Drugs of the Future 2001, 26(9): 889-918

CCC: 0377-8282/2001

Information Update

Volume 1-25, Number 9

Estimated developmental phase for this month's updated products:

Phase I

CS-682 (oncolytic; Sankyo)

Phase II

AMP-579 (treatment of acute myocardial infarction; Aventis Pharma)
Annamycin (oncolytic; Aronex)
Bryostatin 1 (oncolytic; Cancer Res. Campaign, Natl. Cancer Inst.)
Devazepide (treatment of neurogenic pain; ML Laboratories, Panos Therapeutics)
MCI-154 (treatment of heart failure; Mitsubishi-Tokyo Pharm.)
MKC-733 (treatment of GERD; Mitsubishi-Tokyo Pharm., Janssen)
Natalizumab (treatment of IBD, treatment of multiple sclerosis; Athena Neurosciences, Biogen)
OM-89 (immunomodulator; OM Pharma)

Phase III

9-Aminocamptothecin (oncolytic; Natl. Cancer Inst.)
Aripiprazole (antipsychotic; Otsuka, Bristol-Myers Squibb)
Brain-derived neurotrophic factor (treatment of ALS, Regeneron, Amgen, Sumitomo)
Duloxetine (antidepressant, treatment of urinary incontinence; Lilly, Shionogi)
Edatrexate (oncolytic; SRI)
Leteprinim potassium (antiparkinsonian, treatment of Alzheimer's disease; NeoTherapeutics)
Palonosetron hydrochloride (antiemetic; Roche Bioscience, Helsinn, MGI)
Ranolazine (antianginal, treatment of heart failure; Roche Bioscience, CV Therapeutics, Innovex)
Rasagiline mesilate (antiparkinsonian, treatment of Alzheimer's disease; Teva, Lundbeck)
Sitafloxacin hydrate (quinolone antibacterial; Daiichi Pharm., Beijing General)

Preregistered

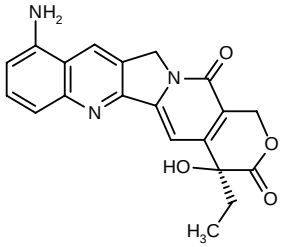
Cetuximab (oncolytic; ImClone, Merck KGaA, Bristol-Myers Squibb)
Norastemizole (treatment of allergic rhinitis; Sepracor)
Pegvisomant (treatment of acromegaly; Genentech, Sensus)

Launched/Year

Atorvastatin calcium (hypolipidemic; Pfizer)/1997
Buprenorphine hydrochloride (opioid analgesic, treatment of opioid dependency; Reckitt & Colman, Titan, DrugAbuse Sciences, Grünenthal)/1982
Etanercept (antiarthritic, antipsoriatic; Immunex, Wyeth-Ayerst)/1998
Fluvastatin sodium (hypolipidemic; Novartis, Tanabe Seiyaku, AstraZeneca)/1994
Imiquimod (treatment of genital warts, oncolytic; 3M Pharm., Daiichi Pharm.)/1997
Memantine hydrochloride (treatment of Alzheimer's disease, treatment of diabetic neuropathy; Merz, Neurobiological Technologies, Lundbeck, Forest)/1982
Rosiglitazone maleate (antidiabetic; GlaxoSmithKline, Bristol-Myers Squibb)/1999
Triptorelin (treatment of prostate cancer; Debio RP)/1986
Venlafaxine hydrochloride (antidepressant, anxiolytic, treatment of diabetic neuropathy; Wyeth-Ayerst, Almirall Prodesfarma)/1994

9-Aminocamptothecin *Oncolytic*

EN: 184764



$C_{20}H_{17}N_3O_4$ **Natl. Cancer Inst. (US)**

A study was conducted to correlate the antitumor activity of 9-aminocamptothecin (9-AC) in a panel of pediatric solid tumor xenografts with the systemic exposure of the drug. The minimum effective dose resulting in regression of advanced tumors was determined for i.v. and oral 9-AC administration for 1, 2 or 3 weeks and for 1 or 3 cycles. The association of drug lactone plasma concentration-time profiles with the lowest dose achieving a response revealed that the systemic exposure necessary for 9-AC antitumor efficacy is more than that achievable in patients (1).

1. Kirstein, M.N., Houghton, P.J., Cheshire, P.J., Richmond, L.B., Smith, A.K., Hanna, S.K., Stewart, C.F. *Relation between 9-aminocamptothecin systemic exposure and tumor response in human solid tumor xenografts.* Clin Cancer Res 2001, 7(2): 358.

Original monograph - Drugs Fut 1996, 21: 881.

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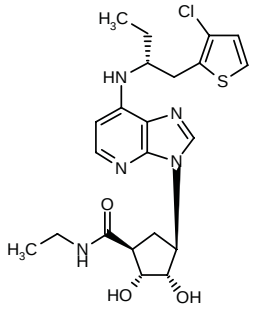
Howe, J.N. et al. *Plasma protein binding interactions of clinical and experimental camptothecins monitored directly by fluorescence spectroscopic methods.* Proc Amer Assoc Cancer Res 2001, 42: Abst 2060.

Kehrer, D.F.S. et al. *Modulation of camptothecin analogs in the treatment of cancer: A review.* Anti-Cancer Drugs 2001, 12(2): 89.

Li, M.L. et al. *Pharmacological determinants of 9-aminocamptothecin cytotoxicity.* Clin Cancer Res 2001, 7(1): 168.

AMP-579 *Treatment of Acute Myocardial Infarction*
RPR-100579

EN: 267815



$C_{22}H_{28}ClN_5O_3S$ **Aventis Pharma**

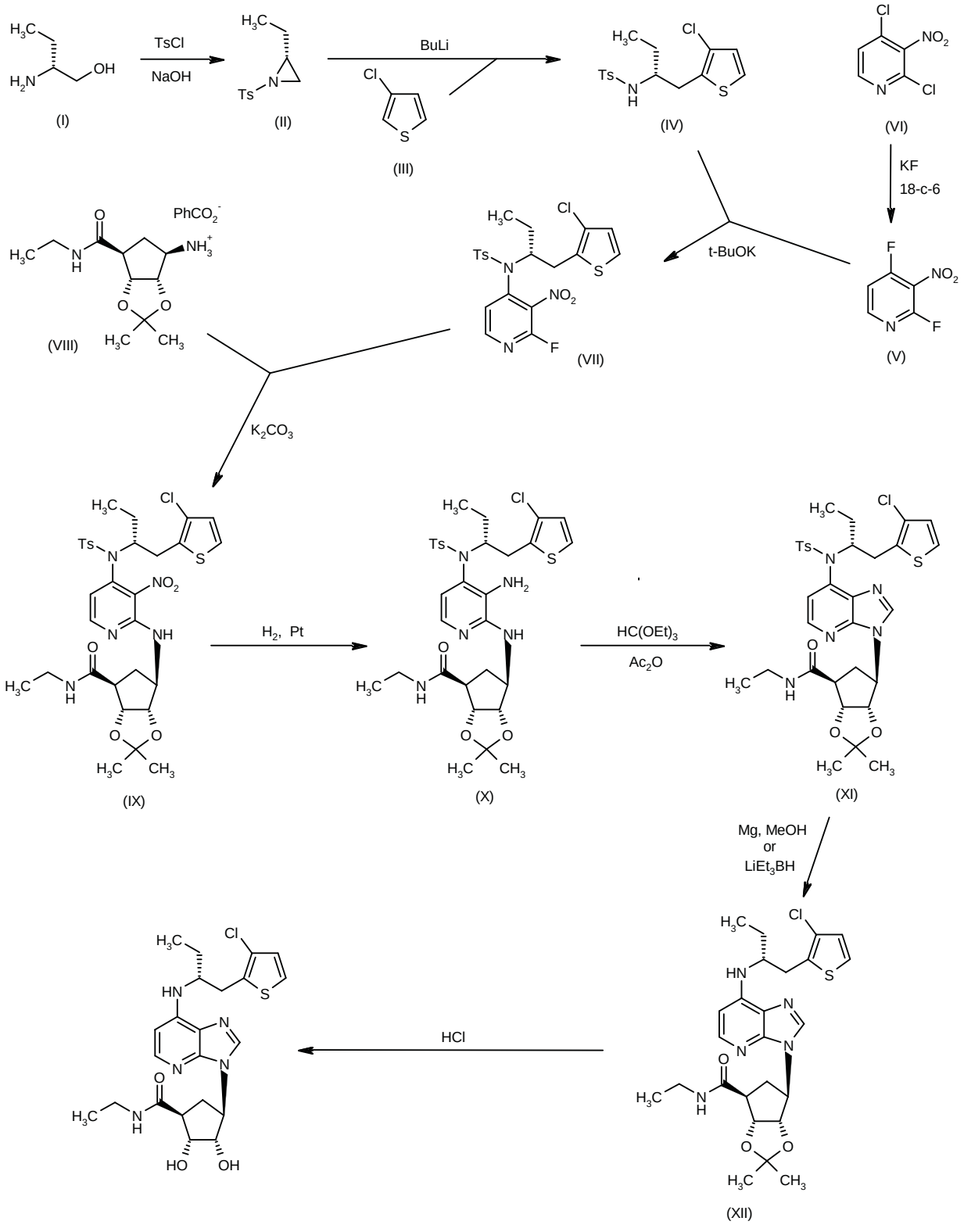
An efficient synthesis of AMP-579 has been reported: Reaction of the chiral amine (I) with tosyl chloride and NaOH in methyl *tert*-butyl ether (MTBE) gives the tosyl aziridine (II), which is condensed with 3-chlorothiophene (III) by means of BuLi to yield the tosyl amide (IV). Condensation of amide (IV) with 2,4-difluoro-3-nitropyridine (V) – obtained by reaction of 2,4-dichloro-3-nitropyridine (VI) with KF and 18-crown-6 (18-C-6) in hot 1-methyl-2-pyrrolidinone (NMP) – by means of *t*-BuOK in THF affords the disubstituted tosyl amide (VII). Condensation of compound (VII) with the cyclopentanecarboxamide (VIII) by means of K_2CO_3 in NMP provides the corresponding adduct (IX), which is hydrogenated with H_2 over Pt in methanol/ethyl acetate to give the aminopyridine (X). Cyclization of (X) with $HC(OEt)_3$ by means of hot Ac_2O yields the imidazo-pyridine (XI), which is detosylated with Mg in MeOH or $LiEt_3BH$ in THF to afford the protected deazapurine (XII). Finally, the acetonide group of (XII) is eliminated by treatment with concentrated HCl in THF (1). Scheme 1.

