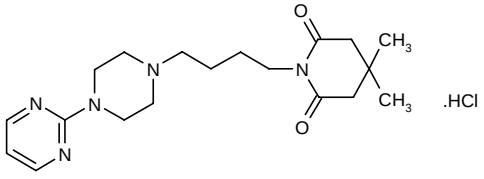
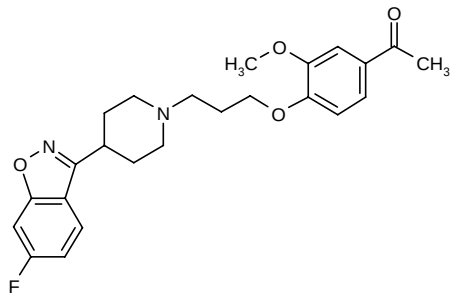
Gepirone Hydrochloride



The FDA recently determined that Organon's NDA for the use of extended-release gepirone hydrochloride (Ariza®, Variza®) in major depressive disorder was not approvable. The decision follows an amendment to Organon's NDA submitted to the FDA in December 2003 and Organon now plans to withdraw the application (1).

1. *Gepirone ER NDA deemed not approvable*. DailyDrugNews (Daily Essentials) June 30, 2004.

Iloperidone

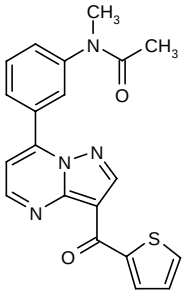


Vanda Pharmaceuticals has acquired from Novartis the worldwide rights to develop and commercialize iloperidone, Titan's proprietary antipsychotic agent in phase III development for the treatment of schizophrenia and related disorders. Vanda will pursue completion of the iloperidone phase III program and product registration. All of Titan's rights and economic interests in iloperidone, including royalties, remain unchanged under the license agreement. Iloperidone is one of a class of drugs known as SDAs, or serotonin/dopamine receptor antagonists (1).

1. *Vanda acquires rights to iloperidone from Novartis*. DailyDrugNews.com (Daily Essentials) June 14, 2004.

Original monograph – Drugs Fut 2000, 25(1): 29.

Indiplon



Indiplon is a unique nonbenzodiazepine agent that binds preferentially to the specific subtype of $GABA_A$ receptors within the brain believed to be responsible for promoting sleep. Both immediate- and modified-release

formulations of indiplon are being developed by Neurocrine Biosciences in partnership with Pfizer. Neurocrine Biosciences plans to submit NDAs in adult and elderly patients early this year. One NDA will be for the immediate-release formulation and one will be for the modified-release formulation.

Neurocrine and Pfizer have conducted a thorough dose evaluation to ensure that the filing for both indiplon formulations will contain data supporting an effective, safe and well-tolerated new medicine for the treatment of insomnia. A phase III trial with the modified-release formulation (15 mg) in elderly patients has been completed. Results will be available in the third quarter of 2004, at which time optimal doses for filing will be selected. Neurocrine and Pfizer anticipate a launch date of late 2005. To date, 14 phase III studies, including double-blind and safety studies, have been completed. Additional studies will be conducted to provide supplemental data on the efficacy and safety of indiplon to support and expand the label. Neurocrine has reported that data from patients who completed 6 months of treatment in the long-term phase III studies for immediate-release indiplon (RESTFUL trial) and modified-release indiplon (SLEEP trial) have been analyzed. Results for both the immediate- and modified-release formulation studies demonstrated that indiplon was well tolerated and that efficacy was sustained in the patients with chronic insomnia who completed 6 months of treatment. The multicenter, randomized, double-blind, placebo-controlled, parallel-group RESTFUL study evaluated nightly administration of 2 doses of immediate-release indiplon (10 and 20 mg) relative to placebo in 700 adult chronic insomnia patients. The study, conducted at 67 centers worldwide, involved patients aged 21-64 who received treatment over a 3-month period. With either of the dose levels of immediate-release indiplon, patients achieved rapid sleep onset and slept longer with minimal sleep disturbances. Efficacy results with the 10- and 20-mg doses demonstrated a highly statistically significant improvement in patient-reported latency to sleep onset (LSO) at all time points as compared to placebo: a 30% improvement over placebo and more than 27 min over baseline. Secondary endpoints, including patient-reported total sleep time (sTST), wake after sleep onset (sWASO), number of awakenings after sleep onset (sNAASO) and sleep quality, also demonstrated a highly statistically significant improvement for both doses as compared to placebo. Indiplon demonstrated a highly statistically significant improvement in patient-reported outcome as assessed by the Insomnia Severity Index. Investigator-reported Global Rating for Severity of insomnia and Change (IGR-S; IGR-C) as a result of treatment were both highly statistically significant over placebo and in favor of indiplon. With this study, all 7 phase III trials for registration of immediate-release indiplon have been completed. Meanwhile, data have also been reported from the multicenter, randomized, double-blind, placebo-controlled, parallel-group SLEEP trial evaluating nightly administration of 2 doses of modified-release indiplon (20 and 30 mg) relative to placebo in 740 adult chronic insomnia patients aged 21-64 years with sleep maintenance difficulties. Preliminary results demonstrated that patients who took modified-release indiplon nightly over the 3-month period achieved rapid sleep onset, maintained high-quality sleep throughout the night, and showed improvement in quality of life endpoints. Indiplon treatment demonstrated a highly statistically significant improvement in sleep for all primary and secondary endpoints compared to placebo for both doses and all time points. Patients on both doses of indiplon reported an increase of up to 75 min compared to placebo in sTST, the primary endpoint for the study, and improvement of up to 90 min over baseline. This positive effect was sustained over the 3-month period. Secondary sleep maintenance endpoints including patient-reported total wake time (sTWT), sWASO and sNAASO also demonstrated highly statistically significant improvement for both doses as compared to placebo over the entire dosing period. For sleep initiation endpoints, patient-reported LSO was also highly statistically significant for both doses compared to placebo and sleep quality was improved in the indiplon groups compared to placebo. Indiplon demonstrated a highly statistically significant improvement in patient-reported outcomes including measures of quality of life such as vitality and the Insomnia Severity Index when compared to placebo. The IGR-S and IGR-C as a result of treatment were both highly statistically significant in favor of indiplon compared to placebo. The SLEEP study was the first long-term phase III trial with modified-release indiplon. With respect to the long-term safety of indiplon (up to 12 months), 2 studies have been completed with the immediate-release formulation, 1 in adults and another in the elderly. Together, these studies enrolled 757 chronic insomnia patients in either open-label studies or open-label extensions of double-blind studies. The alliance is also completing 2 long-term open-label extension/safety studies of the modified-release formulation, which enrolled 597 adult and elderly chronic insomnia patients. Preliminary safety results from these trials are consistent with short-term trials, demonstrating that indiplon was safe and well tolerated throughout the treatment period (1-10).

Earlier this year, Neurocrine Biosciences purchased all of Wyeth's financial interest in indiplon and will now retain all milestone, royalty and other payments on indiplon commercialization that would otherwise have been payable to Wyeth. Wyeth will assign to Neurocrine its license agreement with DOV Pharmaceutical and all of Wyeth's right, title and interest in and to the indiplon composition patent filed by Neurocrine in Wyeth's name. Wyeth and DOV signed a license agreement in 1998, under which Wyeth licensed the indiplon technology to DOV in exchange for milestone payments and royalties on future sales of indiplon. Neurocrine signed an exclusive license and development agreement with DOV in 1998 for indiplon and all therapeutic indications of this compound. In 2002, Neurocrine entered a worldwide agreement with Pfizer for the development and commercialization of indiplon for the treatment of insomnia (11, 12).

Results from a phase I study of immediate-release indiplon showed that elderly subjects given indiplon doses of 5 or 10 mg in the middle of the night did not experience next-morning residual effects as compared to placebo using standard measurements of psychomotor function and alertness. This compared to significant impairment the next morning in patients given zopiclone 3.75 mg. The randomized, double-blind, placebo- and active drug-controlled, crossover trial assessed the safety and tolerability of indiplon and zopiclone compared with placebo. It enrolled 36 healthy elderly subjects aged 65-73 years on an inpatient basis. Subjects were awakened to an alert state 4 h after they had fallen asleep, at which time indiplon, zopiclone or placebo was administered. After falling back to sleep, subjects were awakened 4 h postdose and psychomotor tests were conducted over the next 4 h. Next-day residual effects were assessed immediately after awakening at 4 h, and also at 6 and 8 h postdosing. Both doses of the immediate-release formulation of indiplon were well tolerated and there were no statistically significant differences in next-day residual sedation, as measured by the Digital Symbol Substitution Test (DSST), Symbol Copy Test (SCT) and a visual analogue scale (VAS), as compared with placebo. On the other hand, zopiclone 3.75 mg was associated with statistically significant impairment the next morning as compared with placebo at 4 and 8 h postdose using the DSST. A trend toward impairment was also demonstrated for zopiclone at 4 and 6 h postdose using the SCT (13).

Positive preliminary results were also reported from a phase II/III trial of the immediate-release (IR) formulation of indiplon. The multicenter, randomized, placebo-controlled, double-blind, parallel-group study assessed the efficacy and safety of middle-of-the-night (MOTN) administration of indiplon at doses of 10 and 20 mg compared to placebo in 264 adult patients with chronic primary insomnia and a history of frequent and prolonged MOTN awakenings. This study was conducted on an outpatient basis over a 4-week treatment period. Data show that administration of indiplon IR 10 and 20 mg following MOTN awakening resulted in a highly statistically significant improvement in the primary endpoint of patient-reported LSO relative to placebo. This improvement was sustained throughout the study. Patients treated with indiplon were more alert the next morning upon awakening as compared to placebo using the standard VAS for sleepiness. All secondary endpoints were also highly statistically significant for both doses based on patient self-assessments, including WASO, NAASO, TST and sleep quality, and it was not associated with any next-day residual sedation (14).

The first phase III clinical results for indiplon IR (5 and 10 mg) given for 2 weeks to 360 elderly patients with chronic insomnia were described early in 2004. Compared with placebo, indiplon reduced the LSO by 40% and significantly improved other sleep parameters, including the patient-reported TST, WASO, NAASO and sleep quality. No treatment-related adverse events were found (15).

In 60 adults aged 65-75 years with primary insomnia, modified-release indiplon (10, 20, 30 and 35 mg) was effective in improving sleep efficiency and sleep quality, and in reducing latency to persistent sleep and wake after sleep onset. Indiplon-MR was well tolerated in this patient population (16). The results from this and several of the following studies are summarized in Table VI.

A total of 194 adult patients with primary chronic insomnia for at least 3 months were enrolled in a double-blind, randomized clinical trial and received placebo or immediate-release indiplon (indiplon-IR) for 5 weeks. At the end of the treatment period, latency to persistent sleep was shorter with indiplon (28 and 27 min with 10 and 20 mg/day, respectively) than placebo (37 min). Both indiplon doses also significantly improved latency to sleep onset and sleep quality, and no evidence of discontinuation withdrawal or rebound insomnia was found (17).

A total of 211 adult outpatients with insomnia for at least 3 months were given indiplon-MR (30 mg) or placebo for 2 weeks. At the end of the treatment, indiplon-MR significantly increased subjectively rated total sleep time (367 min *vs*. 336 min with placebo), reduced average latency to sleep onset (27.3 min *vs*. 33.2 min with placebo) and improved sleep quality. Indiplon was well tolerated in this patient population (18).

In a placebo-controlled, crossover clinical trial, 42 patients aged 65-82 years with primary chronic insomnia were treated with indiplon-IR (5, 10 and 20 mg) or placebo. Indiplon dose-dependently reduced latency to persistent sleep, increased total sleep time, and was also effective in improving both latency to sleep onset and sleep quality in this population of elderly patients (19).

The potential respiratory side effects of indiplon-MR were assessed in a double-blind, crossover phase I clinical trial that randomized 12 healthy male volunteers to receive a single dose of placebo, indiplon-MR (30 mg) or codeine sulfate (60 mg). A carbon dioxide challenge test found no clinically significant effects of indiplon-MR on minute ventilation, mouth occlusion pressure and the level of arterial oxygen saturation of the patients compared to placebo, whereas codeine sulfate induced respiratory suppression on minute ventilation (20).

The respiratory safety of indiplon-MR (20 mg) was also evaluated in a double-blind, randomized, placebo-controlled, crossover phase I clinical trial that enrolled 18 patients with mild to moderate chronic obstructive pulmonary disease. The level of arterial oxygen saturation was similar with both study treatments over the entire night (93.6% with indiplon-MR and 93.4% with placebo), during REM sleep (93.0% *vs.* 92.8%) and during non-REM sleep (93.0% *vs*. 92.9%). No significant differences between treatments were found in the average respiratory distress index, and more patients treated with indiplon-MR classified their sleep quality as very good or excellent (21).

The results of a double-blind, randomized clinical trial suggested that indiplon-IR may play a role in the

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

Indication	Design	Treatments	n	Conclusions	Ref.
Insomnia	Randomized Double-blind Crossover	Indiplon, 10 mg Indiplon, 20 mg Indiplon, 30 mg Indiplon, 35 mg Placebo	60	Indiplon was well tolerated and significantly improved sleep onset, maintenance and overall sleep quality in elderly patients with chronic insomnia	16
Insomnia	Randomized Double-blind	Indiplon, 10 mg x 5 wks Indiplon, 20 mg x 5 wks Placebo	194	Indiplon was more effective than placebo in improving sleep parameters in patients with chronic insomnia. No evidence for tolerance, discontinuation withdrawal or rebound was found	17
Insomnia	Randomized Double-blind	Indiplon, 30 mg x 2 wks Placebo	211	Compared with placebo, indiplon was safe and effective in improving and maintaining sleep in patients with chronic primary insomnia	18
Insomnia	Randomized Double-blind Crossover Multicenter	Indiplon, 5 mg Indiplon, 10 mg Indiplon, 20 mg Placebo	42	Indiplon dose-dependently improved the mean latency to persistent sleep, the mean total sleep time and the latency to sleep onset in elderly patients with insomnia. The drug was well tolerated, and no serious adverse events were reported	19
Insomnia	Randomized Double-blind	Indiplon, 10 mg [at bedtime] Indiplon, 20 mg [at bedtime] Placebo	593	Both indiplon dose levels were well tolerated and effective in inducing sleep, improving overall sleep quality and increasing sleep duration in subjects with experimentally induced transient insomnia. No evidence of next-day residual sedation was found	22

treatment of transient insomnia. A total of 593 healthy volunteers with experimentally induced transient insomnia were given a single dose of indiplon-IR (10 or 20 mg) or placebo. Both indiplon-IR doses were well tolerated and significantly reduced latency to persistent sleep and latency to sleep onset, increased total sleep time and improved sleep quality, without inducing any next-day effects (22).

1. *Pfizer reports Q3 R&D highlights*. Pfizer Press Release 2003, Oct 22.

2. *Neurocrine Biosciences reports Q3 R&D highlights*. Neurocrine Biosciences Press Release 2003, Nov 3.