The combined adenosine A_1/A_{2A} receptor agonist AMP-579 was previously suggested to attenuate lethal reperfusion injury via an inhibitory effect on neutrophils, but a new hypothesis whereby the compound activates the p42/p44 MAPK survival signal pathway was recently tested *in vitro* in Langendorff-perfused rat hearts subjected to ischemia/reperfusion and in open-chest rabbits subjected to left coronary artery occlusion followed by reperfusion. AMP-579 during reperfusion limited infarct size in both isolated rat hearts and rabbit hearts, and the effect in rats hearts was inhibited by coperfused PD-98059, an inhibitor of p42/p44 MAPK activation. This study thus provides the first evidence that adenosine receptor agonists may protect the myocardium from lethal reperfusion injury via activation of a survival signal pathway (2).

The mechanism of cardioprotection of AMP-579 was investigated in ischemia and reperfusion induced in excised hearts from male Sprague-Dawley rats. AMP-579 (1 μM) was infused for 65 min beginning 5 min before reperfusion and PD-98059 was coperfused in some hearts to inhibit p42/p44 MAPK activation. AMP-579 increased coronary flow rate during early reperfusion, and this effect was not abolished by PD-98059. Transient bradycardia was also noted during the first 30 min of reperfusion with AMP-579. AMP-579 significantly reduced infarct size during early reperfusion and this activity was neutrophil-independent. Inhibition of p42/p44 MAPK by PD-98059, however, abolished the infarct-limiting effect of AMP-579 (3).

Activation of the A_{2a} receptor during reperfusion was found to play a part in the protective action of AMP-579 in a rabbit model of acute myocardial infarction. Rabbits were treated with AMP-579 (30 μg/kg i.v. bolus 10 min before reperfusion followed by 3 μg/kg/min for 70 min) or vehicle. Two groups of rabbits were randomized to treatment with the A_{2a} antagonist ZM-241385 (1 mg/kg i.v. bolus 5 min before AMP-579 or vehicle) and another group of animals was treated with the A_{2a} agonist CGS-21680 (30 μg/kg i.v. bolus 10 min before reperfusion

Scheme 1: Synthesis of AMP-579



followed by 3 μg/kg/min for 70 min). Both AMP-579 and CGS-21680 reduced mean arterial pressure (~20 mmHg) during the infusion period. ZM-241385 pretreatment abolished the depressor effect of AMP-579 and attenuated the ability of AMP-579 to limit infact size, whereas CGS-21680 did not limit infarct size (4).

1. Sledeski, A.W., Kubiak, G.G., O'Brien, M.K., Powers, M.R., Powner, T.H., Truesdale, L.K. *Efficient synthesis of AMP579, a novel adenosine A_1/A_2 receptor agonist.* J Org Chem 2000, 65(23): 8114.

2. Baxter, G.F., Ebrahim, Z., Yellon, D.M. *AMP579, an A_1/A_{2a} agonist, limits infarct size at reperfusion via a p42/p44 MAPK-dependent pathway.* Circulation 2000, 102(18, Suppl.): Abst 1028.

3. Baxter, G.F., Ebrahim, Z., Yellon, D.M. *AMP579, an adenosine A_1 and A_{2a} receptor agonist, attenuates lethal reperfusion injury in rat heart via the p42/p44 MAPK pathway.* Br J Pharmacol 2001, 133(Suppl.): Abst 7P.

4. Baxter, G.F., Kis, A., Yellon, D.M. *AMP579, an adenosine A_1 and A_{2a} receptor agonist, limits infarct size in rabbit heart in vivo when given at reperfusion: Role of A_{2a} receptor activation.* Br J Pharmacol 2001, 133(Suppl.): Abst 8P.

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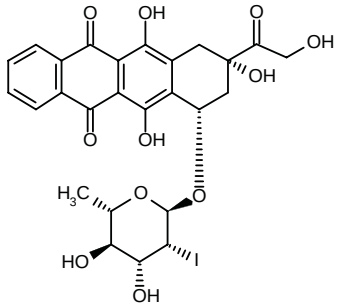
Annamycin

Oncolytic

EN: 110329



$C_{26}H_{25}IO_{11}$ **Aronex**

In a phase I study, liposome-entrapped annamycin (1-2 h i.v. at 3-week intervals) was administered to 36 patients with relapsed solid tumors. Doses ranging from 3-240 mg/m^2 were given for 109 courses. Thrombocytopenia was the dose-limiting toxicity and 5 patients had probable allergic reactions, resulting in 1 discontinuation. Endomyocardial biopsy of 4 patients revealed no cardiac toxicity; there was only limited gastrointestinal toxicity and no alopecia was observed. Treatment did not induce objective tumor responses. A biexponential plasma concentration-*versus*-time profile was seen in pharmacokinetic studies of the 24, 120 and 240 mg doses. The relationship between the dose and the maximal plasma concentration was linear. Plasma clearance values were relatively constant. Though the maximum tolerated dose was 210 mg/m^2, 190 mg/m^2 will be used in future studies due to a change in the formulation of the drug (1).

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Original monograph - Drugs Fut 1997, 22: 948.

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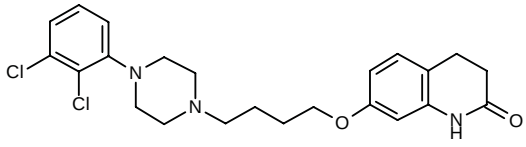
Aripiprazole
Abilitat®

Antipsychotic

EN: 162295



$C_{23}H_{27}Cl_2N_3O_2$ **Otsuka; Bristol-Myers Squibb**

The cardiovascular effects of aripiprazole were compared to those of haloperidol in a halothane-anesthetized canine model. The drugs were infused over 10 min at escalating doses of 0.03, 0.3 and 3.0 mg/kg with 20-min intervals between doses. Aripiprazole doses of 0.03-0.3 mg/kg had positive chronotropic, inotropic and dromotropic effects and resulted in shortening of the ventricular effective refractory period and repolarization phase. Dose-dependent decreases in total peripheral resistance were also observed. A 0.1 mg/kg/min dose of esmolol inhibited these changes. The 3.0 mg/kg dose of aripiprazole attenuated the cardiac effects produced by the lower doses and induced negative chronotropic, dromotropic and hypotensive actions and prolongation of the ventricular effective refractory period and repolarization phase. The only significant change seen with the lowest dose of haloperidol was a decrease in the peripheral resistance. Haloperidol 0.3-3.0 mg/kg dose-dependently brought about negative chronotropic, inotropic and hypotensive actions, intraventricular conduction delay and prolongation of the ventricular effective refractory period and repolarization phase. These effects were accompanied by a further decrease in peripheral resistance. Aripiprazole had less potent inhibitory effects on cardiovascular parameters than haloperidol at clinically relevant exposures, and appeared to be safer than haloperidol as it did not induce afterdepolarization or prolong the ventricular electrical vulnerable period (1).

  CCC: 0377-8282/2001

Bristol-Myers Squibb reported that it intends to file an NDA in late 2001 for aripiprazole for the treatment of schizophrenia (2).

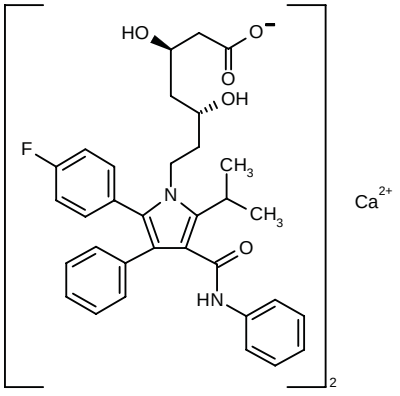
1. Sugiyama, A., Satoh, Y., Hashimoto, K. *In vivo canine model comparison of cardiohemodynamic and electrophysiological effects of a new antipsychotic drug aripiprazole (OPC-14597) to haloperidol.* Toxicol Appl Pharmacol 2001, 173(2): 120.

2. *Bristol-Myers Squibb updates investors at healthcare conference.* DailyDrugNews.com (Daily Essentials) Nov 3, 2000.

Original monograph - Drugs Fut 1995, 20: 884.