3. *Pfizer reports 2003 year-end R&D highlights*. Pfizer Press Release 2004, Jan 22.

4. *Indiplon NDA filings planned for fourth quarter 2004*. DailyDrugNews.com (Daily Essentials) July 20, 2004.

5. *Pfizer reports Q1 R&D highlights*. Pfizer Press Release 2004, April 20.

6. *Pfizer reports Q2 R&D highlights*. Pfizer Press Release 2004, July 21.

7. *DOV Pharmaceutical reports Q1 R&D highlights*. DOV Pharmaceutical Press Release 2004, May 10.

8. *Neurocrine Biosciences reports Q1 R&D highlights*. Neurocrine Biosciences Press Release 2004, May 3.

9. *Neuroscrine Biosciences reports 2003 year-end R&D highlights*. Neurocrine Biosciences Press Release 2004, Jan 29.

10. *Positive results from phase III indiplon trials*. DailyDrugNews.com (Daily Essentials) March 29, 2004.

11. *Reorganization of indiplon agreements*. DailyDrugNews.com (Daily Essentials) March 3, 2004.

12. *Hart-Scott-Rodino wait over for Neurocrine purchase of indiplon rights*. DailyDrugNews.com (Daily Essentials) March 19, 2004.

13. *No morning residual effects after middle-of-night administration of indiplon*. DailyDrugNews.com (Daily Essentials) Nov 13, 2003.

14. *Immediate-release indiplon shows promise for MOTN administration*. DailyDrugNews.com (Daily Essentials) Dec 12, 2003.

15. *Neurocrine reports positive results for the first indiplon phase III trial in elderly patients with chronic insomnia*. Neurocrine Biosciences Press Release 2004, Feb 18.

16. Walsh, J.K., Lankford, A., Krystal, A.D., Roth, T., Garber, M. *Efficacy and tolerability of indiplon modified release in elderly patients with chronic sleep-maintenance insomnia*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR568.

17. Walsh, J.K., Roth, T., Lankford, A., Rosenbere, R., Jochelson, P. *Efficacy and safety of 35-days of treatment with*

indiplon immediate release in adults with chronic insomnia. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR569.

18. Scharf, M.B., Roth, T., Walsh, J.K., Jochelson, P., Garber, M. *Efficacy of indiplon-MR in inducing and maintaining sleep in patients with chronic sleep maintenance insomnia*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR703.

19. Scharf, M.B., Rosenberg, R., Cohn, M., Zammit, G.K., Jochelson, P. *Efficacy and safety of indiplon immediate release in elderly patients with chronic insomnia*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR704.

20. Cohn, M., Jochelson, P., Gately, N., Baron, C., Boyd, M. *Assessment of respiratory effects of indiplon-MR*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR834.

21. Hull, S., Fogarty, C., Chediak, A., Vince, B., Jochelson, P., Gately, N. *Safety of indiplon-MR in mild-to-moderate COPD*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR841.

22. Roth, T., Scharf, M.B., Rosenberg, R., Lankford, A., Alexander, T. *Efficacy and tolerability of indiplon immediate release in transient insomnia*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR837.

Original monograph – Drugs Fut 2003, 28(8): 739.

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Garber, M., Burke, J., Farber, R., Jochelson, P., Campbell, B. *A crossover comparison of middle of the night dosing with indiplon-IR, zolpidem, and zopiclone in healthy volunteers*. 24th CINP Congr (June 20-24, Paris) 2004, Abst P02.548.

Garber, M. et al. *Residual effects of middle of the night dosing: A placebo-controlled crossover study of indiplon-IR, zolpidem, and zopiclone in healthy volunteers*. Sleep 2004, 27(Suppl.): Abst 582.

Hull, S. et al. *Safety of indiplon-MR in patients with mild-to-moderate COPD*. Sleep 2004, 27(Suppl.): Abst 587.

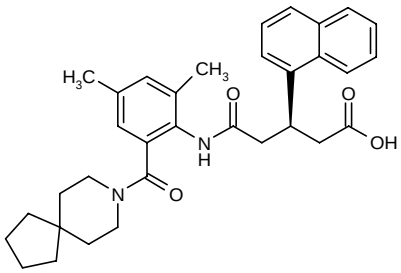
Jochelson, P. et al. *Efficacy of indiplon in inducing and maintaining sleep in patients with chronic sleep maintenance insomnia*. Sleep 2004, 27(Suppl.): Abst 588.

Scharf, M. et al. *Efficacy and tolerability of indiplon-IR in the treatment of transient insomnia*. Sleep 2004, 27(Suppl.): Abst 599.

Walsh, J.K. et al. *Treatment of primary insomnia for five weeks with indiplon-IR*. Sleep 2004, 27(Suppl.): Abst 581.

Walsh, J.K., Roth, T., Rosenberg, R., Lankford, D.A., Jochelson, P. *Treatment of primary insomnia for five weeks with indiplon-IR*. 24th CINP Congr (June 20-24, Paris) 2004, Abst P01.529.

Itriglumide



The anthranilic acid derivative itriglumide (CR-2945) is a potent and selective cholecystokinin CCK_2 receptor antagonist under development at Rotta as an antiulcer agent, for the treatment of gastrin- and CCK-dependent tumors and as an anxiolytic, with phase I trials under way. The compound proved to be safe and well tolerated following single oral doses to healthy volunteers and phase II trials are planned in patients with peptic ulcers, panic disorders and anxiety.

Original monograph – Drugs Fut 1999, 24(5): 483.

L-759274

Merck & Co. was last reported to be conducting late-stage clinical trials with L-759274, a novel tachykinin NK_1 receptor antagonist, in major depression.

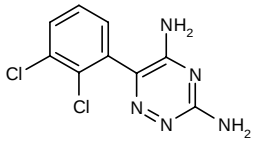
L-759274 40 mg or placebo was given once daily for 6 weeks to patients with major depression and melancholic features in a randomized, double-blind trial. The active treatment was generally well tolerated and significantly improved Hamilton Depression Scale 17 (HAMD-17) total scores and Clinical Global Impression (CGI) scale scores compared to placebo (1) (see Table VII).

1. Kramer, M.S., Winokur, A., Kelsey, J. et al. *Demonstration of the efficacy and safety of a novel substance P (NK1) receptor antagonist in major depression*. Neuropsychopharmacology 2004, 29(2): 385.

Table VII: Clinical studies of L-759274 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Depression	Randomized Double-blind	L-759274, 40 mg/d p.o. x 6 wks (n=66) Placebo (n=62)	128	L-759274 was generally well tolerated and significantly effective in patients with major depression	1

Lamotrigine



Lamotrigine is a dual sodium channel blocker and glutamate release inhibitor developed by GlaxoSmithKline for use in epilepsy and, more recently, bipolar disorder. The product was cleared for marketing in both the U.S. and the E.U. last year for the maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy.

Original monograph – Drugs Fut 1986, 11(6): 456.

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Goodwin, F.K., Bowden, C.L., Calabrese, J.R., Paska, W., Stewart, R. *Concomitant use of lamotrigine and lithium in bipolar I disorder*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR340.

Goodwin, G.M. et al. *A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder*. J Clin Psychiatry 2004, 65(3): 432.

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Marcotte, D.B. *Long-term use of lamotrigine for bipolar disorder in patients over 55 years of age*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR877.

McElroy, S.L. et al. *A 52-week, open-label continuation study of lamotrigine in the treatment of bipolar depression*. J Clin Psychiatry 2004, 65(2): 204.

Preston, G.A. et al. *Borderline personality disorder in patients with bipolar disorder and response to lamotrigine*. J Affect Disord 2004, 79(1-3): 297.

Schindler, F., Anghelescu, I. *The LILA-study: An observational study comparing the efficacy of lithium vs lamotrigine as an augmentation strategy for treatment-resistant depression (TRD)*. 59th Annu Meet Soc Biol Psychiatry (April 29-May 1, New York) 2004, Abst 140.

Swope, G.S., Hoopes, S.P., Amy, L.S., Laragan, J., Fransure, B. *An open-label study of lamotrigine in adolescents with bipolar mood disorder*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR733.

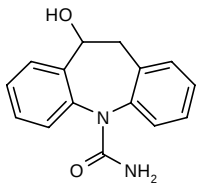
LAX-101

Miraxion™ (formerly known as LAX-101) is a semi-synthetic highly purified derivative of eicosapentaenoate (EPA), an n-3 fatty acid, which is in clinical development at Amarin for the treatment of both Huntington's disease (HD) and treatment-unresponsive depression. Amarin previously licensed the rights to the compound from Laxdale and is now in the process of acquiring the company. Phase III trials are under way in HD, for which fast track status has been granted in the U.S. and orphan drug designation in both the U.S. and the E.U.; the product was submitted for approval in the E.U. for this indication last year. Encouraging results have also been reported from phase II trials in treatment-unresponsive depression. Miraxion™ has been partnered for HD in major European markets and for depression in Japan. Amarin plans to seek another development and marketing partner to accelerate the program in depression (1, 2).

1. *Amarin to acquire Laxdale.* DailyDrugNews.com (Daily Essentials) July 15, 2004.

2. *Gene variant data analysis for Miraxion in Huntington's disease.* DailyDrugNews.com (Daily Essentials) Aug 26, 2004.

Licarbazepine

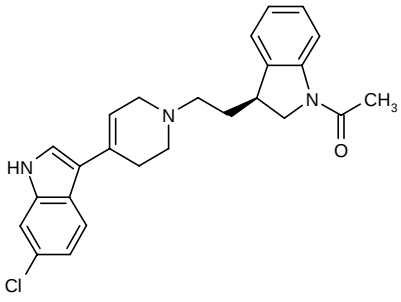


A voltage-dependent sodium current blocker, licarbazepine (LIC-477) has reached phase II clinical trials at Novartis for bipolar disorder.

Lif-247

Lif-247 (LI-247) apparently continues in late-stage clinical development for depression at Enhance Lifesciences.

Lu-31-130/Lu-AA-21004/ Lu-35-138

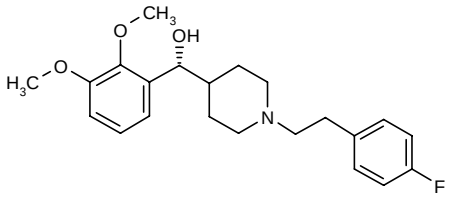


Lu-35-138

Lundbeck has advanced Lu-31-130, a new antipsychotic agent, and Lu-AA-21004, a new antidepressant, into phase I studies. The trials will evaluate the tolerability and pharmacokinetics of the compounds. Pharmacological data indicate that Lu-31-130 has antipsychotic activity combined with a reduced side effect liability *in vivo*. The atypical antipsychotic has potential for the treatment of various psychotic indications. Lu-AA-21004 has shown antidepressant potential *in vivo* and has a new pharmacological profile due to the combination of serotonin reuptake inhibition with a number of other characteristics. Given the progress of Lu-31-130, Lundbeck has decided to discontinue further development of the phase I antipsychotic Lu-35-138 (1).

1. *Lundbeck advances new compounds into phase I*. DailyDrugNews.com (Daily Essentials) Dec 29, 2003.

MDL-100907

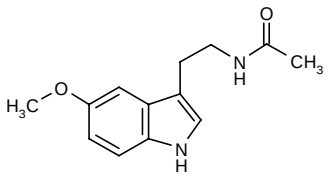


MDL-100907 (100907) has progressed to phase IIb clinical trials for the treatment of insomnia at Aventis (now part of Sanofi-Aventis) (1). MDL-100907 is a selective 5-HT_{2A} receptor antagonist with the potential to improve restorative sleep and sleep continuity by reducing nighttime awakenings.

1. *Aventis Pharma reports 2003 year-end R&D highlights*. Aventis Pharma Press Release 2004, Feb 5.

Original monograph – Drugs Fut 1998, 23(9): 955.

Melatonin, Controlled-Release Tablets

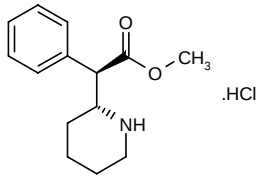


The Therapeutic Products Directorate (TPD) of Health Canada informed Neurim last year that the new drug submission (NDS) for Circadin® controlled-release melatonin tablets would not be approved. The company was seeking approval of the product for the treatment of sleep disorders in the elderly. Paladin acquired the exclusive Canadian distribution rights for Circadin® from Neurim in 1997 and Nycomed Pharma holds rights in Europe (1). Following Health Canada's recent classification of melatonin as a natural health product, Paladin has decided that it does not fit well within the company's overall marketing strategy and will not be commercialized (2).

1. *Canadian notice of noncompliance for Circadin*. DailyDrugNews.com (Daily Essentials) Dec 17, 2003.

2. *Paladin realigns product pipeline and announces change to management team*. Paladin Labs Press Release 2004, Sept 22.

Methylphenidate Hydrochloride, Patch

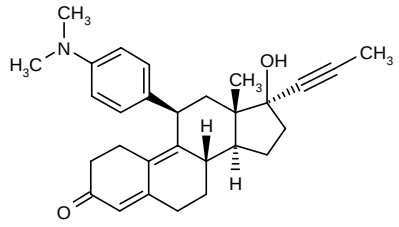


Following a meeting with the FDA, Noven and Shire are to proceed with the development of the MethyPatch® transdermal methylphenidate system (SPD-485) for the treatment of ADHD, which Shire licensed from Noven last year. Noven and Shire discussed with the FDA their jointly prepared development plan intended to address issues raised in a not approvable letter received in April 2003. The plan, submitted for FDA review in March 2004, included protocol summaries for possible additional clinical studies. Development efforts are expected to include additional clinical work, including another phase III study. The studies will be managed by Shire and funded by Noven. If the additional studies are successful, the parties intend to file an amendment to the pending NDA during 2005. The amendment is expected to receive a 6-month review by the FDA. Shire continues to have certain rights to terminate the license, including if Shire determines that submission of the results of the additional clinical studies to the FDA would not result in approval of a commercially viable product. If Shire were to terminate on this basis, all product rights would be returned to Noven, and Noven would retain the USD 25 million previously paid by Shire in April 2003. Shire continues to have the right to require Noven to repurchase rights to the system for USD 5 million under certain circumstances (1, 2).

1. *Noven Pharmaceuticals reports 2003 year-end R&D highlights*. Noven Pharmaceuticals, Inc. Press Release 2004, Feb 26.

2. *Noven and Shire to proceed with further development of MethyPatch*. DailyDrugNews.com (Daily Essentials) June 18, 2004.

Mifepristone



Mifepristone is a glucocorticoid receptor antagonist that selectively blocks the binding of the steroid hormone cortisol to one of its two receptors. Corcept Therapeutics is conducting late-stage clinical trials with the drug (Corlux™) for the treatment of psychotic features of psychotic major depression (PMD). It is thought to exert its efficacy in this disorder by modifying the level and release pattern of cortisol in the human body. Mifepristone is currently marketed as Mifeprex for terminating early pregnancy. A clinical study has also been initiated to evaluate the tolerability and efficacy of mifepristone in improving cognition in patients with mild to moderate Alzheimer's disease.