Atorvastatin Calcium *Hypolipidemic*
Lipitor®

EN: 180072



$C_{66}H_{68}CaF_2N_4O_{10}$ **Pfizer**

HMG-CoA reductase inhibitors, also known as statins, are now thought to have cardioprotective effects above and beyond their lipid-altering properties. In order to investigate the potential mechanisms involved, researchers assessed the impact of atorvastatin calcium on the production of reactive oxygen species (ROS) in rat aortic vascular smooth muscle cells (VSMCs). Results showed that pretreatment of VSMCs with atorvastatin caused an inhibition of angiotensin II-induced ROS production via a time- and concentration-dependent decrease in AT_1 receptor mRNA levels and AT_1 receptor density. The effect of atorvastatin on AT_1 receptor gene expression was reversed by L-mevalonate but not by hydroxycholesterol. Moreover, the inhibition of AT_1 receptor transcript levels induced by atorvastatin was mimicked by geranylgeranyltransferase inhibition but not by farnesyltransferase inhibition. The inhibition of AT_1 receptor gene expression was due to a decrease in the half-life of AT_1 receptor mRNA, and not to a reduction in gene transcription. Atorvastatin also inhibited the angiotensin II-induced increase in activity of the GTP-binding protein rac1, as well as the geranylgeranyl-dependent translocation of rac1 to the cell membrane. The use of *Clostridium sordellii* lethal toxin to specifically inhibit rac1 attenuated the angiotensin II-induced release of free radicals. *In vivo* studies in rats showed that atorvastatin administration led to downregulation of aortic AT_1 receptor mRNA expression and lowered aortic superoxide production. Therefore, one of the mechanisms by which statins offer cardiovascular protection appears to be through downregulation of AT_1 receptor gene expression and rac1 inhibition, which in turn lead to decreased ROS production (1).

Researchers explored the possible involvement of changes in VEGF synthesis in the atheroprotective activity of atorvastatin. In this *in vitro* study, plasma collected at baseline from 14 males with hypercholesterolemia and angiographically confirmed coronary artery disease (CAD) induced more VEGF in human smooth muscle cells (hSMCs) than plasma collected from these same participants after 2 months of treatment with atorvastatin (20 mg/day). However, incubation of hSMCs with atorvastatin did not produce alterations in VEGF production. Therefore, the diminished level of VEGF production in CAD patients receiving treatment with atorvastatin is probably due to metabolites of atorvastatin rather than to the parent drug (2).

Scientists have conducted an evaluator-blind, placebo-controlled, parallel-group trial to determine the potential pharmacokinetic and/or pharmacodynamic interaction between ezetimibe, a new selective cholesterol absorption inhibitor, and atorvastatin. A total of 32 hypercholesterolemic individuals (LDL cholesterol 130 mg/dl or more) following the National Cholesterol Education Program (NCEP) Step I Diet were randomized to 10 mg atorvastatin, 10 mg ezetimibe, 10 mg atorvastatin plus 10 mg ezetimibe or placebo. Serum lipids were determined in the morning on days 1, 7 and 14 prior to dosing. Neither ezetimibe nor atorvastatin had effects on the pharmacokinetics of the other drug. Compared to administration of ezetimibe or atorvastatin alone, coadministration of the two drugs produced a significant reduction in LDL cholesterol, without effects on HDL cholesterol or triglycerides. Moreover, the combined administration of these compounds was safe and well tolerated in this study. Therefore, combination therapy with ezetimibe and atorvastatin may prove to be a safe alternative to higher doses of atorvastatin alone (3).

A prospective, open-label, parallel study by Italian researchers assessed the effects on lipid profiles of atorvastatin, alone or in combination with different hormone replacement therapies (HRTs), in 136 postmenopausal women with severe hypercholesterolemia (280 mg/dl). The treatments used in this study were: 1) atorvastatin 10 mg; 2) atorvastatin 10 mg + conjugated equine estrogens 0.625 mg and continuous combined medroxyprogesterone 2.5 mg (ACEEM); 3) atorvastatin 10 mg + estradiol valerate and cyproterone acetate (AEC); and 4) atorvastatin 10 mg + 100 mg transdermal 17β-estradiol and norethisterone acetate (ATEN). As compared to baseline, determination of plasma lipids at 6 months of therapy showed that atorvastatin alone significantly reduced plasma total cholesterol, triglycerides and LDL

cholesterol, and raised HDL cholesterol levels, but did not modify lipoprotein(a) (Lp[a]). The addition of transdermal HRT to atorvastatin therapy produced no significant changes in any lipoprotein parameter, in contrast to oral HRT, which significantly lowered total cholesterol, triglycerides, LDL cholesterol and Lp(a), and raised HDL cholesterol. Moreover, NCEP goals were achieved by significantly more women in the atorvastatin plus oral HRT group than in the atorvastatin alone or atorvastatin plus transdermal HRT groups (4).

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Original monograph - Drugs Fut 1997, 22: 956.

Brain-Derived Neurotrophic Factor

Treatment of ALS

EN: 198453

Regeneron; Amgen; Sumitomo

A study examined the effects of subcutaneously administered brain-derived neurotrophic factor (BDNF) on motor neuron protection in sciatic or facial nerve axotomy models. These results were compared with concomitant plasma BDNF concentrations. When BDNF treatment was begun 1 week after surgery, choline acetyltransferase reduction in sciatic nerve axotomy models was delayed (1).

BDNF was found to have potential as a therapy to protect against or delay neurodegeneration associated with the gp120 envelop protein in HIV-1 infection. Using primary culture of cerebellar granule neurons from 8 day-old rats, 24-h exposure to gp120 (5 nM) induced a time- and concentration-dependent neurotoxicity, causing apoptosis in 80% of cells. The morphological appearance of the neurons was also altered by gp120. Preincubation with BDNF (50 ng/ml) 12 h before exposure to gp120 (5 nM) rescued 80% of cerebellar granule neurons from apoptosis; total protection was observed when neurons were exposed to lower concentrations (200 pm) of gp120 (2).

To investigate the role of neurotrophins in the innervation of skin in birds, the distribution of NGF, NT-3 and BDNF was assessed. The distribution of BDNF was found to be higher in chick epidermis than dermis and the opposite was true in mouse skin. NGF and NT-3 were distributed similarly in mouse and chick skin. An *in vitro* study of the effects of BDNF on embryonic NGF-dependent dorsal root ganglion neurons found that the neurotrophin caused individual growth cones to collapse and prevented outgrowth of neurites toward BDNF-secreting fibroblasts. Chick specific p75-neutralizing antibody, but not K252a, an inactivator of trk receptors, inhibited BDNF-induced growth cone collapse. BDNF, therefore, appeared to inhibit cutaneous axon growth cones via p75. High concentrations of the neurotrophin may prevent the innervation of avian epidermis (3).

The effect of BDNF on the channel activity of NMDA receptors has been investigated by measuring the NMDA-induced intracellular Ca^{2+} concentration in cultured neocortical neurons, including GABA-positive neurons. BDNF (100 ng/ml for 20 min) signficantly enhanced NMDA-induced Ca^{2+} responses in GABA-positive neurons, an effect which was blocked by pretreatment with the trk kinase inhibitor K252a (200 nM) and the Src-family kinase inhibitor PP2 (1 μM). Pretreatment with these inhibitors also inhibited the increase in NMDA-evoked currents in bipolar or multipolar neurons induced by treatment with BDNF. It was concluded that BDNF enhances NMDA channel activity in GABAergic neurons through activation of Src-family kinases (4).

In order to determine whether increases in protein expression of AMPA-type glutamate receptors by BDNF enhances receptor function, cultured rat neocortical neurons were treated with BDNF 50 ng/ml daily for 4 days. Treatment was found to increase the frequency of GluR1-positive cells in glutamic acid decarboxylase-immunopositive cells. The GABAergic interneurons appeared to respond to BDNF most strongly. Chronic treatment with BDNF greatly increased AMPA currents while its effect on NMDA currents was modest. BDNF enhanced GABA release induced by the AMPA analog willardiine. Similar BDNF effects were found in HEK293 cells expressing trkB, GluR1 and GluR2 (5).

The ability of BDNF to regenerate axotomized rubrospinal neurons 1 year after neuronal injury has been tested in rats. Researchers injected Fast Blue into the rubrospinal tract at the low cervical spinal cord after which the left lateral funiculus was transected at C3/4. After 1 year, the right sciatic nerve was cut and ligated. A segment of the distal, predegenerated nerve was excised and inserted into the refreshed C3 cervical injury site. Dil was introduced into the free end of the peripheral nerve and BDNF (12 μg/day) was infused into the vicinity of the red nucleus for 2 weeks. Rats were allowed to survive for 2 months, at which time between 20-40 rubrospinal

neurons were found to be double-labeled with Fast Blue and DiI, suggesting regeneration (6).

A study was undertaken to assess whether direct infusion of recombinant BDNF and NT-3 into the hippocampal dentate gyrus of rats has antidepressant effects. Sprague Dawley rats received bilateral infusions of BDNF, NT-3, NGF or vehicle and were evaluated in the learned helplessness and forced swim test models of depression. BDNF and NT-3 treatment resulted in significant improvements in failure number and latency to escape in the learned helplessness model. These improvements were similar to the effect of chemical antidepressants. Infusion with NGF did not significantly alter responses. Another antidepressant-like effect, a significant reduction of immobility time, was found in BDNF- and NT-3-treated rats in the forced swim test (7).

A study performed in male Zucker fatty rats administered either BDNF or vehicle has shown that acute administration of BDNF improves liver-specific insulin resistance (8).

The results of a study in STZ mice have suggested that BDNF potentiates insulin signaling in the liver by acting on the central nervous system and has a blood glucose-lowering effect (9).

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2. Bachis, A., De Bernardi, M.A., Monchetti, I. *Brain-derived neurotrophic factor protects cerebellar granule cell against GP120-mediated cell death.* Soc Neurosci Abst 2000, 26(Part 1): Abst 8908.