Corcept Therapeutics has reached a special protocol assessment (SPA) agreement with the FDA for the design of 2 pivotal phase III trials evaluating mifepristone for the treatment of the psychotic features of PMD. Mifepristone has fast track designation for this indication. The primary endpoint for the 2 randomized, double-blind, placebo-controlled trials is the proportion of patients with at least a 50% improvement in the Brief Psychiatric Rating Scale Positive Symptom Subscale (BPRS PSS) at both day 7 and day 56. Patients must have at least mild psychotic symptoms (BPRS PSS of 12 or greater) to enter the studies and will be hospitalized if clinically necessary. BPRS PSS assessments will also be made at days 14, 28 and 42. The first of the trials, Corcept 07, will begin immediately and will enroll up to 280 patients at approximately 20 U.S. sites. Patients in the treatment arm will receive 600 mg of mifepristone once daily for a period of 7 days. All patients are to be off any antidepressant and antipsychotic medication for at least 1 week before beginning the 7-day treatment period. After the 7 days of mifepristone treatment, all patients will receive antidepressant therapy through day 56. Treatment with antipsychotic medications or electroconvulsive therapy will not be allowed at any time during the study. The second trial, Corcept 06, will start in the fourth quarter of 2004 and will enroll approximately 440 patients at about 30 U.S. sites. These patients will be randomized to active dose groups (300, 600 and 1200 mg) or a placebo group, receiving once-daily dosing for a period of 7 days. The three dosing levels fulfill the FDA's request to supplement data on a range of potential doses beyond that provided by a 33-patient dose-ranging study completed in 2001. All patients in the study must be off any antidepressant and antipsychotic medication for at least 1 week before the 7-day treatment period and will receive antidepressant therapy starting on day 1 through day 56. As with Corcept 07, treatment with antipsychotic medications or electroconvulsive therapy will not be allowed at any time during this study. Initial results from the studies are expected in the first half of 2006. Corcept has completed 4 studies of mifepristone for the treatment of psychotic features of PMD. In January 2001, a dose-finding trial evaluating the efficacy, tolerability and dose-response showed that after 1 week of treatment, approximately two-thirds of the patients in the higher dose groups (600 and 1200 mg) experienced clinically meaningful reductions in psychosis, as measured by the BPRS. Subsequently, 2 double-blind, placebo-controlled safety and efficacy studies –the 02 study and the 03 study– were conducted in a total of 429 patients. The 02 study showed that mifepristone was well tolerated and that there were no discernible problems with drug interactions with commonly prescribed antipsychotic and antidepressant medications. The 03 study demonstrated with statistical significance that patients in the mifepristone group were more likely than patients in the placebo group to achieve a 50% reduction in the BPRS PSS at day 7, sustained to day 28. There was a statistically significant difference between the mifepristone and placebo groups on the BPRS PSS at day 56. In a fourth trial, an open-label study of the safety of retreatment in 28 patients with a favorable response to treatment in the 02 and 03 studies, it was indicated that patients tolerated their retreatment well (1).

A method has been claimed for the alleviation of psychotic symptoms resulting from the interferon alfa-based therapeutic intervention of hepatitis C viral infections. The claim embodies the administration of pharmaceutical compositions comprising a glucocorticoid receptor antagonist such as mifepristone, concurrently with an interferon alfa-derived compound such as recombinant human interferon alfa-2a and an additional antiviral agent such as ribavarin (2).

1. *SPA agreement for pivotal studies of Corlux*. DailyDrugNews.com (Daily Essentials) Sept 1, 2004.

2. Belanoff, J.K. (Corcept Therapeutics, Inc.) *Methods for treating psychosis associated with interferon-alpha therapy*. WO 0404653.

Original monograph – Drugs Fut 1984, 9(6): 755.

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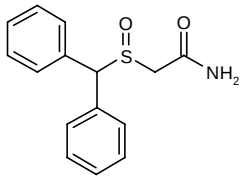
Belanoff, J.K., DeBattista, C. *Mifepristone in psychotic major depression*. 59th Annu Meet Soc Biol Psychiatry (April 29-May 1, New York) 2004, Abst 683.

Schatzberg, A.F., Flores, B., Solvason, H.B., Keller, J., Gumina, H.K. *Mifepristone in psychotic major depression*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR397.

Modafinil



Cephalon's modafinil (Provigil®) is the first in a new class of wake-promoting agents shown to promote wakefulness without causing generalized stimulation in the brain. It is believed to work selectively through the sleep/wake centers to activate the cortex of the brain. Modafinil is currently available for the treatment of excessive sleepiness associated with narcolepsy, obstructive sleep apnea and shift work sleep disorder in doses of 100 and 200 mg. It has been approved in more than 20 countries. Phase III clinical trials are under way with a new once-daily dosage form of modafinil to expand its indications to the treatment of ADHD in children and adolescents. Data from three 9-week, multicenter, double-blind, placebo-controlled trials show that the new once-daily dosage forms significantly improve symptoms of ADHD in children and adolescents. In the studies, 600 children and adolescents (aged 6-17 years) with ADHD were randomized to receive either placebo or an optimized new proprietary dosage form of modafinil. The primary endpoint was the teacher-completed school version of the ADHD Rating Scale IV. All of the modafinil-treated groups showed a highly statistically significant improvement in the primary endpoint compared to placebo. Modafinil was generally well tolerated, and the most common side effects were consistent with those observed in other studies. Full phase III data are expected to be presented over the next 12 months. Because children metabolize modafinil differently from adults, proprietary dosage strengths of 340 and 425 mg were identified for these studies. Cephalon now plans to accelerate the filing of its application with the FDA from the first quarter of 2005 to the fourth quarter of 2004. Modafinil for the treatment of children and adolescents with ADHD will be manufactured as smaller, film-coated tablets in unique dosage strengths (1-3).

1. *Approval for Provigil expanded label*. DailyDrugNews.com (Daily Essentials) Jan 29, 2004.

2. *Expanded Provigil label approved in U.K.*. DailyDrugNews.com (Daily Essentials) April 15, 2004.

3. *New modafinil formulation shows promise for children with ADHD*. DailyDrugNews.com (Daily Essentials) Aug 24, 2004.

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

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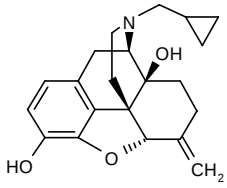
Duane, D. et al. *An open-label assessment of modafinil on attention and fatigue in adolescent and adult AD(H)D subjects*. Sleep 2004, 27(Suppl.): Abst 103.

Turner, D.C. et al. *Modafinil improves cognition and response inhibition in adult attention-deficit/hyperactivity disorder*. Biol Psychiatry 2004, 55(10): 1031.

Nalmefene



BioTie Therapies is developing the specific opioid receptor antagonist nalmefene for the treatment of impulse control disorders, including pathological gambling, and for the treatment of alcoholism and alcohol abuse, for which it is in phase II and III clinical trials, respectively. The company holds exclusive U.S. rights for the use of opioid receptor antagonists in impluse control disorders, as well as several other patents and intellectual property rights on nalmefene and its use in the U.S., Europe and Japan. BioTie recently entered an option agreement with Somaxon Pharmaceuticals for the North American rights to nalmefene for impluse control disorders (1, 2). Nalmefene has been available for a number of years as Revex™ for reversing opioid effects and for opioid overdose.

During 2003, BioTie completed a phase II clinical study of nalmefene in the treatment of impulse control disorders. The multicenter, placebo-controlled study of 200 patients in the U.S. focused on the safety and efficacy of daily oral administration of nalmefene in patients suffering from pathological gambling. A psychometric scale (PG-YBOCS, developed at Mount Sinai Hospital, New York) measuring gambling-related thoughts, urges and behavior was used for primary efficacy evaluation. Study results showed nalmefene to be effective in patients suffering from pathological gambling. After 4 months of treatment, mean scores on the PG-YBOCS scale were almost twice as high in patients who were on placebo when compared to the patients receiving nalmefene. The difference between the study groups was found to be statistically significant and no serious adverse effects related to the use of nalmefene were reported. The company has also completed the first phase III clinical studies of nalmefene tablets as a potential treatment for alcoholism. The multicenter, placebo-controlled studies, which took place in Finland and the U.K., focused on the safety and efficacy of nalmefene in the treatment of alcoholism and alcohol abuse without supporting psychosocial therapy in patients who considered themselves to be incapable of controlling their drinking, and included 400 patients in Finland and 150 patients in the U.K. Drug therapy in both studies lasted 28 weeks and patients were instructed to take the study drug before drinking alcohol. In both studies, patients receiving nalmefene felt

that the treatment was beneficial more often than the patients receiving placebo. Furthermore, no serious adverse effects related to the use of nalmefene were observed during the studies (3, 4).

1. *Interim report on BioTie Therapies Corp. January 1-June 30, 2004*. BioTie Therapies Press Release 2004, Aug 19.

2. *BioTie signs a cooperation and option agreement with Somaxon Pharmaceuticals Inc. for the North American rights to nalmefene for the treatment of impulse control disorders*. BioTie Therapies Press Release 2004, July 20.

3. *BioTie Therapies reports 2003 year-end R&D highlights*. BioTie Therapies Press Release 2004, Jan 28.

4. *BioTie Therapies reports Q1 R&D highlights*. BioTie Therapies Press Release 2004, April 23.

Original monograph – Drugs Fut 1984, 9(7): 518.

NBI-34041

Single- and multiple-dose phase I studies have been completed with NBI-34041, a compound from Neurocrine Biosciences' small-molecule CRF_1 receptor antagonist program partnered with GlaxoSmithKline. This compound is targeted for anxiety and depression.

ND-1251

Neuro3d's ND-1251 has entered phase I trials for the treatment of depression. The phase I trials aim to establish the safety, tolerability and pharmacokinetics of ND-1251, and to demonstrate activity in the brain. ND-1251 is an orally active phosphodiesterase type 4 (PDE4) inhibitor and the only PDE4 inhibitor in clinical trials for depression worldwide. In animal models, ND-1251 did not exhibit the typical side effects such as emesis and sedation that prevented the clinical use of previously developed PDE4 inhibitors. ND-1251 has a good safety profile, showing no prohibitive effects on respiratory, cardiac or central nervous system (CNS) parameters. In preclinical studies, ND-1251 has shown antidepressant, memory-enhancing and antiinflammatory effects, indicating that it may have potential application in other disorders, such as Alzheimer's disease, mild cognitive impairment, multiple sclerosis and certain respiratory diseases (1).

1. *ND-1251 enters phase I for depression*. DailyDrugNews.com (Daily Essentials) June 3, 2004.

NGD-96-3

Pfizer is currently evaluating data from phase I human clinical studies conducted to date assessing the safety, tolerability, pharmacokinetics and commercial profile of NGD-96-3, a lead candidate from Neurogen's collaboration with Pfizer to develop drugs for the treatment of insomnia. NGD-96-3 is a selective modulator of certain subtypes of the GABA receptor in the brain. Neurogen believes this approach may offer an improved side effect profile with regard to next-day hangover and sedative effects, memory and motor skill impairment, and alcohol interaction (1, 2).

1. *Neurogen reports Q3 R&D highlights*. Neurogen Corp. Press Release 2003, Nov 12.

2. *Neurogen Corp. reports Q1 R&D highlights*. Neurogen Corp. Press Release 2004, May 5.

NS-2359

NeuroSearch has completed enrollment in a phase II study of NS-2359, a triple monoamine reuptake inhibitor being developed under an alliance with GlaxoSmithKline, in ADHD. The study at 3 U.S. sites involves 126 adult ADHD patients, half of whom are treated with 0.5 mg of NS-2359 once a day and half of whom receive placebo. The primary aim of the study is to evaluate the efficacy of NS-2359 in the treatment of ADHD symptoms and secondarily to evaluate the tolerability of NS-2359. The study is expected to conclude in the autumn of 2004 (1-4).

The therapeutic potential of NS-2359 (4.25, 5.5 and 10 mg total dose during weeks 1, 2 and 3, respectively) was assessed in a brain monoamine transporter occupancy study in 6 healthy male subjects over a period of 3 weeks. Occupancy was evaluated by β-CIT single photon emission computerized tomography. Areas of the brain with abundant serotonin and dopamine levels revealed dose-associated decreases in radiolabeled β-CIT, indicative of NS-2359 occupancy. Results support the further use of this methodology in the clinical arena (5).

1. *NeuroSearch, GlaxoSmithKline collaborate on CNS drug development*. DailyDrugNews.com (Daily Essentials) Dec 29, 2003.

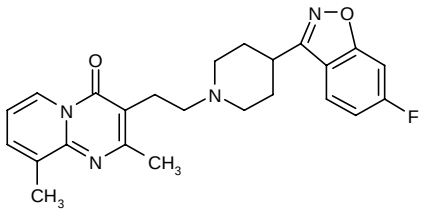
2. *NeuroSearch reports 2003 year-end R&D highlights*. NeuroSearch A/S Web Site 2004, March 10.

3. *Enrollment completed in ADHD phase II study of NS-2359*. DailyDrugNews.com (Daily Essentials) May 27, 2004.

4. *NeuroSearch A/S reports Q1 R&D highlights*. NeuroSearch A/S Web Site 2004, April 28.

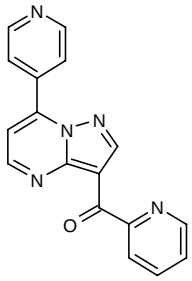
5. Seibyl, J.P., Tabamo, R., Jennings, D., Tamagnan, G., Marek, K. *NS2359 demonstrates dose-related dopamine and serotonin transporter occupancy in healthy male subjects with 123I beta CIT SPECT imaging*. Neurology 2004, 62(7, Suppl. 5): Abst P04.074.

Ocaperidone



Neuro3d is conducting phase II clinical studies with ocaperidone, an atypical antipsychotic agent licensed from Janssen. Ocaperidone is a mixed 5-HT_2/dopamine D2 receptor antagonist with potential in the treatment of schizophrenia. Janssen retains an option to repurchase rights to the compound following phase II trials.

Ocinaplon



The nonbenzodiazepine anxiolytic, ocinaplon (DOV-273547) appears to act by selectively modulating a specific subset of $GABA_A$ receptors thought to be involved in anxiety. DOV Pharmaceutical licensed the product from Wyeth in 1998 and is developing it for the treatment of generalized anxiety disorder (GAD).

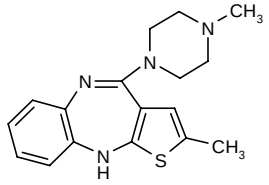
In June, the FDA agreed to lift its clinical hold on ocinaplon, subject to its review of a revised clinical trial protocol that includes more frequent liver enzyme testing. DOV intends to submit a revised protocol shortly and expects to commence the phase III pivotal trial in 2004. The start of the trial was placed on hold in October 2003 when the FDA requested additional safety information, which was subsequently submitted. Subject to further protocol review, the FDA will allow DOV to proceed with a 28-day, multicenter, randomized, placebo-controlled, double-blind, efficacy and safety trial in which up to 270 patients with GAD will receive a maximum daily dose of 60 mg of ocinaplon and 90 patients will receive placebo. Revisions to the protocol primarily include strengthened safety measures to more closely monitor potential abnormal liver enzyme elevations (1, 2).