3. Cahoon-Metzger, S.M., Scott, S.A. *BDNF inhibits growth of chick NGF-dependent sensory neurons in vitro.* Soc Neurosci Abst 2000, 26(Part 1): Abst 318.7.

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6. Liu, J., Tetzlaff, W. *Infusion of BDNF to the red nucleus promotes regeneration of chronically injured rat rubrospinal neurons into peripheral nerve graft even one year after injury.* Soc Neurosci Abst 2000, 26(Part 1): Abst 114.7.

7. Shirayama, Y., Chen, A.C.H., Duman, R.S. *Antidepressant-like effects of BDNF and NT-3 in behavioral models of depression.* Soc Neurosci Abst 2000, 26(Part 1): Abst 387.3.

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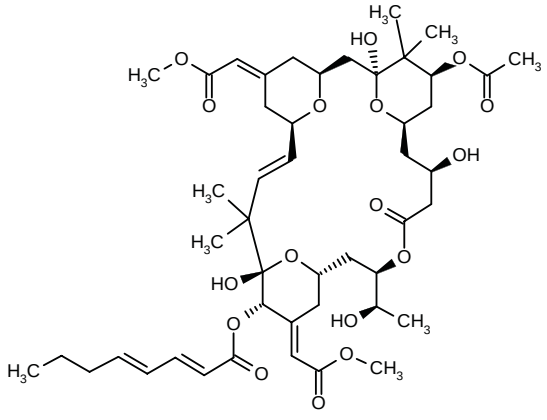
Bryostatin 1

Oncolytic

EN: 165188



$C_{47}H_{68}O_{17}$

Cancer Res. Campaign; Natl. Cancer Inst. (US)

Bryostatin 1 showed potential as an adjuvant for immunotherapy or chemotherapy in melanoma in cytotoxicity studies using a human radial growth phase melanoma cell line (WM35) and a human metastatic melanoma cell line (A375). Both cell lines treated with bryostatin 1 were shown to have significantly increased susceptibility to Fas-mediated apoptosis and cisplatin-induced apoptosis. The drug exhibited a biphasic effect, inhibiting apoptosis at low concentrations while potentiating susceptibility to apoptosis at high concentra-

tions. The mechanism of action of bryostatin 1 appeared to involve expression of death receptors and downstream antiapoptotic factors (1).

A multicenter phase I trial was conducted in 27 evaluable patients with progressive chronic lymphocytic leukemia (CLL) or refractory, indolent non-Hodgkin's lymphoma (NHL). The treatment regimen consisted of 24-h infusion of bryostatin 1 at an initial dose of 16 μg/m^2 before or after fludarabine 12.5-25 mg/m^2/day i.v. for 5 days. Dose-limiting toxicity for fludarabine has been leukopenia. Six patients have had a partial response and two patients with NHL have had a complete response. The investigators plan to escalate the bryostatin 1 dose to determine the MTD in combination with fludarabine 25 mg/m^2/day, and then perform a phase II trial at these doses in progressive CLL or refractory, indolent NHL (2).

Bryostatin 1 has been examined for efficacy and safety in phase I clinical trials in leukemia patients, one in combination with high-dose 1-β-D-arabinofuranosylcytosine (HiDAC) and the other in combination with fludarabine. In the trial, 23 patients with refractory acute myelogenous (AML) or lymphoblastic leukemia (ALL) or chronic myelogenous leukemia-myeloid blast crisis (CML-MBC) received a 24-h infusion of bryostatin 1 at an initial dose of 12.5 μg/m^2, followed on days 1 and 2 by HiDAC 1.5 g/m^2 as a 3-h infusion every 12 h and a second course of HiDAC on days 9 and 10 followed by the same dose of bryostatin 1. The maximum tolerated dose (MTD) of bryostatin 1 was found to be 50 μg/m^2, with prolonged cytopenia, myalgias and elevated liver function tests being dose-limiting. Complete responses have been obtained in 5 patients and 1 patient receiving a bone marrow transplant was disease-free for over 6 months. Based on these findings, a multicenter phase II trial of bryostatin at the MTD with HiDAC at doses of 1.5-3.0 g/m^2 in patients with refractory or poor-prognosis acute leukemia/lymphoblastic lymphoma is planned (3).

A phase II study has investigated the use of bryostatin 1 in 17 patients with progressive indolent NHL. Patients who had prior chemotherapy received a median of 6 once-weekly i.v. infusions of bryostatin 1 (25 μg/m^2 over 24 h). No responses were seen in the 14 evaluable patients; 1 patient achieved stable disease lasting 9 months. The most common adverse events were myalgia and phlebitis. Two patients discontinued treatment due to toxicity, 3 discontinued due to toxicity and disease progression and 5 discontinued due to progressive disease (4).

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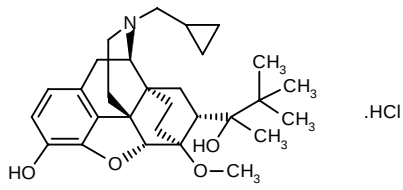
Buprenorphine Hydrochloride

Transtec®

Opioid Analgesic
Treatment of Opioid Dependency

EN: 091355



.HCl

$C_{29}H_{41}NO_4$.HCl

Reckitt & Colman; Titan; DrugAbuse Sciences; Grünenthal

Buprenorphine Depot, a mixed agonist-antagonist opiate, is an extended-release injectable form of buprenorphine utilizing LACTIZ™ technology. The product, in preclinical development, is designed to be administered once every 4-6 weeks (1).

Preclinical data have demonstrated the efficacy of Titan's novel long-term drug delivery system applied to the administration of buprenorphine for the treatment of opiate dependence. A preclinical study demonstrated that controlled-release buprenorphine was able to deliver buprenorphine at a constant rate and maintain the targeted therapeutic plasma level for the entire 3-month study period. Based on the observed drug release rate, it is expected that therapeutic levels of buprenorphine can potentially be delivered with this product for 6 months. No product-related adverse effects were observed in the trial, including an absence of local irritation or inflammation. Based on these encouraging results, the company intends to carry out clinical studies (2).

Starting in September, Grünenthal will launch buprenorphine transdermal system (Transtec®), a new transdermal analgesic system comprised of a thin polymer matrix patch containing the opioid buprenorphine for moderate to severe nonacute pain, in Germany. Transtec®, which was granted marketing authorization in July of 2001, can be applied to the skin where it lasts for 72 h, constantly releasing the drug into the systemic circulation. The patch will be available in three sizes with three different release rates: 35, 52.5 and 70 μg/h. Transtec® is already available in Switzerland and other European countries are expected to approve the product soon, as Germany is serving as the reference member state for Europe (3).

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Cetuximab
C225

Oncolytic

EN: 230562

Immunoglobulin G_1 (human-mouse monoclonal C225 γ_1-chain anti-human epidermal growth factor receptor), disulfide with human-mouse monoclonal C225 κ-chain dimer

ImClone; Merck KGaA; Bristol-Myers Squibb

C225 was investigated alone and in combination with a vascular endothelial growth factor antisense oligonucleotide (VEGF-AS) in human GEO colon cancer cells. C225 dose-dependently inhibited VEGF, basic fibroblast growth factor (bFGF) and transforming growth factor-α (TGF-α) *in vitro* production in GEO cells. VEGF-AS treatment selectively inhibited *in vitro* VEGF expression by GEO cells. Both VEGF-AS and C225 cytostatically and reversibly inhibited tumor growth in immunodeficient mice with established GEO xenografts. Mice treated with both agents demonstrated prolonged inhibition of tumor growth and significant improvements in survival compared to controls or mice treated with VEGF-AS. While all mice died by 8 weeks in the control, C225 and VEGF-AS groups, half of those treated with both VEGF-AS and C225 lived at least 13 weeks and 10% lived 20 weeks with no evidence of tumors. VEGF-AS treatment reduced VEGF expression and microvessel count in GEO tumor xenografts and C225 treatment reduced microvessel count and VEGF, bFGF and TGF-α expression. Few microvessels were found after combined

treatment, which also significantly potentiated inhibition of VEGF expression (1).

The effects of EGF receptor (EGFR) blockade by C225 on the *in vivo* and *in vitro* growth of human non-small cell lung carcinoma xenografts has been studied. Compared to control animals, C225-treated animals had significantly suppressed growth ($p < 0.05$) of established EGFR-positive tumors of squamous, neuroendocrine and adenocarcinoma origin. Tumor cell proliferation was decreased while tumor necrosis and apoptosis were increased. The antitumor effect was enhanced by combination therapy with taxane and platin-based drugs (2).

A study in several non-small cell lung cancer cell lines, with varying levels of EGFR expression, demonstrated that C225 potentiates radiation and chemotherapy cytotoxicity. C225 was administered alone and in combination with cisplatin, paclitaxel and navelbine. C225 alone resulted in cell cycle shifts at 48 h from S-phase to $G_{0/1}$, including a 20% shift in H226 cells. Combination with radiation induced greater $G_{0/1}$ shifts in the H226 and A549 lines while no effect was seen in the H322 line. C225 alone also inhibited growth in the high EGFR expression A431 and H226 lines but not in the moderate and low EGFR A548, H157 and H322 lines. Synergy with C225 and radiation or chemotherapy was seen with A431, H226 and A549 cells with high/moderate EGFR. Synergy was not found with H157 cells. C225 in combination with cisplatin and navelbine demonstrated synergy in the A431 and A549 cells and additive effects were observed with C225 combined with paclitaxel. In a H157 xenograft model, tumor growth inhibition was greatly enhanced by combined treatment with C225 and radiation, as compared to either treatment alone (3).