1. *FDA lifts clinical hold on ocinaplon*. DailyDrugNews.com (Daily Essentials) June 30, 2004.

2. *DOV Pharmaceutical reports Q1 R&D highlights*. DOV Pharmaceutical Press Release 2004, May 10.

Original monograph - Drugs Fut 2003, 28(2): 118.

Olanzapine



Lilly's olanzapine (Zyprexa®) is indicated in the E.U., the U.S., Australia and Canada for the acute and long-term treatment of schizophrenia and for the short-term treatment of acute manic episodes associated with bipolar disorder. It was also recently approved in the U.S. and Europe for maintenance in the treatment of bipolar disorder. In Australia, olanzapine is also indicated for preventing the recurrence of manic, mixed or depressive episodes in bipolar I disorder and in the E.U. for the prevention of recurrence in patients with bipolar disorder whose manic episode has responded to olanzapine treatment. Early this year the company launched an injectable form of the drug in a number of European countries, the U.S., Australia and Canada for acutely agitated, noncooperative patients with schizophrenia or bipolar disorder in hospital emergency rooms or other crisis situations (1-5).

The combination of olanzapine and fluoxetine hydrochloride was also launched earlier this year in the U.S. by Lilly as Symbyax™ for the treatment of depressive episodes associated with bipolar disorder. This combination was approved in December 2003 and is the first FDA-approved medication for bipolar depression. One study showed how Symbyax™ helped to treat the symptoms of bipolar depression more effectively and at a significantly faster rate than placebo. In the pooled 8-week studies, patients in the Symbyax™ group experienced significantly greater improvement in depressive symptoms at weeks 1, 3, 4, 6 and 8 compared to patients taking placebo. The improvement was sustained throughout the 8 weeks of the study. Symbyax™ patients had no statistically greater risk of treatment-emergent mania than patients taking placebo (6-8).

An 8-week, randomized, double-blind, placebo-controlled trial enrolled 833 patients with bipolar I depression to compare treatment with olanzapine and the combination of olanzapine and fluoxetine. Olanzapine doses were between 5 and 20 mg/day and olanzapine/fluoxetine doses were 6/25, 6/50 or 12/50 mg/day. The active treatment groups showed significantly greater improvement than the placebo group, and the combination therapy was significantly superior to olanzapine monotherapy during

weeks 4-8. The incidence of mania was similar among groups (9).

According to a new report by NOP World Health based on internet interviews with 100 psychiatrists in February 2003, the olanzapine/fluoxetine combination is likely to take share primarily from the antidepressant market, particularly from SSRIs (selective serotonin reuptake inhibitors). Physicians expect a 10% net decrease in their antidepressant prescribing now that Symbyax™ is available. Symbyax™ had high awareness among psychiatrists even before its launch. The combination's perceived strengths include its synergistic dual effect and its efficacy for depression/bipolar depression and psychoses. Fixed dosing, weight gain and the risk of cycling depression patients into mania were identified as weak points. The report stated that Symbyax™ is unlikely to get first-line use, since physicians need to titrate the individual components to realize the maximum therapeutic benefit. Psychiatrists do not appear to view a combined product positively, preferring instead to prescribe individual agents (10).

The olanzapine/fluoxetine combination and olanzapine alone significantly reduced suicidal ideation compared with placebo in patients with bipolar I disorder, according to a *post hoc* analysis of data from a randomized, double-blind study. Changes in suicidal ideation were correlated with reductions in measures of sadness, inner tension, pessimism and depressed mood (11).

1. *Zyprexa approved for maintenance in bipolar disorder treatment*. DailyDrugNews.com (Daily Essentials) Jan 19, 2004.

2. *Roll-out of Zyprexa*. DailyDrugNews.com (Daily Essentials) Feb 5, 2004.

3. *EMEA warns over safety of olanzapine*. DailyDrugNews.com (Daily Essentials) March 17, 2004.

4. *Lilly reports 2003 year-end R&D highlights*. Eli Lilly and Co. Press Release 2004, Jan 29.

5. *Zyprexa Intramuscular approved for acute agitation*. DailyDrugNews.com (Daily Essentials) April 5, 2004.

6. *Symbyax approved for bipolar depressive episodes*. DailyDrugNews.com (Daily Essentials) Jan 7, 2004.

7. *First launch for Symbyax*. DailyDrugNews.com (Daily Essentials) Feb 2, 2004.

8. *Lilly reports 2003 year-end R&D highlights*. Eli Lilly and Co. Press Release 2004, Jan 29.

9. Tohen, M., Vieta, E., Calabrese, J. et al. *Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression*. Arch Gen Psychiatry 2003, 60(11): 1079.

10. *NOP World Heath report on Symbyax*. DailyDrugNews.com (Daily Essentials) March 4, 2004.

11. Houston, J.P., Degenhardt, E.L., Kaiser, C., Ahl, J., Baker, R.W., Tohen, M. *Suicidal ideation changes in depressed bipolar I patients treated with olanzapine/fluoxetine combination*. 59th Annu Meet Soc Biol Psychiatry (April 29-May 1, New York) 2004, Abst 826.

Original monograph – Drugs Fut 1994, 19(2): 114.

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Corya, S.A., Briggs, S.D., Case, M., Tohen, M.F. *Effect of olanzapine/fluoxetine on core mood symptoms in bipolar depression*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR784.

Corya, S.A., Briggs, S.D., Case, M., Tohen, M.F. *Olanzapine/fluoxetine for bipolar depression with comorbid anxiety symptoms*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR785.

Corya, S.A. et al. *Olanzapine/fluoxetine combination in treatment-resistant depression with current SSRI failure*. 12th Assoc Eur Psychiatr Congr (April 14-18, Geneva) 2004, Abst.

Corya, S.A., Keck, P.E. Jr., Thase, M.E., Dube, S., Briggs, S.D., Case, M., Tohen, M.F. *Olanzapine/fluoxetine combination: Rapid onset with low risk of mania*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst 66.

Houston, J., Kaiser, C., Ahmed, S., Berg, P., Roychowdhury, S. *A comparison of the reduction of agitation in schizophrenic patients treated with olanzapine vs. ziprasidone in a 28-week double-blind study*. Schizophr Res 2004, 67(1, Suppl. 1): Abst 320.

Houston, J.P., Degenhardt, E.L., Ahl, J., Easom, H.M., Kaiser, C., Kinon, B.J. *Suicidal ideation changes in depressed bipolar I patients with olanzapine-fluoxetine combination*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR707.

Houston, J.P., Hill, A., Kinon, B.J., Liu-Seifert, H., Hay, D.P. *Olanzapine orally-disintegrating tablets adherence: Agitation improvement in noncompliant schizophrenia patients*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR628.

Rothschild, A.J., Williamson, D.J., Tohen, M.F., Schatzberg, A., Andersen, S.W., Van Campen, L.E., Sanger, T.M., Tollefson, G.D. *A double-blind, randomized study of olanzapine and olanzapine/fluoxetine combination for major depression with psychotic features*. J Clin Psychopharmacol 2004, 24(4): 365.

Shi, L., Namjoshi, M.A., Swindle, R., Yu, X., Risser, R., Baker, R.W., Tohen, M. *Effects of olanzapine alone and olanzapine/fluoxetine combination on health-related quality of life in patients with bipolar depression: Secondary analyses of a double-blind, placebo-controlled, randomized clinical trial*. Clin Ther 2004, 26(1): 125.

Tohen, M. et al. *Clinical predictors of response to olanzapine or olanzapine/fluoxetine combination for bipolar depression*. 12th Assoc Eur Psychiatr Congr (April 14-18, Geneva) 2004, Abst.

Tohen, M. et al. *Long-term use of olanzapine or olanzapine/fluoxetine for bipolar depression*. 12th Assoc Eur Psychiatr Congr (April 14-18, Geneva) 2004, Abst.

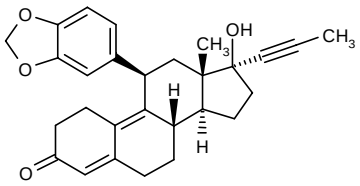
Tohen, M., Vieta, E., Calabrese, J.R., Ketter, T.A., Mitchell, P.B., Briggs, S.D., Case, M. *Clinical predictors of response to olanzapine or olanzapine/fluoxetine combination for bipolar depression*. 59th Annu Meet Soc Biol Psychiatry (April 29-May 1, New York) 2004, Abst 824.

Org-24448

Cortex's partner Organon announced its intention to continue development of the Ampakine® Org-24448 in a phase II trial as a potential treatment for schizophrenia. Organon has already obtained favorable results from phase I trials. The company hopes to advance the compound to phase III by the fourth quarter of 2004 (1).

1. *R&D highlights from the Rodman & Renshaw Techvest Healthcare Conference: Cortex*. DailyDrugNews.com (Daily Essentials) Nov 25, 2003.

Org-34517

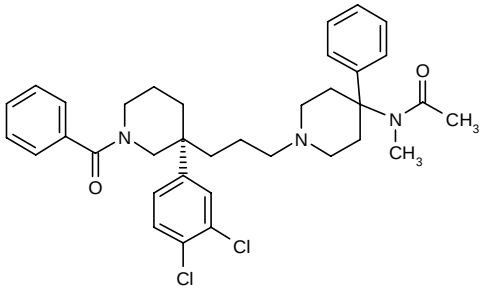


Org-34517, a selective glucocorticoid receptor antagonist, is a hypothalamic-pituitary-adrenal (HPA) modulator developed at Organon and currently in phase II evaluation for the treatment of depression.

Org-50081

Organon's 5-HT_2 blocker Org-50081 is in phase II trials for sleep disorders.

Osanetant

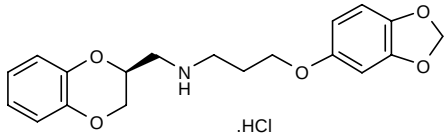


Sanofi-Aventis (the former Sanofi-Synthélabo) is conducting phase IIb clinical trials with its NK_3 receptor antagonist osanetant (SR-142801) for the treatment of schizophrenia.

Although osanetant 200 mg/day did not improve efficacy outcomes in a randomized, double-blind, placebo-controlled study in outpatients with panic disorder, the drug was well tolerated and did appear to affect endocrine stress responses. In the trial, 52 patients who had responded to a cholecystokinin tetrapeptide challenge were treated for 4 weeks and received a second cholecystokinin tetrapeptide challenge at the study's end. At least one adverse event was seen in 58.3% and 50% of patients in the osanetant and placebo groups, respectively. Improvements in panic symptoms were also similar between groups. Osanetant was associated with significant changes in plasma prolactin concentrations after the second cholecystokinin tetrapeptide challenge (1).

1. Kronenberg, G., Heuser, I. *Randomized, double-blind study of SR142801 (osanetant), a novel neurokinin-3 (NK3) receptor antagonist in panic disorder with pre- and posttreatment cholecystokinin tetrapeptide (CCK-4) challenges*. 59th Annu Meet Soc Biol Psychiatry (April 29-May 1, New York) 2004, Abst 443.

Osemozotan Hydrochloride

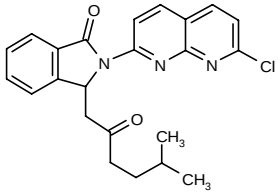


MediciNova has acquired a potential treatment for anxiety disorders from Mitsubishi Pharma. The compound, referred to by Mitsubishi as MKC-242 (osemozotan hydrochloride), has undergone phase II testing and will be designated as MN-305 at MediciNova. MediciNova obtains exclusive worldwide rights to MN-305, except for an ophthalmic solution and excluding Japan, China and other Southeast Asian countries. MN-305, a 5-HT_{1A} receptor agonist, is a potentially rapid-acting agent specific for anxiety disorders that appears to lack the sedation of benzodiazepines or the side effects of selective serotonin reuptake inhibitors (SSRIs) and norepinephrine reuptake inhibitors (SNRIs). A phase IIb trial is planned in patients with generalized anxiety disorder in late 2004 (1).

1. *MediciNova acquires anxiety compound from Mitsubishi*. DailyDrugNews.com (Daily Essentials) June 14, 2004.

Original monograph – Drugs Fut 1997, 22(3): 225.

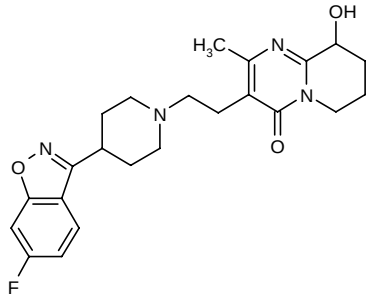
Pagoclone



A novel member of the cyclopyrrolone class, pagoclone (Indevus) acts as a GABA receptor modulator and is thought to increase the action of GABA, thereby reducing excess neuronal activity and alleviating the symptoms of anxiety and panic. Following reacquisition of the worldwide rights to the product from Pfizer, where it had reached phase III clinical trials, Indevus is currently pursuing new partnerships for the development of pagoclone. A phase III trial for the treatment of generalized anxiety disorder (GAD) is planned for 2004.

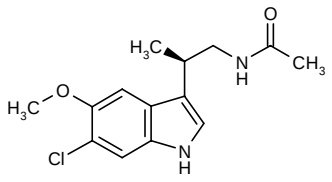
Original monograph – Drugs Fut 2001, 26(7): 651.

Paliperidone ER



Paliperidone ER, an extended-release formulation employing the OROS® drug delivery system that delivers the drug over 24 hours, is a late-stage development candidate for schizophrenia from Johnson & Johnson. Paliperidone is the active metabolite of the known atypical antipsychotic risperidone.

PD-6735



Phase 2 Discovery successfully completed a phase I trial of PD-6735 (LY-156735), a melatonin analogue acquired from Lilly under development for the treatment of sleep disorders. In the randomized, placebo-controlled trial, 40 healthy volunteers received PD-6735 as single oral doses of 20-100 mg. All doses of PD-6735 were well tolerated. Several subjects receiving PD-6735 reported feeling sleepy. The time to peak plasma concentration and the half-life of the drug were similar in all study groups and showed average values of 1.11 h and 1.04 h, respectively. The mean maximum plasma concentration increased with dose and ranged from 44.83 ng/ml with 20 mg to 410.3 ng/ml with 100 mg. No drug-treated patients showed consistent changes in body temperature, heart rate, blood pressure or other vital signs. The incidence of adverse events did not increase with dose, and the most common event was sleepiness (which in turn was considered to be a drug effect). One patient withdrew from the study after syncope following blood sampling. Based on these results, Phase 2 Discovery initiated phase II trials to further explore the dose-response effects of PD-6735 on sleep latency in patients with primary insomnia. In the randomized, placebo-controlled, crossover study, 40 patients with moderate primary insomnia received placebo and three doses of PD-6735. Patients experienced statistically significant improvements in sleep latency after each dose of PD-6735, *i.e.*, a 31% improvement after 20 mg, a 32% improvement after 50 mg and a 41% improvement after 100 mg. These doses also induced significant reductions in subjective time to fall asleep (13%, 15% and 16%, respectively, compared to placebo). All other polysomnographic sleep evaluation parameters and subjective evaluations were unaffected by PD-6735. The treatment was well tolerated and no evidence of psychomotor impairment was found during the morning after its administration Based on the positive results from this and 2 prior phase II clinical trials, Phase 2 Discovery plans to commence phase III development of PD-6735 by the end of 2004. PD-6735 is a high-affinity agonist at melatonin MT_1 and MT_2 receptors, with high selectivity for these over nonmelatonin receptors. It is being developed as a treatment for sleep and circadian rhythm disorders. Its novel mode of action, different from that of available benzodiazepine receptor ligands, is expected to produce minimal side effects and risk of abuse (1-4) (see Table VIII).