The effects of the caspase-8-specific inhibitor z-IETD-fmk and the caspase-9-specific inhibitor z-LEDH-fmk on apoptosis induced by C225 have been examined to clarify the mechanism of action of the monoclonal antibody. Pretreatment of DiFi colon cancer cells with z-IETD-fmk, but not z-LEHD-fmk, inhibited C225-induced apoptosis, suggesting that caspase-8 had a role in initiating C225-induced apoptosis. Further investigation revealed that the mechanism of action by which C225 activates caspase-8 and triggers apoptosis does not involve Fas ligand/MAb, tumor necrosis factor (TNF-α) or TNF-related apoptosis-inducing ligand (TRAIL) pathways (4).

Clinical and biochemical improvement in a patient with Menetrier's disease upon treatment with C225 was reported. Menetrier's disease, or hypoproteinemic hypertrophic gastropathy, is a rare, acquired, precancerous disorder of the stomach. Although infection with cytomegalovirus and *Helicobacter pylori* has been implicated as causal, no consistent benefits have been seen with a variety of treatments, including drugs eradicating *H. pylori*. Based on evidence implicating increased EGFr signaling, U.S. researchers treated a 48-year-old patient with the disease and no response to drug therapy including prochlorperazine, promethazine, ondansetron, lansoprazole, cisapride, octreotide and glycopyrrolate, with 2-h i.v. infusions of the antibody as a loading dose of 490 mg/m^2 followed by 3 weekly treatments at 250 mg/m^2. An immediate reduction in nausea and vomiting was reported, with a decrease in vomiting from an average of 70 episodes per week to a little over 1 episode per week after 1 month of treatment with C225. Improvement in biochemical parameters including an increase in serum albumin and gastrin levels and a reduction in stool α_1-antitrypsin levels was also seen after 1 month of treatment. Further studies are recommended based on this promising case report, especially in combination with TNF-α-converting enzyme (TACE) owing to the proposed involvement of TGF-α in several disease features (5).

In a study in 120 patients with irinotecan-refractory and EGFR-positive colorectal cancer, combination of C225 and irinotecan produced a 22.5% partial response rate and a 7.5% disease stabilization rate, with a median duration of response of 186 days. Toxicity consisted mainly of adverse events typical of irinotecan (diarrhea, neutropenia, nausea, fatigue) and the only side effects attributable to C225 were allergic reactions and an acne-like rash (6).

The results from a 40-patient trial evaluating combination of C225 and gemcitabine in patients with pancreatic cancer have been reported. A partial response was achieved in 5 patients and 21 had disease stabilization. The median time to disease progression was 3.5 months, median overall survival was 6.75 months and the 1-year survival rate was 32.5% (7).

An ongoing phase II study is evaluating the combination of C225 and cisplatin in 63 patients with stable disease or progressive disease following treatment with cisplatin for metastatic head and neck cancer. One complete and 9 partial responses have been obtained in 41 patients with stable disease following cisplatin therapy, with a median duration of response of 24 weeks. Moreover, of the 22 patients refractory to cisplatin, 5 have achieved partial responses with a median duration of 12 weeks. The combination was well tolerated, and addition of C225 did not appear to exacerbate cisplatin toxicities (8).

ImClone Systems has commenced patient dosing in a phase II trial of C225 in combination with carboplatin and paclitaxel in patients with newly diagnosed non-small cell lung carcinoma. ImClone is currently studying C225 in a series of phase II and III clinical trials. In phase II trials, C225 is being evaluated in combination with standard therapies in refractory colorectal carcinoma, refractory head and neck carcinoma and pancreatic carcinoma. Two phase III trials are evaluating the use of C225 as first-line treatment in head and neck carcinoma, one study combining C225 with chemotherapy and the other with radiotherapy. In November 2000, favorable results were reported from a phase II trial evaluating C225 in combination with the chemotherapeutic agent irinotecan for the company's initial commercialization indication, refractory colorectal carcinoma. The C225/irinotecan combination resulted in tumor shrinkage and a slowing of disease progression (9).

ImClone Systems has completed the first steps in the submission of a rolling BLA for cetuximab, the company's anticancer agent assigned fast track designation by the FDA. The company is seeking approval of cetuximab in combination with irinotecan to treat irinotecan-refractory colorectal cancer which is positive for the EGFR. IMC-C225 was granted fast track designation by the FDA in February 2001 (10).

ImClone Systems has announced that it has entered into an agreement with Bristol-Myers Squibb to codevelop and copromote cetuximab in the U.S., Canada and Japan. Merck KGaA acquired the worldwide rights to develop and commercialize the cancer drug outside the U.S. and Canada in 1998, and the company also holds codevelopment and comarketing rights for the drug in Japan. The transaction between BMS and ImClone comprises a commercial agreement for the codevelopment and copromotion of cetuximab, as well as the acquisition of a significant equity stake in ImClone (11).

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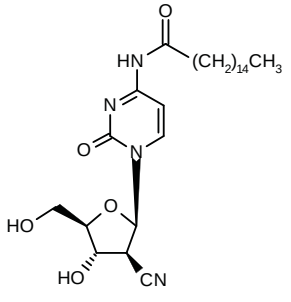
CS-682 *Oncolytic*

EN: 195704



$C_{26}H_{42}N_4O_5$ **Sankyo**

CS-682 was evaluated in a preclinical study of mice implanted with either syngeneic tumors or human tumor xenografts. Treatment resulted in many complete tumor

regressions and cures, with a total response rate of more than 95%. CS-682 (40 mg/kg/day x 10) significantly retarded primary KM12L4a human colon tumor growth and reduced liver metastases. Magnetic resonance imaging revealed reduced tumor volume of AC3488UM human colon carcinoma metastatic to the liver. In C57BL6 mice implanted with GFP-B16 melanoma, treatment with CS-682 resulted in a significant delay of tumor growth and a significant reduction in the average number of tumor foci in the lungs of the mice (1).

CS-682 was the subject of a phase I study to determine the pharmacokinetics and the maximum tolerated dose of the drug in patients with refractory solid tumors. Oral doses of 1-67 mg/m^2 were administered to 46 patients 5 days a week for 4 weeks. Dose-limiting, grade 4 neutropenia was observed in 4 of 12 patients at the 40 mg/m^2 dose, in 2 of 4 patients at 50 mg/m^2 and in 1 of 2 patients at 67 mg/m^2. CS-682 is converted *in vivo* to CNDAC, which is the principal species in plasma. At doses of 30-50 mg/m^2 there was substantial interpatient variability in CNDAC exposure, which was correlated with neutropenia severity. Between 5-45% of the CS-682 dose was excreted in the urine. A minor response was found in 1 patient with ovarian cancer and 1 lung cancer patient had stable disease for 5 months. The recommended dose for phase II was 40 mg/m^2 (2).

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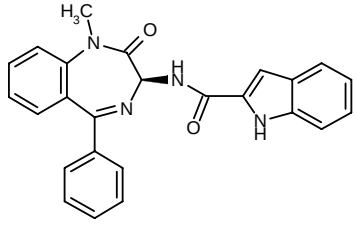
Devazepide
Devacade®

Treatment of Neurogenic Pain

EN: 132939



$C_{25}H_{20}N_4O_2$ **ML Laboratories; Panos Therapeutics**

The role of cholecystokinin (CCK) in postprandial sleep was investigated in rats starved for 4 days, refed and then administered L-364718 (500 µg/kg i.p.) or vehicle. Control animals experienced increases in rapid eye movement (REM) sleep and nonrapid eye movement sleep (NREM) as well as decreases in NREM sleep intensity in response to refeeding. L-364718 treatment delayed the NREM sleep responses and blocked changes in NREM intensity. L-364781 treatment reduced the amount of REM sleep to below baseline levels (1).

The early indication of positive results from ML Laboratories' phase II clinical trial of devazepide in patients suffering from neuropathic pain has been confirmed by completion of the analysis of the data relating to all participating patients. In this study, 40 patients with moderate to severe neuropathic pain were administered two strengths of devazepide or placebo in addition to their existing opioid and other analgesic therapy. During treatment with devazepide at the higher dose, 50% of patients reported significantly improved pain relief compared to their current therapy, with no reports of severe side effects. The significant pain-relieving action of devazepide was complemented by indications of improvements in quality of life measures. Devazepide is the first orally administered product in this class of compounds specifically targeted for neuropathic pain and offers a new way of treating this type of pain. Preclinical data indicate that devazepide may similarly enhance the pain-relieving action of milder opiates such as codeine. ML and its development partner Panos Therapeutics are currently considering the next phase of clinical development of the drug for the treatment of neuropathic pain, which is due to begin later this year. A marketing authorization application is scheduled for 2003 (2).

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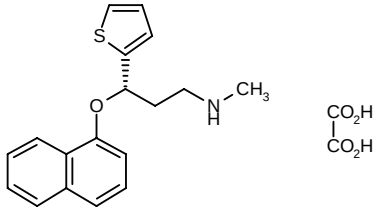
Duloxetine Oxalate

Antidepressant
Treatment of Urinary Incontinence

EN: 142924



$C_{18}H_{19}NOS.C_2H_2O_4$ **Lilly; Shionogi**

The effects of duloxetine on serotonin and norepinephrine uptake were evaluated in 27 healthy volunteers.

Male volunteers with no history of psychiatric disorder were randomized to placebo, clomipramine 100 mg/day, duloxetine 20 mg/day or duloxetine 60 mg/day. Administration of clomipramine and both doses of duloxetine decreased blood serotonin concentrations, but only clomipramine inhibited the increase in blood pressure following intravenous infusion of tyramine. Duloxetine therefore acted as a selective serotonin reuptake inhibitor without affecting the norepinephrine reuptake process (1).

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

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

In a multisite, double-blind, placebo-controlled phase II trial, 173 patients with DSM-IV-defined major depression were randomly assigned to receive either duloxetine, fluoxetine (positive control) or placebo for 8 weeks. Results indicated that duloxetine produced statistically significantly greater improvement in depressive symptoms *versus* placebo as measured by the 17-item Hamilton Depression Rating Scale (HAMD17). In addition, statistically significantly more patients receiving duloxetine achieved remission from their depression as compared to those receiving placebo (remission was prospectively defined in the study protocol as a score of ≤ 7 in the HAMD17). Adverse effects were generally mild and the drug was well tolerated. A multisite, double-blind, placebo-controlled phase III trial with duloxetine has been completed and results from the study are consistent with those seen in the phase II trial. The trial randomly assigned 353 patients with DSM-IV-defined major depression to receive duloxetine at doses of 40 or 80 mg/day, paroxetine 20 mg/day or placebo for 8 weeks. Remission was defined the same way as in the phase II trial. Patients receiving 80 mg/day duloxetine experienced statistically significantly greater improvement in depressive symptoms on the HAMD17 than those randomized to placebo or paroxetine. In addition, a significantly higher rate of duloxetine-treated patients (50.0%) achieved remission from depression *versus* patients receiving placebo (29.5%). No statistically significant differences between the duloxetine- and placebo-treated patients were reported in the incidence of sustained hypertension (2% for both groups) (4).

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

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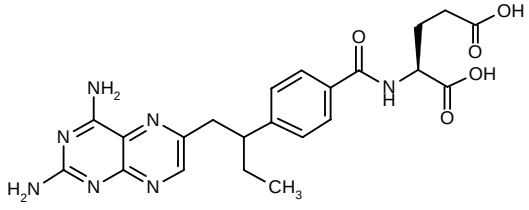
Edatrexate

Oncolytic

EN: 108334



$C_{22}H_{25}N_7O_5$ **SRI**

Escalating doses of edatrexate in combination with cisplatin were evaluated in a phase I study in 39 patients with head and neck and non-small cell lung cancer. Edatrexate was started at a dose of 40 mg/m^2 with doses escalated in increments of 10 mg/m^2 up to a maximum of 80 mg/m^2. Two administration schedules were used: 11 patients received cisplatin 120 mg/m^2 every 4 weeks and edatrexate weekly, while 28 patients received cisplatin

60 mg/m^2 and edatrexate every 2 weeks. Leukopenia, mucositis and renal insufficiency were dose-limiting toxicities on the first schedule, wherein the maximum tolerated weekly dose was 40 mg/m^2. On the second schedule, the maximum tolerated dose of biweekly edatrexate was 80 mg/m^2 and leukopenia and mucositis were the dose-limiting toxicities. Cisplatin possibly affected the clearance of edatrexate on day 8 on the first schedule, whereas no clear effect of cisplatin on day 15 clearance was seen on the second schedule. Major responses were achieved by 5 of 9 patients on the first schedule and 8 of 25 on the second schedule. Patients with both types of cancer had responses. One patient in each schedule group had a complete response. Biweekly cisplatin 60 mg/m^2 and edatrexate 80 mg/m^2 was recommended for phase II studies (1).

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Original monograph - Drugs Fut 1989, 14: 849.

Etanercept
Enbrel®

Antiarthritic
Antipsoriatic

EN: 213242

1-235-Tumor necrosis factor receptor (human) fusion protein with 236-467-immunoglobulin G_1 (human γ_1-chain Fc (fragment) dimer

Immunex; Wyeth-Ayerst

Pharmacia researchers have described the use of combinations of a selective cyclooxygenase-2 inhibitor and a tumor necrosis factor antagonist for the treatment of inflammatory diseases. These combinations reduce the inflammation and increase the range of joint motion in patients suffering from arthritic disease, providing a method for the treatment of rheumatoid arthritis with reduced side effects. A preferred TNF antagonist is etanercept (1).

An independent data monitoring board has indicated that ongoing studies of etanercept for the treatment of chronic heart failure (CHF) would not be able to meet efficacy endpoints. Based on this report, Immunex and American Home Products have decided not to proceed with the large phase II/III studies in CHF. Development decisions for etanercept in CHF will be made following a full analysis of all data by the companies (2).

Health Canada has approved etanercept (Enbrel®) for adult use for the reduction in signs and symptoms of moderately to severely active rheumatoid arthritis in patients who have had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs). In addition, etanercept can be used in combination with methotrexate in adult patients who do not respond adequately to methotrexate alone. In a phase III clinical trial in 234 rheumatoid arthritis patients, responses to etanercept were rapid, often appearing within 1-2 weeks after initiation of therapy, and nearly always within 3 months. At 3 months, study results demonstrated that 62% of the patients receiving a 25-mg dose of etanercept reached the primary endpoint of 20% improvement by ACR criteria. At 6 months, the secondary endpoints of this study demonstrated a 69% median improvement in swollen joint counts and an 88% median reduction in duration of morning stiffness. Supplemental applications of polyarticular-course JRA and first-line treatment of moderately to severely active rheumatoid arthritis in adults will be filed soon. Enbrel® is manufactured by Immunex and distributed in Canada by Wyeth-Ayerst, a subsidiary of American Home Products (3).

A 24-week, open-label extension study has continued an initial 12-week evaluation of etanercept treatment in patients with psoriatic arthritis and psoriasis. In the extension study, the median PASI scores decreased from 5.5 to 3.2 in patients treated with etanercept in the initial study and from 6.8 to 2.1 in patients originally treated with placebo. Improvements begun by the original etanercept patients were continued and similar improvements began in patients originally given placebo once they started etanercept treatment. Eighteen psoriasis patients were taking methotrexate concomitantly at baseline, 56% of whom decreased the dose after the extension study and 39% of whom discontinued methotrexate altogether. At the end of the extension study, 82% of psoriatic arthritis patients had achieved the PsARC response criteria and 74% the ACR20 criteria (4).

Positive preliminary results from the first clinical study of etanercept in psoriasis have been announced. In this phase II clinical study, 112 patients with moderate to severe plaque psoriasis were randomized evenly to receive 25 mg of etanercept or placebo twice a week for 6 months. The primary endpoint of the study was the proportion of patients achieving a 75% improvement in PASI scores after 12 weeks. Patients treated with etanercept in this study experienced significant improvement compared to those on placebo, with 30% of the etanercept patients achieving PASI 75 compared to 2% of those on placebo. Furthermore, patients on etanercpet continued to improve over time. After 6 months of treatment, approximately half of the patients receiving etanercept achieved an improvement of 75% or better in the PASI score, compared to 5% improvement for patients on placebo. In addition, approximately 20% of patients administered etanercept for 6 months improved by 90% or more, whereas no patients in the placebo group achieved that level of response. Etanercept was generally well tolerated in this study. Side effects seen more frequently within the first 12 weeks of the study in patients receiving etanercept included mild infections (46% compared to 24% of placebo patients), the majority of which were upper respiratory infections similar to colds (5).

Immunex and Wyeth-Ayerst will sponsor a 10,000-patient rheumatoid arthritis (RA) study. RADIUS (Rheumatoid Arthritis DMARD Intervention and

  CCC: 0377-8282/2001

Utilization Study) is designed to gain more comprehensive knowledge regarding current treatment for this disease. The RADIUS trial is specifically designed to collect data on RA treatment practice patterns, tolerability of RA therapies and efficacy of current disease modifying antirheumatic drugs (DMARDs) and biologic response modifiers. An independent advisory board comprised of academic and community-based rheumatologists has provided input into the design and implementation of the study. This board will also be involved in evaluating and interpreting data collected in RADIUS, which is divided into two parts. RADIUS 1 is a study of 5000 adult patients who meet the ACR criteria for RA diagnosis and currently require an introduction of a new DMARD to RA therapy. This is a multicenter trial, and patients will be recruited by 600 investigators nationwide. RADIUS 1 is scheduled to begin in the late summer of 2001 and data will be collected for at least 2 years. RADIUS 2 will study an additional 5000 adult patients who will begin new treatment with etanercept. These patients will meet the same criteria as for RADIUS 1. This will also be a multicenter trial and patients will be recruited by the same 600 investigators. RADIUS 2 is targeted to begin in 2002 when additional supplies of etanercept become available. Data will also be collected for at least 2 years (6).

The FDA has granted priority review status for Immunex's supplemental BLA for the use of etanercept in the treatment of psoriatic arthritis. Etanercept is the first product ever reviewed by the FDA to treat the signs and symptoms of psoriatic arthritis. Immunex submitted its sBLA for etanercept in July 2001 (7).

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Original monograph - Drugs Fut 1998, 23: 951.