The FDA has granted orphan drug designation to PD-6735 for the treatment of circadian sleep disorders in totally blind individuals. Melatonin analogues taken consistently at an appropriate time of day are known to help resynchronize sleep/wake cycles in totally blind individuals who are unable to differentiate day from night (5).

1. *PD-6735 successfully completes phase I trial, enters phase II*. DailyDrugNews.com (Daily Essentials) May 10, 2004.

2. *Phase 2 Discovery receives positive results from phase II trial with PD-6735*. DailyDrugNews.com (Daily Essentials) May 25, 2004.

3. Mulchahey, J.J., Zemlan, F.P. *Melatonin agonist LY156735: Pharmacodynamics, pharmacokinetics and safety*. 33rd Annu Meet Soc Neurosci (Nov 8-12, New Orleans) 2003, Abst 617.7.

Table VIII: Clinical studies of PD-6735 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized	PD-6735, 20 mg o.d. (n=8) PD-6735, 35 mg o.d. (n=8) PD-6735, 50 mg o.d. (n=8) PD-6735, 100 mg o.d. (n=8) Placebo (n=8)	40	PD-6735 at doses up to 100 mg was well tolerated when administered to healthy volunteers	3
Insomnia	Randomized Double-blind Crossover	PD-6735, 20 mg PD-6735, 50 mg PD-6735, 100 mg Placebo	40	PD-6735 was safe and dose-dependently reduced sleep latency and subjective time to fall asleep in patients with primary insomnia	4

4. Mulchahey, J., Zemlan, F., Mayleben, D., Scharf, M., Rosenberg, R., Lankford, A. *Multicenter study of the safety and efficacy of the melatonin agonist LY156735 in primary insomnia*. 86th Annu Meet Endocr Soc (June 16-19, New Orleans) 2004, Abst P2-223.

5. *Orphan drug status for PD-6735*. DailyDrugNews.com (Daily Essentials) June 1, 2004.

PD-200390

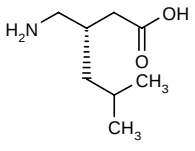
One of Pfizer's midstage development compounds, PD-200390 (phase II) represents a unique approach to insomnia, acting as a voltage-gated calcium channel $\alpha 2$-δ subunit modulator to reduce night awakenings.

PH-80/PH-94B

PH-80 is a vomeropherin discovered at Pherin Pharmaceuticals that is in phase II testing for use in premenstrual syndrome (PMS). The vomeropherins are substances that, following local intranasal administration, have a physiological effect as a consequence of their binding to receptors in the human vomeronasal organ (VNO), directly initiating neural impulses to the hypothalamus.

Another Pherin vomeropherin, PH-94B, is in phase II clinical trials for acute social phobia, or social anxiety disorder.

Pregabalin



The GABA analogue pregabalin (Lyrica®), developed by Pfizer, acts as a voltage-dependent calcium channel $\alpha 2$-δ subunit ligand and possesses analgesic, anticonvulsant and anxiolytic properties.

The European Commission approved pregabalin in July in all E.U. member states for the treatment of peripheral neuropathic pain and as an adjunctive therapy for partial seizures in patients with epilepsy. The company has also received approvable letters from the FDA for the treatment of neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia and as adjunctive therapy in the treatment of partial seizures in adults. However, a nonapprovable letter was issued for pregabalin for the treatment of generalized anxiety disorder (GAD). The E.U. approval was based on the submission of 10 clinical trials involving over 9,000 patients in 10 countries. In controlled trials involving patients with neuropathic pain associated with shingles and diabetic neuropathy, significant pain relief was seen as early as week 1 and lasted throughout the studies. On average, up to 47% of patients treated with pregabalin experienced a 50% reduction in pain, as measured by a standard rating scale. Pregabalin-treated patients also experienced a significant reduction in pain-related sleep interference across the studies. In trials involving epilepsy patients who continued to experience partial seizures despite treatment, adding pregabalin to their standard treatment provided up to 51% seizure reduction in patients within the first week of treatment (1-7).

Pharmacokinetic studies of pregabalin in healthy volunteers and patients with renal disease revealed little potential for drug-drug interactions as there was no hepatic metabolism and excretion was primarily renal. Renal function was therefore a determinant of pregabalin clearance. Dose-proportional exposure was seen after single and multiple doses, and pregabalin pharmacokinetics were linear and predictable (8).

No drug interaction was seen in a pharmacokinetic study in which 16 female subjects were given an oral contraceptive (OrthoNovum®) and concomitant pregabalin. OrthoNovum® was given once daily during the first 21 days of 3 menstrual cycles, and pregabalin 200 mg was given every 8 h during the first 21 days of the third cycle. Coadministration of the agents was well tolerated and did not hinder the prevention of ovulation (9, 10). These results and those from some of the studies described below are summarized in Table IX.

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

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Open	Norethindrone/ethinylestradiol, p.o. o.d. 21x/28 d on d 1-21, 29-49 & 57-77 + Pregabalin, 200 mg t.i.d. on d 57-77	16	Oral contraceptives such as norethindrone/ethinylestradiol were well tolerated when administered alone or combined with pregabalin. Pregabalin had no effects on the pharmacokinetics or the inhibition of ovulation induced by norethindrone/ ethinylestradiol in healthy female volunteers	10
Healthy volunteers	Randomized Double-blind Multicenter	Pregabalin, 200 mg t.i.d. x 14 wks (n=30) Placebo (n=16)	46	Pregabalin had no adverse effects on spermatogenesis or sex steroid hormone metabolism in healthy male volunteers	11
Anxiety, generalized	Pooled/meta-analysis	Pregabaline x 4-6 wks Lorazepam, 6 mg/d x 4-6 wks Alprazolam, 1.5 mg/d x 4-6 wks Venlafaxine, 75 mg/d x 4-6 wks Placebo		Pregabalin demonstrated efficacy similar to lorazepam, aprazolam and venlafaxine in patients with generalized anxiety disorder	14
Anxiety, generalized	Randomized Double-blind Pooled/meta-analysis	Pregabalin, 200 mg x 46 wks (n=78) Pregabalin, 300 mg x 46 wks (n=91) Pregabalin, 400-450 mg x 46 wks (n=364) Pregabalin, 600 mg x 46 wks (n=335) Placebo (n=414)	1282	Pregabalin was more effective than placebo in improving the Hamilton Rating Scale for Anxiety scores by at least 30% after just 1 week of treatment in patients with generalized anxiety disorder. No dose-dependent effect was found	15
Anxiety, generalized	Randomized Double-blind Pooled/meta-analysis	Pregabalin, 150-600 mg/d x 8 [max.] wks		In patients with generalized anxiety disorder, a reduction in anxiety scores was directly associated with exposure to pregabalin	16

Two clinical trials evaluated the effects of pregabalin therapy on the reproductive function of males and on the effectiveness of oral contraceptives in females. A total of 46 healthy male volunteers aged 18-55 years were included in a multicenter, double-blind trial and received placebo or pregabalin (200 mg t.i.d.) for 14 weeks. No significant differences were found in the percentage of sperm with normal motility, sperm concentration and semen volume between the study groups at the end of the treatment period and after an 8-week washout phase. No evidence suggesting that pregabalin may have adverse effects on male reproductive function (*e.g.,* changes in the metabolism and binding of sex hormones) was found (11).

The effect of pregabalin on cognitive and psychomotor responses was evaluated in 24 healthy volunteers in a randomized, double-blind, placebo-controlled, 3-way crossover study. Alprazolam-treated subjects were included as positive controls. Although both drugs were associated with minor alterations in CNS function, pregabalin had no significant deleterious effect on cognitive and psychomotor abilities compared with alprazolam (12).

The pharmacokinetics of pregabalin in healthy subjects were determined in 5 studies in which single and multiple doses of 1-300 mg were investigated. The drug was rapidly absorbed and demonstrated linear, dose-proportional pharmacokinetics after both single- and multiple-dose administration. Food did not affect the extent of pregabalin absorption. Repeated administration led to the achievement of steady state after 1-2 days. The primary means of elimination was renal clearance (13).

In four 4-6-week, placebo-controlled studies, pregabalin demonstrated efficacy similar to lorazepam (6 mg/day), alprazolam (1.5 mg/day) and venlafaxine (75 mg/day) in patients with GAD (14).

Analysis of data from phase II/III studies in patients with GAD (n=1,282) showed that pregabalin responder rates were significantly higher than those for placebo in the following subgroups: males, the elderly, those with severe anxiety, those with subsyndromic depression, those with severe somatic symptoms and those with severe insomnia (15).

A recent analysis evaluated the relationship between response and drug exposure to pregabalin in patients with GAD who were included in 6 placebo-controlled clinical trials and received pregabalin (150-600 mg/day) for up to 8 weeks. The analysis of the Hamilton Anxiety scale (HAMA) scores of the patients suggested that improvements were correlated with drug exposure and that the time course of the response was associated with the placebo effect (16).

1. *Pfizer reports Q3 R&D highlights*. Pfizer Press Release 2003, Oct 22.

2. *Positive European opinion for Lyrica*. DailyDrugNews.com (Daily Essentials) March 30, 2004.

3. *Pfizer reports 2003 year-end R&D highlights*. Pfizer Press Release 2004, Jan 22.

4. *FDA response for Lyrica*. DailyDrugNews.com (Daily Essentials) Sept 7, 2004.

5. *Pfizer reports Q1 R&D highlights*. Pfizer Press Release 2004, April 20.

6. *Lyrica approved in E.U.* DailyDrugNews.com (Daily Essentials) July 12, 2004.

7. *Pfizer reports Q2 R&D highlights*. Pfizer Press Release 2004, July 21.

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PRX-00023

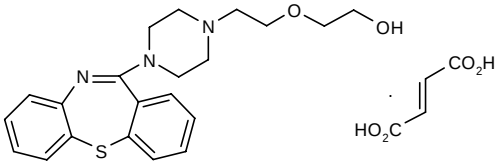
Predix Pharmaceuticals has successfully completed single- and multiple-dose phase I trials of PRX-00023, a proprietary dual-acting 5-HT_{1A} receptor agonist/σ_1 antagonist intended to treat anxiety, depression, ADHD and other neuropsychiatric disorders. Based on the safety and surrogate marker data obtained in these studies, the company plans to begin phase II trials for the treatment of generalized anxiety and depression. The studies were performed in healthy volunteers who received single doses of 10-60 mg or these doses once daily for 28 days. The superior selectivity, metabolic and safety profiles compared to currently used 5-HT_{1A} agonists emerging from preclinical studies were confirmed in these early clinical studies. The drug was very well tolerated, the half-life was consistent with once-daily dosing, and robust induction of surrogate markers of 5-HT_{1A}-agonist activity was seen at doses of 30-60 mg. Following these trials, conducted in partnership with RRD International, Predix intends to outlicense the series of compounds (1-3).

1. *Predix and RRD team up to expedite development of PRX-00023*. DailyDrugNews.com (Daily Essentials) Nov 17, 2003.

2. *PRX-00023 enters clinical testing*. DailyDrugNews.com (Daily Essentials) Feb 16, 2004.

3. *Predix Pharmaceuticals announces successful completion of phase I single and multiple dose studies for its serotonin 1A agonist for anxiety and depression*. Predix Pharmaceuticals Press Release 2004, Sept 14.

Quetiapine Fumarate



The FDA has approved AstraZeneca's psychotropic drug quetiapine fumarate (Seroquel™) as short-term monotherapy and adjunct therapy for the treatment of mania associated with bipolar disorder. The approval was based on a bipolar disorder clinical program in more than 1,000 patients in 28 countries, in which quetiapine was effective across a broad range of symptoms and well tolerated in treating manic episodes as both monotherapy and in combination with lithium or divalproex. Quetiapine was also fast acting, with improvements in patients' manic symptoms seen within the first week of treatment. Quetiapine was first approved for the treatment of schizophrenia in 1997. It also received approval in 2003 under the European mutual recognition procedure to extend its use to treat mania associated with bipolar disorder, and has additionally been approved in the U.K. and other markets for this indication (1, 2).

More recently, the FDA approved additional efficacy labeling information based on 12-week data for quetiapine, making it the first medication in its class to include in its label monotherapy safety and efficacy data for acute manic episodes associated with bipolar disorder extending beyond 3 weeks. The new label information is supported by data from two 12-week, double-blind, randomized, placebo-controlled trials assessing the safety and efficacy of quetiapine monotherapy for the treatment of manic episodes in a large cohort of adults with bipolar I disorder. A total of 599 patients experiencing a manic episode were assigned to receive quetiapine (200-800 mg/day), placebo or an active control (lithium or haloperidol). The primary endpoint was change from baseline YMRS (Young Mania Rate Scales) total score at day 21 of treatment (week 3), and secondary endpoints included change from baseline YMRS total score at day 84 (week 12). The combined analysis of the trials showed that after 12 weeks, 66.8% of quetiapine-treated patients achieved a response (defined as a 50% or greater decrease from baseline YMRS score) *versus* 40.0% of the placebo group. In addition, 65.4% of quetiapine patients achieved remission (defined as YMRS of 12 or less) *versus* 35.9% of those treated with placebo. Improvement in manic symptoms based on change in YMRS score in patients treated with quetiapine was significantly greater than in placebo-treated patients as early as day 4 onwards (3).

1. *Seroquel receives FDA approval for bipolar-associated mania*. DailyDrugNews.com (Daily Essentials) Jan 16, 2004.

2. *AstraZeneca reports 2003 year-end R&D highlights*. AstraZeneca Press Release 2004, Jan 29.

3. *New 12-week labeling information approved for Seroquel*. DailyDrugNews.com (Daily Essentials) July 27, 2004.

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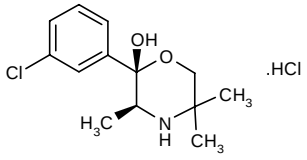
R-1204/R-673

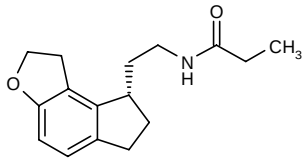
Two new G-protein-coupled receptor (GPCR) modulators from Roche –R-1204 and R-673– are in clinical studies for use in anxiety and depression. R-1204 is in phase I clinical evaluation and R-673, an NK_1 receptor antagonist, is in phase II trials.