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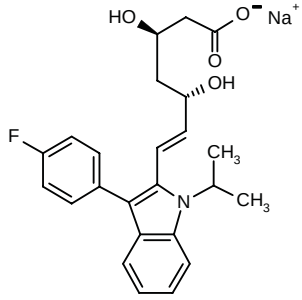

$C_{24}H_{25}FNNaO_4$

Novartis; Tanabe Seiyaku; AstraZeneca

Novartis has received FDA approval for Lescol® XL (fluvastatin sodium) 80 mg, an extended-release formulation to treat excessive cholesterol. The drug is indicated as a starting dose and as an adjunct to diet to reduce elevated total cholesterol, LDL cholesterol, triglycerides and apolipoprotein B levels, and to increase HDL cholesterol levels in patients with primary hypercholesterolemia and mixed dyslipidemia, and to slow the progression of atherosclerosis in patients with coronary heart disease. The approval was based on phase III studies involving 857 patients treated with Lescol® XL 80 mg in 12 countries in Europe and North America. The studies showed a median reduction of up to 38% in LDL cholesterol in patients with dyslipidemia. In patients with triglycerides above 300 mg/dl, the median decrease in triglyceride levels was as high as 31% and the mean increase in HDL cholesterol reached 19%. This new extended-release formulation of fluvastatin provides sustained and slow release of drug over an 8-h period. At high doses, the conventional formulation of fluvastatin displays nonlinear pharmacokinetics, which may be due to saturation of hepatic uptake. In contrast, the extended-release formulation, by steady and slow release of drug, is expected to avoid hepatic saturation and thus enhance inhibition of cholesterol synthesis without compromising the good tolerability and safety (1).

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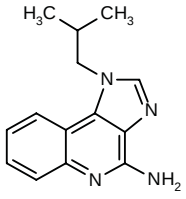
Original monograph - Drugs Fut 1991, 16: 804.

Imiquimod
Aldara®
Zartra®

Treatment of Genital Warts
Oncolytic

EN: 111924



$C_{14}H_{16}N_4$

3M Pharm.; Daiichi Pharm.

Imiquimod 5% cream was applied 3 times a week in 2 patients with intraepidermal carcinoma. In the first patient, 2 lesions resolved with 17 weeks of treatment, without developing erythema or treatment discomfort. Eight months after the initial presentation, a biopsy of the chest revealed a scar with an increased number of blood vessels. The biopsy showed no evidence of carcinoma, and the patient had no recurrence at 15 months post-treatment. Treatment of a single lesion in the second patient was stopped at week 9 when an erythema and small erosions were observed in the treatment area. Three weeks later, the lesion healed without sequelae and no recurrence was seen at 12 months of follow-up (1).

The efficacy and safety of imiquimod were examined in 22 patients with actinic keratosis (AK) who applied the cream to one side of their body, and vehicle cream to the other side, 3 times weekly for 8 weeks or until clearance of lesions. Seventeen patients were evaluable for up to 8 weeks after treatment. Imiquimod-treated patients showed a significant reduction in the average number of lesions. Most patients reported acceptable, mild to moderate adverse events, particularly irritation and reddening of the skin (2).

In a randomized, double-blind study of imiquimod 5% cream for the treatment of AK, 17 patients treated their lesions with imiquimod on one side of the body and with vehicle on the other side. Treatment was 3 times weekly for 8 weeks, allowing patients 1 rest period of up to 3 weeks. Imiquimod treatment significantly improved the reduction of AK lesions as compared to placebo, with lesion counts remaining stable up to 4 weeks posttreatment (3).

Fifty patients with AK were treated with imiquimod over 6-10 weeks in a study with follow-up periods of up to 2 years. Patients were treated 3 times a week until all AK developed a mild erythema, at which time therapy was reduced to 2 times a week. Imiquimod therapy cleared nearly all lesions with no recurrences found during the follow-up periods. No histological signs of persisting AK were detected. Mild erythema was observed in all patients, 2 of whom reported itching, but there were no signs of systemic effects. The activation of the local immune response by the drug was confirmed by comparison of gene expression in lesional biopsies taken before and during treatment (4).

The safety and efficacy of imiquimod 5% cream was studied in a multicenter, open-label, dose-response trial in 99 patients with superficial basal cell carcinoma (sBCC). Patients were randomized to receive imiquimod once daily, twice daily, once daily 3 times a week or twice daily 3 times a week. Histologic clearance rates were 100, 87.9, 73.3 and 69.7% in the twice-daily, once-daily, twice-daily 3 times/week and once-daily 3 times/week regimens, respectively. Dose-related inflammatory skin reactions at the site of application were common but generally well tolerated (5).

Imiquimod 5% cream showed promise as a treatment for superficial basal cell carcinoma (sBCC) in 2 randomized, multicenter, dose response trials. In the first study, patients treated a single sBCC for 6 weeks (once daily, twice daily 3 days/week or once daily 3 days/week). In the second study, patients treated a single sBCC for 12 weeks (once daily, once daily 5 days/week or once daily 3 days/week). The histological tumor clearance rates for the 96 evaluable patients in the first study were 88, 73 and 70% for the once-daily, twice-daily 3 days/week and once-daily 3 days/week treatment groups, respectively. For the 118 evaluable patients in the second study, these rates were 87, 81, 52 and 19% for the once-daily, once-daily 5 days/week, once-daily 3 days/week and the combined vehicle dosing groups, respectively. The incidence of local skin reactions increased in both studies with increasing dosing frequency. Local reactions led to 1 patient discontinuing in the first study and 17 patients in the second study (6).

An almost 90% clearance of sBCC following daily application of imiquimod 5% cream (Aldara®) for 6 weeks was reported. In the multicenter, dose-ranging phase II trial, imiquimod was applied by 99 patients to a single biopsy-proven sBCC tumor for 6 weeks. Treatment efficacy was measured by complete histological clearance of sBCC at posttreatment biopsy. Of the 33 patients in the once-daily regimen, 87.9% showed complete clearance of their sBCC tumor. Based on the results of this study, 3M has decided to advance the product to phase III trials which will include 48 sites in the U.S. and more than 75 international sites (7).

A clinical trial was conducted to evaluate the efficacy of imiquimod on skin metastases of 6 patients with malignant melanoma AJCC III/IV. Epifocal imiquimod was applied 3 times a week for 1 month and patients were observed for 3 months. Treated lesions were completely resolved in 1 patient, and in 2 patients the disease was stabilized with intermittent reduction of tumor growth and local tumor control over 9 and 6 months, respectively. Disease progressed in the other 3 patients. Local skin irritation was the only therapy-related adverse event. Immunomonitoring studies detected the induction of cytotoxic T-cells specific for the melanoma antigenes MelanA/MART1 and gp100, respectively, in 2/3 patients with clinical responses (8).

Imiquimod 5% cream has been investigated for its ability to induce natural interferons and limit the recurrence of keloids after surgical excision. Imiquimod 5% cream was applied directly to the suture line and the surrounding area after 13 keloids were surgically excised from 12 patients. Nightly applications limited to 125 mg of cream were applied for 8 weeks. Eight patients completed the treatment period and a minimum of 6 months follow-up, with none of their excised keloids recurring. No systemic symptoms of interferon toxicity were observed and the degree of application site adverse reactions was deemed acceptable. None of the 5 keloids of 4 other patients who completed treatment and 3-5 months of follow-up have recurred. Thus, imiquimod appears to be a safe and effective treatment for minimizing keloid recurrences (9).

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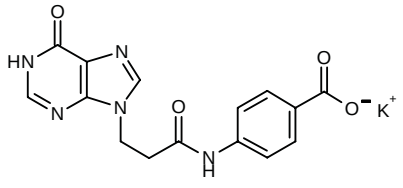
Original monograph - Drugs Fut 1989, 14: 870.

Leteprinim Potassium *Antiparkinsonian*
Neotrofin® *Treatment of Alzheimer's Disease*

EN: 204883



$C_{15}H_{12}KN_5O_4$ **NeoTherapeutics**

The potential of AIT-082 for the therapy of neurodegenerative disorders was demonstrated in a study of the drug's protective activity against long-term excitotoxicity of hippocampal neurons in rats with kainate-induced status epilepticus. Seizures and neurotoxicity were almost completely inhibited by diazepam (20 mg/kg i.p., 20 min before kainate injection), whereas AIT-082 treatment (60 mg/kg/day i.p. for 7 days beginning 20 min before kainate injection) had no effect on seizures but did decrease kainate-induced mortality, the reduction of glutamic acid decarboxylase activity and the loss of hippocampal neurons (1).

The upregulation of nerve growth factor (NGF) by AIT-082 was the subject of a study evaluating the collateral sprouting of undamaged nociceptive fibers in rat skin, which is induced by both endogenous and exogenous NGF. Sprouting of myelinated and unmyelinated nociceptive fibers resulted from systemic injection of AIT-082 in normally innervated skin. AIT-082 also enhanced ongoing sprouting into adjacent denervated skin. NGF levels and the areas of the nociceptive fields were increased by approximately 50% after 19 days of AIT-082 treatment. AIT-082 did not affect axonal regeneration, which is NGF-independent, and did not induce sprouting of NGF-insensitive mechanosensory nerves. Anti-NGF treatment inhibited nociceptive sprouting. This was restored by AIT-082 administration, although the AIT-082-induced sprouting was eliminated by increased anti-NGF treatment. Unlike NGF, however, AIT-082 does not induce hyperalgesia. These findings suggest that AIT-082 might cause an upregulation of cutaneous NGF levels in diabetic patients, thereby promoting NGF-sensitive functions in peripheral nerves compromised by diabetic neuropathy. Upregulation of endogenous NGF in diseased or traumatized CNS might also induce undamaged NGF-sensitive neurons to sprout, contributing to the repair of CNS damage (2).