Radafaxine Hydrochloride



Radafaxine hydrochloride (GW-353162, 353162; GlaxoSmithKline) is a dual norepinephrine/dopamine reuptake inhibitor currently undergoing phase II clinical testing for the treatment of depression, as well as for the treatment of restless legs syndrome (RLS) and neuropathic pain.

Ramelteon



In an overview of the status of its new compounds in development, Takeda highlighted 9 proprietary compounds at various stages of development. The first, ramelteon (TAK-375), a melatonin MT_1/MT_2 receptor agonist, is being studied as a treatment for primary insomnia. The compound is in phase II development in Japan for this indication and in phase III in the U.S. and E.U. Additionally, ramelteon is being studied for the treatment of circadian rhythm sleep disorders in the U.S., where it is in phase II development (1).

The effects of multiple doses of ramelteon on the single-dose pharmacokinetic profile of midazolam, an important marker drug to determine CYP34A-inhibitory and -inducing properties of a test drug, were evaluated in 28 healthy adults. Subjects received a single 10-mg dose of midazolam, followed by a 2-day washout period and oral ramelteon 32 mg once daily for 9 days. Results showed that ramelteon did not affect the AUC or C_{max} of midazolam or its metabolite 1-hydroxymidazolam (2).

In a similar study, healthy subjects received ramelteon 16 mg on day 1, fluoxetine 40 mg on days 3-12 and ramelteon 16 mg and fluoxetine 40 mg on day 13. Results showed that multiple doses of fluoxetine led to significant increases in the systemic exposure of ramelteon (approximately 50%), as well as its active metabolite. However, due to its high interindividual variability and wide therapeutic window, dose adjustment of ramelteon was not required when given with fluoxetine (3, 4).

The effects of fluconazole and ketoconazole on the pharmacokinetics of ramelteon were also evaluated in 2 studies in 28 healthy adults, who were randomized into two 4-day dosing periods separated by a 14-day washout period. In these studies, subjects received either a single dose of ramelteon of 16 mg on day 4 or fluconazole 400 mg on day 1 and 200 mg once daily on days 2-4 plus ramelteon 16 mg on day 4, or a single dose of ramelteon 16 mg on day 4 or ketoconazole 200 mg twice daily on days 1-4 plus ramelteon 16 mg on day 4. Results showed that both fluconazole and ketoconazole significantly increased the systemic exposure of ramelteon, although the findings were not considered clinically relevant due to ramelteon's high variability and flat dose/effect relationship (5).

The effects of dextromethorphan on the systemic exposure of ramelteon, and *vice versa*, were evaluated in

36 healthy adults who were randomized to 1 of 6 treatment sequences consisting of three 1-day dosing periods separated by two 7-day washout periods. Subjects received ramelteon 32 mg/day alone, dextromethorphan 30 mg/day alone or combination of both drugs. Results showed that neither drug affected the systemic exposure or peak concentration of the other, indicating that the drugs can be coadministered without dose adjustments (6).

A 2-period crossover study assessed the drug interaction between ramelteon and theophylline in 36 healthy volunteers. Subjects underwent two 10-day dosing periods separated by a 5-day washout period: 18 subjects received ramelteon 32 mg/day or a combination of ramelteon and theophylline 300 mg/day, and 18 subjects received theophylline 300 mg/day or the combination. Results showed that multiple doses of ramelteon had no effect on the pharmacokinetics of theophylline. Theophylline, however, increased the systemic exposure of ramelteon (by 40%), although not its active metabolite. This increased exposure did not result in the need for dose adjustment when these drugs were taken together due to ramelteon's high variability and wide therapeutic window (7).

A phase I open-label study assessed the absorption, metabolism and excretion of a single oral dose of ramelteon 16 mg in 6 healthy male subjects. Ramelteon was rapidly absorbed and eliminated. Negligible excretion of ramelteon in the urine and low serum levels of the drug suggested that it undergoes extensive first-pass metabolism. All adverse events associated with treatment, with the exception of a moderate headache, were considered mild (8).

A phase I study evaluated the bioavailability of orally administered ramelteon in 18 healthy male volunteers who were randomized to receive a single oral 16-mg dose of ramelteon or an i.v. infusion of 2 mg. The absolute bioavailability following oral dosing was low and variable, ranging from 0.5% to 12% for individual subjects. Both i.v. and oral dosing were associated with similar adverse events, the majority of which included somnolence and fatigue (9).

1. *Takeda Chemical Industries reports Q3 R&D highlights*. Takeda Chemical Industries Web Site 2004, Jan 27.

2. Tolbert, D., Cao, C., Zhao, Z., Sainati, S.M., Karim, A. *The effect of multiple doses of ramelteon (TAK-375) on the single-dose pharmacokinetic profile of midazolam in healthy adult subjects*. Sleep 2004, 27(Suppl.): Abst 104.

3. Karim, A., Tolbert, D., Cao, C., Sainati, S.M. *Effects of multiple doses of fluoxetine on the systemic exposure of a single dose of ramelteon (TAK-375) in healthy adults*. Sleep 2004, 27(Suppl.): Abst 105.

4. Karim, A., Tolbert, D., Cao, C. *Effects of fluoxetine on the systemic exposure of ramelteon (TAK-375)*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR844.

5. Tolbert, D., Cao, C., Zhao, Z., Sainati, S.M., Karim, A. *Effects of fluconazole and ketoconazole on the pharmacokinetics of ramelteon (TAK-375) in normal healthy male and female subjects*. Sleep 2004, 27(Suppl.): Abst 119.

6. Karim, A., Cao, C., Zhao, Z., Johnson, J., Sainati, S.M., Tolbert, D. *Study to assess drug interaction between ramelteon (TAK-375) and dextromethorphan in healthy adults*. Sleep 2004, 27(Suppl.): Abst 111.

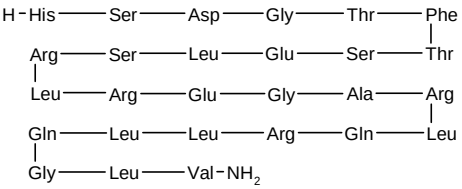
7. Karim, A., Johnson, J., Cao, C., Zhao, Z., Sainati, S.M., Tolbert, D. *Two-period crossover study to assess the drug interaction between ramelteon (TAK-375) and theophylline in healthy adults*. Sleep 2004, 27(Suppl.): Abst 106.

8. Hibberd, M., Stevenson, S.J. *A phase-I open-label study of the absorption, metabolism, and excretion of (14C)-ramelteon (TAK-375) following a single oral dose in healthy male subjects*. Sleep 2004, 27(Suppl.): Abst 121.

9. Hibberd, M., Stevenson, S.J., Amakye, D.D. *A phase I study to investigate the absolute bioavailability of a single oral dose of ramelteon (TAK-375) in healthy male subjects*. Sleep 2004, 27(Suppl.): Abst 120.

Original monograph – Drugs Fut 2003, 28(10): 950.

RG-1068



Repligen's phase III trial of RG-1068 (synthetic human secretin) for autism failed to meet the dual primary endpoints of improvements in social interaction as measured by the Autism Diagnostic Observation Schedule (ADOS) and the parental Clinical Global Impression of Change (CGIC). There was a higher placebo effect in this study than observed in a phase II study, and neither endpoint showed a significant treatment effect in the entire group. A prospectively defined subset analysis of the higher functioning patients showed a statistically significant improvement for RG-1068 *versus* placebo on the ADOS, but not on the CGIC. The double-blind, placebo-controlled trial, conducted at 15 U.S. sites, evaluated 132 children aged 2 years 8 months to 4 years 11 months with moderate to severe symptoms of autism. Each patient received 6 injections of RG-1068 or placebo over 18 weeks and was evaluated for improvements in the symptoms of autism from baseline. Future development in autism will be dependent on an evaluation of the phase III data and discussions with the FDA. However, Repligen plans to continue its efforts in schizophrenia. A double-blind, placebo-controlled phase II trial of RG-1068 is under way in refractory schizophrenia. The trial will evaluate multiple doses of RG-1068 for the treatment of deficits in social cognition in schizophrenia,

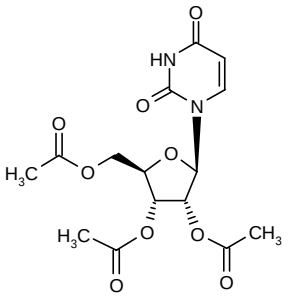
including social interaction and communication deficits. An open-label phase I/II study of RG-1068 in obsessive-compulsive disorder is also scheduled for the second half of 2004 (1-3).

1. *Phase II trial evaluates RG-1068 for refractory schizophrenia*. DailyDrugNews.com (Daily Essentials) Dec 16, 2003.

2. *Phase III trial of RG-1068 in autism fails to meet primary endpoints*. DailyDrugNews.com (Daily Essentials) Jan 8, 2004.

3. *Repligen reports Q3 R&D highlights*. Repligen Corp. Press Release 2004, Feb 11.

RG-2133

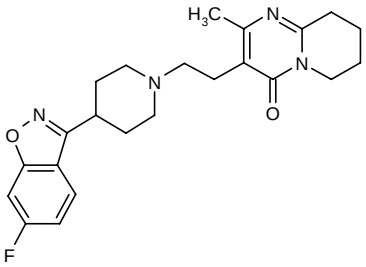


Repligen has reported results of an open-label phase I trial of RG-2133, a prodrug of uridine. The trial assessed the impact of daily oral administration of escalating doses of RG-2133 over a 6-week period on the depressive symptoms associated with either bipolar disorder or unipolar major depression. The study, conducted by investigators at McLean Hospital, involved 19 patients. Results showed that RG-2133 was safe and did not induce mania, while there was early evidence of a clinical effect of the drug. A placebo-controlled phase II trial is scheduled for late 2004 to extend the results in bipolar disorder. Researchers at McLean previously demonstrated that uridine, which is synthesized by mitochondria, is active in a well-validated animal model of depression. Recent reports indicate that certain genes that encode for mitochondrial proteins are significantly downregulated in the brains of bipolar patients, suggesting that the symptoms of bipolar disorder may be linked to dysregulation of energy metabolism of the brain (1, 2).

1. *Repligen reports Q3 R&D highlights*. Repligen Corp. Press Release 2004, Feb 11.

2. *Phase I results for RG-2133 in bipolar disorder and depression*. DailyDrugNews.com (Daily Essentials) June 14, 2004.

Risperidone



Risperidone (Risperdal®) has been marketed in the U.S. by Janssen (Johnson & Johnson) since 1994 for the treatment of schizophrenia and is approved in more than 100 countries for this indication. A long-acting injection formulation, Risperdal® Consta™, is also available for the treatment of schizophrenia in the U.S. and a number of other countries. Risperidone has been marketed outside the U.S. for several years for the adjunctive treatment of acute mania associated with bipolar disorder, and late last year the compound was approved by the FDA for use as monotherapy or in combination with lithium or valproate for the short-term treatment of acute manic or mixed episodes associated with bipolar I disorder (1-4). Additionally, risperidone is under regulatory review at the FDA for the treatment of autism in children.

The efficacy of risperidone in treating acute manic or mixed episodes of bipolar disorder was established in 3 studies –2 testing the medication as monotherapy and 1 in combination with lithium or valproate. In all studies, patients who received risperidone experienced significantly greater symptom improvement than those in the control groups. In a 3-week, placebo-controlled study in 246 adult patients with bipolar I disorder who were in an acute manic episode with or without psychotic symptoms, risperidone was superior to placebo in reducing the Young Mania Rating Scale (YMRS) total score. Risperidone-treated patients experienced on average an 11-point reduction on the YMRS compared to a 5-point reduction in placebo patients. A 50% or greater reduction in total manic symptom scores was seen in 43% of risperidone patients *versus* 24% of placebo patients. In a second, similarly designed monotherapy trial in 286 bipolar I patients with manic or mixed episodes, risperidone patients had a total reduction of 22.7 points on the YMRS *versus* a 10.5-point reduction in placebo patients. At endpoint, 73% of patients receiving risperidone compared to 36% of patients given placebo achieved clinical response. Finally, in a 3-week, placebo-controlled combination therapy study in 148 adults with bipolar I disorder experiencing a manic or mixed episode, with or without psychotic features, and with or without rapid cycling between moods, risperidone patients experienced on average a total 14.3-point reduction in the YMRS *versus* an 8.2-point reduction among placebo patients. A 50% or greater improvement in manic symptoms was seen in

57% of patients treated with risperidone *versus* 38% of patients who received placebo (4).

1. *U.S. launch of Risperdal Consta*. DailyDrugNews.com (Daily Essentials) Dec 9, 2003.

2. *Johnson & Johnson reports Q3 R&D highlights*. Johnson & Johnson Press Release 2003, Oct 14.

3. *Alkermes reports Q3 R&D highlights*. Alkermes Press Release 2004, Feb 11.

4. *Risperdal approved for bipolar mania*. DailyDrugNews.com (Daily Essentials) Dec 10, 2003.

Original monograph – Drugs Fut 1988, 13(12): 1052.

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Bowden, C.L. et al. *Risperidone in combination with mood stabilizers: A 10-week continuation phase study in bipolar I disorder*. J Clin Psychiatry 2004, 65(5): 707.

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Martin, A. et al. *Weight and leptin changes among risperidone-treated youths with autism: 6-Month prospective data*. Am J Psychiatry 2004, 161(6): 1125.

Pavuluri, M.N. *Open label prospective trial of risperidone in combination with lithium or divalproex sodium in pediatric mania*. 59th Annu Meet Soc Biol Psychiatry (April 29-May 1, New York) 2004, Abst 113.

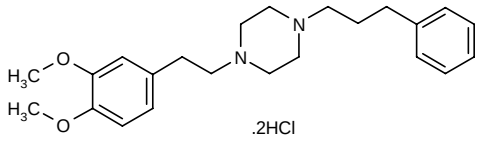
Rupnow, M., Canuso, C.M., Hirschfeld, R.M.A. *Improvement in global functioning with risperidone treatment in bipolar patients*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR806.

Rupnow, M., Canuso, C.M., Janicak, P.G. *Improvement in global functioning in bipolar patients: Results from an open-label risperidone study*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR517.

Vieta, E. et al. *Acute and continuation risperidone monotherapy in mania*. Hum Psychopharmacol 2004, 19(1): 41.

Yatham, L.N. et al. *Risperidone plus lithium versus risperidone plus valproate in acute and continuation treatment of mania*. Int Clin Psychopharmacol 2004, 19(2): 103.

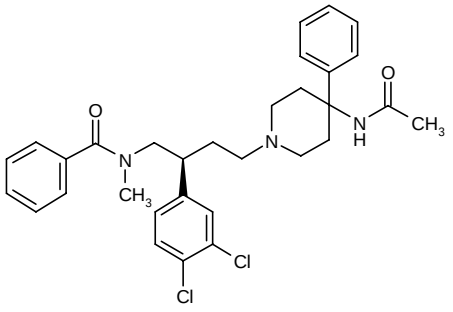
SA-4503 (AGY-94806)



AGY Therapeutics has obtained from M's Science the exclusive rights to develop and commercialize the σ receptor agonist SA-4503 (designated AGY-94806 at AGY and Msc1 at M's Science) for initial investigation for enhancing functional recovery after stroke. AGY plans to begin a phase II trial of AGY-94806 for enhanced functional recovery from stroke by early 2005. A phase I study evaluating the compound as a potential treatment for depression produced promising safety data, while preclinical data have demonstrated poststroke recovery activity. Because AGY-94806 is delivered orally and works by stimulating functional recovery of surviving tissue to compensate for damaged areas, it can potentially be given at any time after a stroke, representing an entirely new approach for the treatment of stroke patients. The agreement also grants AGY development and commercialization rights to AGY-94806 for traumatic brain injury and spinal cord injury, as well as rights to license additional central nervous system indications. M's Science retains other rights and intends to continue developing AGY-94806 for other central nervous system indications. The two companies will coordinate worldwide development of a broad range of indications (1). SA-4503 was originally developed at Santen, which granted M's Science an exclusive worldwide development and marketing license.

1. *AGY Therapeutics licenses sigma receptor agonist compound from M's Science*. DailyDrugNews.com (Daily Essentials) July 22, 2004.

Saredutant

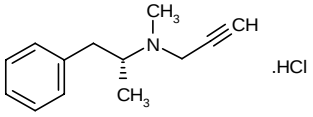


Positive phase IIb trial results were obtained during 2003 for saredutant (SR-48968), a tachykinin NK_2 receptor antagonist, in the treatment of major depressive disorder, which may enable the drug to advance to phase III this year, making it the second antidepressant from Sanofi-Aventis (formerly Sanofi-Synthélabo) to enter phase III after SR-58611 (see below) (1). Saredutant is also in development for the treatment of irritable bowel syndrome.

1. *Sanofi-Synthélabo reports 2003 year-end R&D highlights*. Sanofi-Synthélabo Press Release 2004, Feb 16.

Original monograph – Drugs Fut 1995, 20(7): 701.

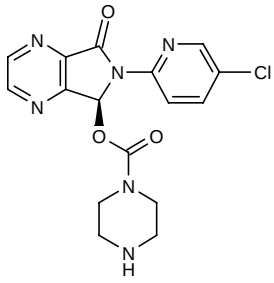
Selegiline, Transdermal



Somerset Pharmaceuticals, a joint venture between Mylan Laboratories and Watson, has received an approvable letter from the FDA for Emsam™ (selegiline), its transdermal therapy for the treatment of major depressive disorder. The FDA has requested phase IV postmarketing pharmacokinetic and safety studies, as well as additional pharmacology/toxicology studies. Labeling will also have to address tyramine dietary restrictions while taking Emsam™. The approvable letter indicates that Somerset has submitted sufficient data to support efficacy in the acute and maintenance treatment of major depressive disorder. Somerset will continue its discussions to outlicense Emsam™ (1).

1. *Approvable letter for Emsam*. DailyDrugNews.com (Daily Essentials) Feb 4, 2004.

SEP-174559/SEP-226332



SEP-174559

Following the completion of a phase I study of SEP-174559 in 2002, Sepracor intends to conduct phase II proof-of-concept studies in anxiety, muscle spasms and spasticity this year. SEP-174559, a zopiclone metabolite, is a $GABA_A$ antagonist with a selectivity profile that favors the $\alpha 2$ subunit of the GABA receptor. Preclinical data suggest that SEP-174559 may provide a rapid onset of action with less sedation than currently marketed agents for acute anxiety (1-3).

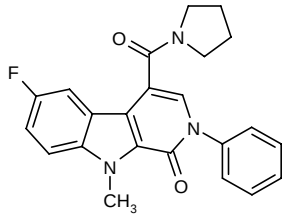
The company also plans to conduct a phase II proof-of-concept study with SEP-226332 (SEP-0226332), a $5\text{-}HT_3$ receptor antagonist, for the treatment of sleep apnea (1-3).

1. *Progress and plans for Sepracor pipeline*. DailyDrugNews.com (Daily Essentials) Jan 14, 2004.

2. *Sepracor reports 2003 year-end R&D highlights*. Sepracor Press Release 2004, Jan 22.

3. *Sepracor reports Q1 R&D highlights*. Sepracor Press Release 2004, April 27.

SL-65.1498



The $GABA_A$ receptor agonist SL-65.1498 is being tested in phase IIb trials at Sanofi-Aventis for its use in the treatment of anxiety and muscle contractions.

SLI-381/SPD-465

Shire's SLI-381 (Adderall XR®, mixed salts of a single-entity amphetamine) was recently approved by the

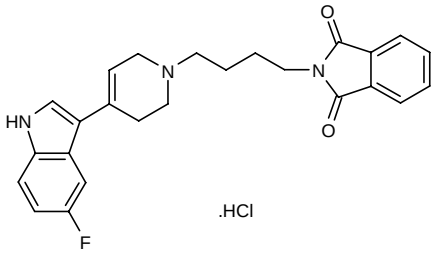
FDA as a once-daily treatment for ADHD in adults. Adderall XR® was approved in November 2001 for use in children. Studies have shown that up to 65% of children with ADHD continue to exhibit symptoms into adulthood. The FDA has also confirmed to Shire that new 40-, 50- and 60-mg dose strengths of Adderall XR® will require additional clinical data for approval. Adderall XR® is a once-daily extended-release product available in doses of 5, 10, 15, 20, 25 and 30 mg. The Adderall XR® capsule contains two types of drug-containing beads designed to give a double-pulsed delivery of amphetamines, which prolongs the release of amphetamine compared to the conventional Adderall® immediate-release formulation (1, 2).

The company is also developing another extended-release formulation of Adderall®, known as SPD-465, for ADHD, currently in phase II and expected to enter phase III evaluation in the near future.

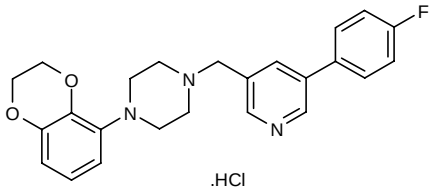
1. *Shire reports 2003 year-end R&D highlights*. Shire Pharmaceuticals Press Release 2004, March 11.

2. *Adderall XR receives FDA approval for use in adults*. DailyDrugNews.com (Daily Essentials) Aug 17, 2004.

SLV-310/SLV-313/SLV-314



SLV-310



SLV-313

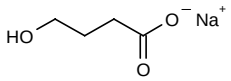
In addition to the putative antipsychotic agent bifeprunox (see above), Solvay and Wyeth have agreed to jointly develop and commercialize other neuroscience compounds developed at Solvay, including SLV-310 and SLV-313, currently in phase II for schizophrenia, and SLV-314, which is in phase I as another potential new treatment for schizophrenia. These compounds may also have potential in bipolar disorder and other CNS conditions (1). SLV-310 and SLV-314 combine potent dopamine D2 receptor antagonism and 5-HT reuptake inhibition, and SLV-313 is a dual-acting dopamine D2 receptor antagonist and 5-HT_{1A} receptor agonist.

1. *Solvay and Wyeth sign bifeprunox development and marketing agreement*. DailyDrugNews.com (Daily Essentials) April 6, 2004.

SM-13496

A serotonin/dopamine antagonist (SDA)-type atypical antipsychotic agent, SM-13496, is being tested by Sumitomo Pharmaceuticals in phase II clinical trials in Japan and the U.S. for the treatment of schizophrenia.

Sodium Oxybate



Sodium oxybate (Xyrem®), a form of γ-hydroxybutyrate, a naturally occurring metabolite of GABA in the CNS, is currently the only FDA-approved medication for the treatment of cataplexy associated with narcolepsy. Based on the promising clinical data obtained, Orphan Medical now plans to submit a supplemental NDA with the FDA before the end of the year, seeking additional approval for its use in the treatment of excessive daytime sleepiness (EDS) associated with narcolepsy. The company is also conducting a trial to evaluate the drug as a treatment for fibromyalgia syndrome. Celltech Pharmaceuticals of the Celltech Group, recently acquired by UCB Pharma, was granted the European rights to the product and submitted the drug for approval under the E.U.'s centralized procedure in April of this year for the treatment of the symptoms of narcolepsy, for which it has been granted orphan drug status. The company is also developing an extended-release once-nightly formulation (1).

Orphan Medical has received strong positive data across both primary and secondary endpoints from the double-blind, randomized, placebo-controlled phase IIIb clinical trial, designated SXB-15, of sodium oxybate for the treatment of EDS in conjunction with stimulants. The trial evaluated improvement in the EDS of patients with narcolepsy when a dose of 4.5, 6.0 or 9.0 g of sodium oxybate oral solution was added to the unchanged stimulant therapy. This trial assessed 228 patients over an 8-week treatment period at 40 sleep centers in North America and 8 in Europe. Primary endpoints of the trial were changes in the Epworth Sleepiness Score (ESS) and Clinical Global Impression of Change (CGIC). Secondary endpoints included changes in the Maintenance of Wakefulness Test (MWT), polysomnography recordings, as well as reductions in inadvertent daytime naps, nighttime awakenings and the number of cat-

aplexy attacks. The trial reaffirmed the efficacy of sodium oxybate at the 6.0- and 9.0-g doses in reducing cataplexy attacks, which had been demonstrated in prior trials. Moreover, the lowest dose in this trial showed efficacy in reducing cataplexy over the 8-week treatment period. The trial also assessed the daytime functioning of narcolepsy patients using the Functional Outcomes Sleep Questionnaire (FOSQ). No new or unexpected adverse events were seen in the SXB-15 trial and the safety profile was similar to that of previous trials and commercial use. The most common adverse events included nausea, dizziness and vomiting, and were dose-related. Disorientation at night, sleepwalking and enuresis occurred infrequently, but more often at the highest dose. Results are expected from the second phase IIIb trial, EXCEEDS, in the third quarter of 2004. The primary endpoint in this trial is the reduction in EDS measured using the objective MWT when sodium oxybate is used with or without modafinil (Provigil®) (2-4).

Researchers conducted a chart review of patients with narcolepsy-cataplexy who had been treated with sodium oxybate. Over a 1-year period, 16 patients were treated for a mean duration of 5 months. Results showed that sodium oxybate was moderately effective in these patients, with a refreshing feeling upon awakening, reduction in episodes of cataplexy and improved daytime alertness observed in approximately half of the subjects. Obstructive sleep apnea, depression and anxiety were observed in subjects who did not respond to treatment. The most common adverse events were constipation and insomnia (5).

An open-label study assessed the efficacy of sodium oxybate on the common symptoms of narcolepsy. Results showed that sodium oxybate also improves daytime sleepiness, hypnogogic hallucinations, sleep paralysis and nocturnal sleep. However, despite education about the benefits and potential adverse effects of the treatment, 28% of patients declined to use sodium oxybate, indicating that patient education and follow-up may be necessary to improve compliance (6).

A postmarketing surveillance study collected 12 months of safety data for commercially available sodium oxybate using a solicited, postapproval surveillance program. Evaluation of the data showed a lower incidence of adverse events than that reported in clinical trials. Doctors are recommended to complete a postmarketing surveillance program form for every patient at 3 and 6 months of therapy (7).

A 12-month evaluation of sodium oxybate was carried out after its approval in October 2002, as part of the Risk Management Program to minimize potential diversion or abuse of the product. Results from this analysis indicated that there were no cases of actual diversion through this program, although there were 13 cases of potential diversion (8).

1. *EMEA accepts Xyrem MAA for review*. DailyDrugNews.com (Daily Essentials) April 5, 2004.

2. *Enrollment completed in phase IIIb Xyrem study*. DailyDrugNews.com (Daily Essentials) March 29, 2004.

3. *Positive data reported from phase IIIb Xyrem study*. DailyDrugNews.com (Daily Essentials) May 25, 2004.

4. *Completion of clinical portion of EXCEEDS phase IIIb study of Xyrem*. DailyDrugNews.com (Daily Essentials) July 30, 2004.

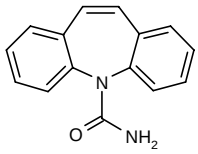
5. Kotagal, S., Silber, M.H., Krahn, L.E., Boeve, B.F., Altchuler, S.I., Moore, W.R. *Response of narcolepsy-cataplexy to treatment with sodium oxybate*. Sleep 2004, 27(Suppl.): Abst 533.

6. Buechler, R.D., Carwile, S.T., Miller, P.P., Husain, A.M. *Use of sodium oxybate in veterans with narcolepsy*. Sleep 2004, 27(Suppl.): Abst 552.

7. Ritzinger, C.A., Nelson, J.A. *Sodium oxybate post-marketing evaluation program: Results from the first 12 months*. Sleep 2004, 27(Suppl.): Abst 554.

8. Stahl, P.J., Ritzinger, C.A., Nelson, J.A., Smith, D. *12-Month evaluation of a novel risk management program for responsible distribution of sodium oxybate treatment for cataplexy*. Sleep 2004, 27(Suppl.): Abst 555.

SPD-417



Shire's SPD-417 (Bipotrol®), for which an NDA was submitted in February 2004, will be the first carbamazepine-based product for bipolar disorder in the U.S. The product, a sodium channel blocker, utilizes a unique dose titration and presentation (1).

1. *Shire reports 2003 year-end R&D highlights*. Shire Pharmaceuticals Press Release 2004, March 11.

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Ginsberg, L.D. *Efficacy of extended-release carbamazepine for pediatric bipolar patients*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR376.

Ketter, T.A. et al. *A 6-month, multicenter, open-label evaluation of beaded, extended-release carbamazepine capsule monotherapy in bipolar disorder patients with manic or mixed episodes*. J Clin Psychiatry 2004, 65(5): 668.

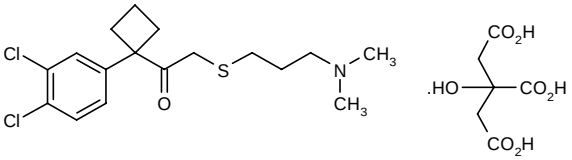
Ketter, T.A., Kalali, A.H., Weisler, R.H. *Three-based extended-release carbamazepine capsule (SPD417) continuation: Maintenance therapy in bipolar disorder*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst 42.

Weisler, R.H. et al. *A multicenter, randomized, double-blind, placebo-controlled trial of extended-release carbamazepine capsules as monotherapy for bipolar disorder patients with manic or mixed episodes*. J Clin Psychiatry 2004, 65(4): 478.

Weisler, R.H., Kalali, A.H., Ketter, T.A. *Carbamazepine extended release treatment of manic and mixed symptoms*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR359.

Weisler, R.H., Keck, P.E. Jr., Swann, A.C. *Treatment of manic and mixed patients with carbamazepine extended release*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR360.

SPD-473



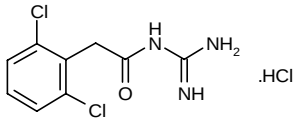
The monoamine reuptake inhibitor SPD-473 (BTS-74398), one of Shire's nonscheduled, nonstimulant ADHD projects, had progressed to a phase II proof-of-concept study but did not meet the company's criteria for continued development in this disorder (1-3).

1. *Shire reports 2003 year-end R&D highlights*. Shire Pharmaceuticals Press Release 2004, March 11.

2. *Shire Pharmaceuticals reports Q1 R&D highlights*. Shire Pharmaceuticals Press Release 2004, April 29.

3. *Strong second quarter results: 2004 proving to be a very good year*. Shire Pharmaceuticals Press Release 2004, July 29.

SPD-503



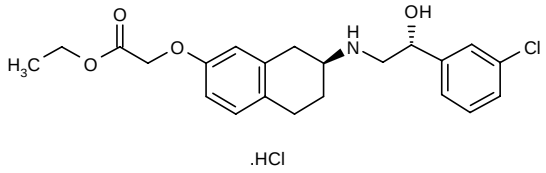
SPD-503 is a reformulated version of the antihypertensive agent guanfacine that is in phase III clinical evaluation at Shire as a nonstimulant, nonscheduled compound for the treatment of ADHD in children and adolescents, with additional potential for use in adults. Key data are now available from the first phase III pediatric study of SPD-503 in ADHD. This 8-week study demonstrated highly statistically significant differences from placebo in ADHD-RS, Conner's Parent and Teacher Rating Scales and Clinician's Global Impression (1, 2).

1. *Shire reports 2003 year-end R&D highlights*. Shire Pharmaceuticals Press Release 2004, March 11.

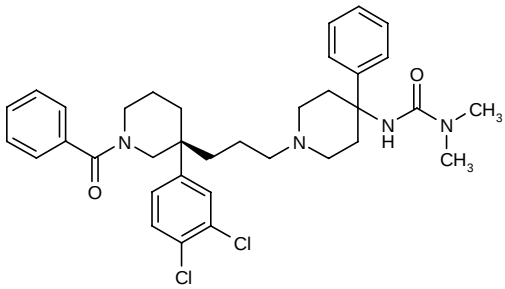
2. *Shire Pharmaceuticals reports Q1 R&D highlights*. Shire Pharmaceuticals Press Release 2004, April 29.

Original monograph – Drugs Fut 1976, 1(4): 167.

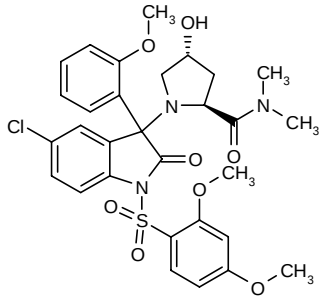
SR-58611/SSR-125047/ SSR-146977/SSR-149415/ SSR-181507



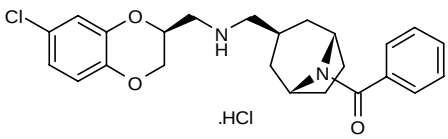
SR-58611



SSR-146977



SSR-149415



SSR-181507

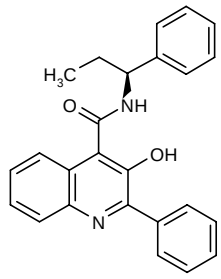
SR-58611, a β_3-adrenoceptor agonist, is in phase III clinical evaluation at Sanofi-Aventis as a potential new antidepressant (1).

Sanofi-Aventis also has several earlier stage products in the pipeline for psychiatric disorders. SSR-125047 is a

central σ-receptor ligand presently in phase I clinical development for schizophrenia. The tachykinin NK_3 receptor antagonist SSR-146977 continues in phase I clinical trials for depression and schizophrenia. SSR-149415 is a selective, orally active, nonpeptide vasopressin V_{1a} receptor antagonist undergoing early clinical testing for its potential as an anxiolytic and antidepressant. Finally, the dual dopamine D2/5-HT_{2A} receptor antagonist SSR-181507 is in phase I clinical trials as a potential new therapy for schizophrenia.

1. *Sanofi-Synthélabo reports 2003 year-end R&D highlights*. Sanofi-Synthélabo Press Release 2004, Feb 16.

Talnetant

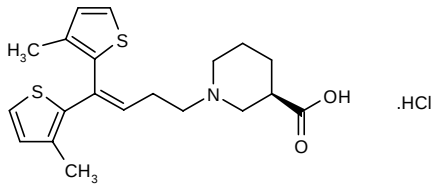


The tachykinin NK_3 receptor antagonist talnetant (SB-223412) is undergoing phase II trials at GlaxoSmithKline as a potential new therapy for schizophrenia, as well as irritable bowel syndrome (IBS) and overactive bladder.

TC-5231

TC-5231, a compound from Targacept that selectively targets neuronal nicotinic acetylcholine receptors (NNRs), is undergoing phase II development for the treatment of ADHD.

Tiagabine Hydrochloride



Cephalon plans to initiate a phase III program in the second half of 2004 evaluating tiagabine hydrochloride (Gabitril®) for the treatment of anxiety disorders. The decision to move forward follows positive results from a phase II study in adults with generalized anxiety disorder (GAD). The 8-week, multicenter, double-blind, randomized, placebo-controlled study with a flexible-dose design included 260 adult patients with GAD and was designed to determine the dose, time of onset and magnitude of its effect in GAD. Statistically significant improvements were seen at several time points, including week 1, in patients receiving tiagabine *versus* those receiving placebo, as measured by the Hamilton Anxiety Scale (HAMA). Pilot studies were previously completed in 2003 for the treatment of anxiety. Tiagabine is a selective GABA reuptake inhibitor (SGRI), thus increasing the levels of synaptic GABA. It is currently indicated as adjunctive therapy in adults and children 12 years and older with partial seizures (1). The product is also in phase II trials for insomnia and neuropathic pain.

1. *Gabitril to enter phase III trial in second half of 2004*. DailyDrugNews.com (Daily Essentials) April 15, 2004.

Original monograph – Drugs Fut 1993, 18(12): 1129.

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Randazzo, A.C. et al. *The effects of tiagabine on the sleep of older adults*. Sleep 2004, 27(Suppl.): Abst 117.

Roth, T., Walsh, J.K. *Sleep-consolidating effects of tiagabine in patients with primary insomnia*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR839.

Schwartz, T.L., Khan, A. *Tiagabine as SSRI augmentation therapy in patients with generalized anxiety disorder: An open-label study*. 24th CINP Congr (June 20-24, Paris) 2004, Abst P01.236.

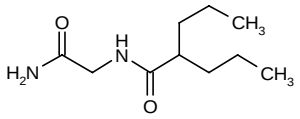
Walsh, J.K. et al. *Sleep-consolidating effects of tiagabine in patients with primary insomnia*. Sleep 2004, 27(Suppl.): Abst 575.

Weisler, R. et al. *The effect of tiagabine on sleep in patients with posttraumatic stress disorder*. Sleep 2004, 27(Suppl.): Abst 772.

Worthington, J.J. III., Kinrys, G.D., Simon, N.M., Reese, H., Melo, M., Fischmann, D., Pollack, M.H. *Tiagabine augmentation for treatment-refractory anxiety disorders*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR403.

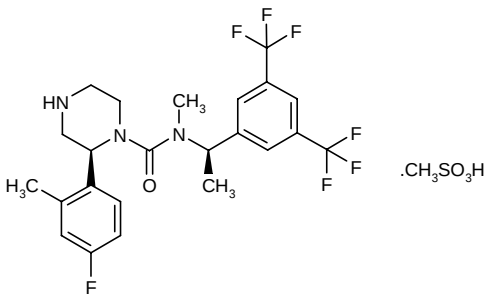
Zwanzger, P., Romeo, E., Eser, D., Michele, F.D., Baghai, T.C., Schule, C., Ella, R., Pasini, A., Moller, H., Rupprecht, R. *Panic reduction after treatment with the GABA-reuptake blocker tiagabine associated with decrease in 3alpha-reduced neurosteroid concentrations*. 24th CINP Congr (June 20-24, Paris) 2004, Abst P02.246.

Valrocemide



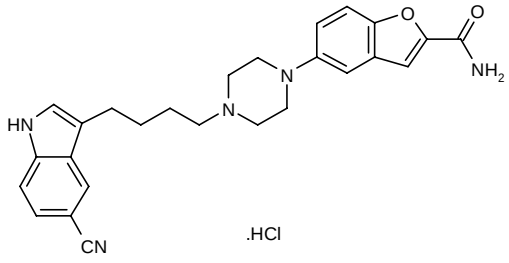
Acorda, in collaboration with originator Teva, is developing the valproic acid derivative valrocemide (TVP-1901) for several indications, including epilepsy, bipolar disorder and neuropathic pain. Phase II clinical studies have been conducted in patients with refractory epilepsy, evaluating add-on therapy, with indications of clinical efficacy, and phase II trials in bipolar disorder are also planned.

Vestipitant Mesilate



The tachykinin NK_1 receptor antagonist vestipitant mesilate (GW-597599, 597599) is in development at GlaxoSmithKline for several different disorders. Phase II trials are in progress for depression and anxiety, as well as functional dyspepsia and chemotherapy-induced nausea and vomiting.

Vilazodone Hydrochloride



Genaissance Pharmaceuticals just acquired an exclusive worldwide license to develop and market a potential new antidepressant from Merck KGaA. The compound, vilazodone hydrochloride, is a small-molecule selective serotonin reuptake inhibitor (SSRI) and $5\text{-}HT_{1A}$ receptor partial agonist which has demonstrated efficacy and a favorable side effect profile in phase II clinical trials in over 1,000 patients. Genaissance plans to commence phase II trials including pharmacogenomic characterization of the patients during the first half of 2005, with the aim of identifying genetic markers to be used to select a population of patients who will respond to the drug (1).

1. *Merck KGaA grants vilazodone rights to Genaissance*. DailyDrugNews.com (Daily Essentials) Sept 28, 2004.

VPI-013 (OPC-14523)

Vela Pharmaceuticals (VelaPharm) has licensed from Otsuka a phase II molecule to treat depression. VelaPharm, which has designated the molecule VPI-013 (formerly OPC-14523), will have exclusive marketing rights in the U.S. and Europe, while Otuska will retain marketing rights in Japan and several other countries. VPI-013's unique mechanism combines $5\text{-}HT_{1A}$ receptor agonism, 5-HT reuptake inhibition and σ receptor agonism. VPI-013 may be effective in treating depression with fewer side effects than SSRIs or dual reuptake inhibitors (SNRIs). The FDA later cleared the company's IND for VPI-013 and VelaPharm began enrollment in a double-blind, placebo-controlled study that will assess the efficacy and safety of VPI-013 in patients with major depressive disorder (1, 2).

1. *Vela licenses late-stage molecule for depression from Otsuka*. DailyDrugNews.com (Daily Essentials) April 13, 2004.

2. *FDA clears IND for study of VPI-013 in patients with major depressive disorder*. DailyDrugNews.com (Daily Essentials) July 2, 2004.

XBD-173

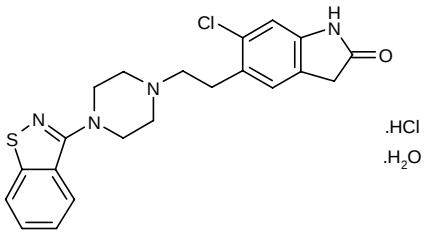
The potential new anxiolytic XBD-173 is presently in phase I clinical testing at Novartis.

YKP-10A/YKP-1358

YKP-10A (R-228060) is a potential antidepressant with a structure distinct from the tricyclic antidepressants and the serotonin reuptake inhibitors. Synthesized at SK Bio-Pharmaceuticals and developed up to phase II, it was subsequently licensed to the Johnson & Johnson subsidiary Janssen for further development.

SK Bio-Pharmaceuticals is also developing a compound for schizophrenia –YKP-1358– which is in phase I clinical trials in the U.S.

Ziprasidone Hydrochloride



The FDA has approved the use of Pfizer's atypical antipsychotic ziprasidone hydrochloride (Geodon®) for the treatment of acute bipolar mania, including manic and mixed episodes. In 2 randomized, double-blind trials involving 416 hospitalized patients with acute bipolar mania, ziprasidone-treated patients showed greater improvement compared with placebo from day 2 through the end of the trial (day 21). No significant adverse effects on weight gain or lipids were seen. Patients treated with ziprasidone were started on a dose of 80 mg/day with an increase permitted to 160 mg/day on day 2 in the first study and on day 3 in the second study. Ziprasidone, a serotonin/dopamine antagonist (SDA) approved in the U.S. in 2001 for the treatment of schizophrenia, is licensed in 67 countries. An oral suspension was recently approved in 10 E.U. member states (1-4).

Pfizer has also submitted a supplemental NDA requesting changes in the product information for ziprasidone that would help physicians to utilize the drug in their patients with schizophrenia. The sNDA requests inclusion in the product label of ziprasidone's lack of adverse effects on blood lipids and glycemic control; greater initial dosing flexibility; and modification of language regarding the drug's effect on heart rhythm. The recommended changes for ziprasidone are in part a response to an FDA request in September 2003 sent to all manufacturers of atypical antipsychotics regarding language about the metabolic effects of these products being included in the product information. Ziprasidone's effects on metabolic parameters were recently reported. After 6 weeks of ziprasidone therapy, schizophrenic patients switched from olanzapine or risperidone showed decreases in body weight and blood levels of cholesterol and triglycerides compared to baseline (5, 6).

1. *Pfizer reports Q3 R&D highlights*. Pfizer Press Release 2003, Oct 22.

2. *Pfizer reports 2003 year-end R&D highlights*. Pfizer Press Release 2004, Jan 22.

3. *Pfizer reports Q2 R&D highlights*. Pfizer Press Release 2004, July 21.

4. *Geodon approved for acute bipolar mania*. DailyDrugNews.com (Daily Essentials) Aug 25, 2004.

5. *Pfizer submits sNDA for Geodon product label changes*. DailyDrugNews.com (Daily Essentials) Jan 30, 2004.

6. *Pfizer reports Q1 R&D highlights*. Pfizer Press Release 2004, April 20.

Original monograph – Drugs Fut 1994, 19(6): 560.

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Potkin, S.G., Keck, P.E., Giller, E., Ice, K., Warrington, L., Dunn, J. *Ziprasidone in bipolar mania: Efficacy across patient subgroups*. 59th Annu Meet Soc Biol Psychiatry (April 29-May 1, New York) 2004, Abst 300.

Potkin, S.G., Keck, P.E. Jr., Giller, E. Jr., Ice, K., Warrington, L., Dunn, J. *Ziprasidone in bipolar mania: Efficacy across patient subgroups*. 157th Annu Meet Am Psychiatr Assoc (May 1-6, New York) 2004, Abst NR777.

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