To assess whether or not AIT-082 acts through purine receptors, researchers have exposed hippocampal neurons to glutamate for 10 min and then observed recovery in the presence of AIT-082 plus antagonists for the A_1, A_{2A}, A_{2B}, A_3 and P_2 receptors. As antagonism of these receptors did not affect the neuroprotective activity of AIT-082, it was concluded that the agent's activity is not mediated by these purinergic receptors (3).

An analysis of the absorption, excretion and formation of metabolites of AIT-082 was recently performed in male CFW mice. Fasted mice were administered unlabeled AIT-082 (30 mg/kg) spiked with radiolabeled AIT-082 (50 μCi). Urine and feces samples collected at 8 and 24 h were analyzed for ^{14}C content. The mean ^{14}C recovery from urine after i.p. administration was 80.4% of the total radioactivity and 22.8% was found in the feces. After oral administration, a mean recovery of 11.6% of the total radioactivity was detected in urine and 80.6% in the feces. After 24 h, between 1-5% residual ^{14}C remained in the body. Administration of AIT-082 did not result in the formation of a significant amount of metabolites or degradation products (4).

A quantification method for the quantitative analysis of leteprinim potassium in dog urine has been developed. Leteprinim potassium is deionized at pH 3 and the free acid is extracted with octanol. This solution is reextracted with PBS (pH 7.4) to regenerate the salt, which is analyzed by reverse phase HPLC, in conjunction with a diode-array-detector set at 269 nm. This method was validated over the range 4-200 μg/ml using a calibration curve with a dynamic range of 47 ng/ml to 47 μg/ml. Experiments showing the accuracy, precision, ruggedness, specificity, linearity and system suitability have been completed successfully. At the limit of quantification, the mean accuracy and precision are within 20% for quadruplicate samples (5).

Recent research indicates that the saturable efflux mechanism(s) mediating the transport of AIT-082 from brain to blood are present at the capillary endothelium. This was shown through intraparenchymal administration of ^{14}C-labeled AIT-082 in mice accomplished with a stereotaxic apparatus. After drug administration, the brain was removed at different times and the radioactivity was measured. The $t_{1/2}$ of disappearance from brain was found to be 38.2 ± 2.4 min, while the $t_{1/2}$ for sucrose disappearance was 101.1 ± 6.5 min. Further research revealed that 600-fold excess unlabeled AIT-082, MK-571, verapamil and salicylic acid all significantly inhibited the efflux of ^{14}C-AIT-082 from brain after intraparenchymal injection (6).

Results from preclinical trials with leteprinim potassium indicate that the agent stimulated the proliferation of brain stem cells in adult mice. Stimulation of neurogenesis may be a means of repopulating the brain with new neurons and therefore provide a therapeutic approach to slowing and even reversing the damage done by disease or injury. In two blinded, dose-response studies, mice were given a single administration of leteprinin and 24 h later the number of newly formed brain stem cells was counted. Analysis revealed that in animals treated with doses between 1 and 10 mg/kg of leteprinin, there was a significantly higher number of newly generated brain cells. Studies are currently ongoing to examine the effect of multiple doses of leteprinim and to determine whether the newly formed brain stem cells will mature to become neurons (7).

AIT-082 was found to mildly stimulate septodentate sprouting but to have no effect on lesion-induced locomotor hyperactivity in a study of rats with entorhinal cortex (EC) lesions. Rats with EC lesions and sham-operated rats were injected with AIT-082 (30 mg/kg i.p.) or saline just after surgery and each day thereafter. The measure of septodentate sprouting was the intensity of acetylcholinesterase (AChE) label assessed by optical densitometry. At 4 days postlesion, AIT-082 produced an elevation of the AChE-label in the outer molecular layer of the ventral dentate gyrus. An elevation of the AChE-label in the outer molecular layer of the dorsal dentate gyrus was found at 15 days postlesion. Bilateral EC lesions caused increases in locomotor activity from 3-14 days postlesion which were not affected by AIT-082 treatment (8).

Two studies have been conducted to evaluate the effect of AIT-082 on cognitive and neuromotor function after traumatic brain injury in male Sprague-Dawley rats. In both studies rats were anesthetized and subjected to either lateral fluid percussion brain injury or sham injury. In the first study, 10 min after injury the rats were randomized to a single dose of AIT-082 (60 mg/kg i.p.) or vehicle. After 48 h, it was found that single bolus injections of AIT-082 did not improve acute posttraumatic memory function as measured by the Morris water maze, nor did it improve edema formation. In the second study, rats were randomized to receive either AIT-082 (60 mg/kg i.p.) or vehicle either 20 min before or 10 min after injury; thereafter the drug was administered daily. No effect was found on posttraumatic learning ability, evaluated on days 12 and 13 postinjury, or on gross neuromotor function, evaluated on days 2, 7 and 14 postinjury. Vestibulomotor function significantly improved, however, at day 5 postinjury ($p > 0.05$) (9).

It has been reported that administration of scopolamine 0.3 mg/kg impairs the performance of rats in a non-match to sample task (NMTS) and that subsequent AIT-082 administration (25 mg/kg) reduces this impairment. In a study conducted to determine if the AIT-082 dose administered in these memory assessments was optimal, scopolamine injection was followed by administration of 15, 30 and 60 mg/kg AIT-082. Performance on the NMTS was evaluated after 1, 2 and 3 administrations of AIT-082 and results revealed that the antiamnestic property of AIT-082 is a function of the number of administrations instead of the acute dosage level (10).

AIT-082 was the subject of a phase I, double-blind, placebo-controlled, multiple-dose study evaluating the safety, tolerance and pharmacokinetics of the drug in 36 patients with mild Alzheimer's disease. The study population included 22 men and 14 women (mean age = 72 years). Patients were randomized to escalating doses of oral AIT-082 100, 500 or 2000 mg/day or placebo once daily for 1 week. Pharmacokinetic and cognitive assessments, including MMSA, ADAS-cog and a neuropsychological battery, were made at the beginning and end of the trial. The drug was well tolerated, there were no serious adverse events and all of the patients completed the study. Analysis of the results is currently in progress (11).

NeoTherapeutics has reported encouraging results following the complete analysis of data from a phase II trial of leteprinim potassium for the reduction of symptoms of Alzheimer's disease. Patients who received leteprinin once daily showed a statistically significant improvement in the Neuropsychiatric Inventory (NPI) rating scale over the course of 90 days of treatment. NPI is a recognized test that measures behavioral symptoms such as psychosis, aggression and hallucinations. The results indicated that those patients who were suffering from more moderate Alzheimer's disease and who received the 500-mg dose of leteprinim improved an average of 1.5 points from baseline on the ADAS-cog after only 90 days of treatment. The study also demonstrated that leteprinim is safe and well tolerated in elderly patients with Alzheimer's disease. Of the 431 patients enrolled in the study, 389 (90%) completed dosing through day 90. The high percentage of patients completing the study is supportive of the drug's tolerability and safety. The frequency of reported adverse effects was similar between patients receiving the study drug and those receiving placebo (12).

The leteprinim potassium spinal cord injury trial has been further expanded to include 2 additional sites. A total of 7 patients are now enrolled in the trial. The trial is expected to enroll a total of 30-40 patients in this open-label study, in which patients with subacute, complete spinal cord injury will receive leteprinim for 12 weeks and will be evaluated at regular intervals. In addition to safety and tolerance assessments, the Standard Neurological Classification of Spinal Cord Injury (SNCSCI) manual motor score will be used as primary evidence of efficacy. Secondary efficacy measures include the SNCSCI sensory exam, the American Spinal Injury Association impairment scale and the Functional Independence Measure (13).

A total of 521 patients have been enrolled in a U.S. double-blind, placebo-controlled, pivotal trial of leteprinim potassium in Alzheimer's disease. All patients are now receiving the study drug or placebo and are expected to complete the first 12 weeks of the study by November of this year, with results expected to be reported during the first quarter of 2002. In this pivotal clinical study, patients are given 500 mg leteprinim or placebo twice daily for 1 week, followed by 1000 mg of leteprinim or placebo twice daily for 11 weeks, assuming no adverse reactions during the first week of dosing. The study incorporates 12 weeks of treatment for the primary analysis, followed by 12 weeks of treatment in order to allow patients initially given placebo to receive leteprinim. No unexpected or serious adverse reactions have been observed to date and nearly all patients who have completed the first week have been escalated to the higher dose, with good tolerability. The primary endpoints for this study are the ADAS-cog for memory and other cognitive deficits, and the Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change (ADCS-CGIC). There are also four secondary endpoints consisting of standard memory and behavioral tests. A second longer term pivotal study is planned to commence in 2002, in which disease course modification will be measured over 1 year of treatment, while effects on symptom improvement will be measured after 12 weeks of treatment. Assuming positive results from the current and the second 12-week studies, the company expects to file an NDA with the U.S. FDA in 2003 (14).

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6. Yan, R., Taylor, E.M. *Further characterization of the saturable efflux of 14C-AIT-082 from brain.* Soc Neurosci Abst 2000, 26(Part 1): Abst 127.3.

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

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10. Gittis, A.G., Byrd, T.A. *The effects of dose and repeat administration on the anti-amnestic properties of AIT-082.* Soc Neurosci Abst 2000, 26(Part 2): Abst 753.8.

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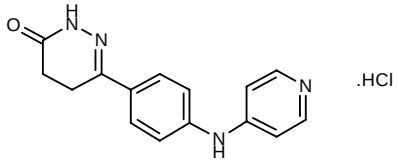
14. *Enrollment completed in pivotal Alzheimer's disease trial of Neotrofin.* DailyDrugNews.com (Daily Essentials) Sept 17, 2001.

Original monograph - Drugs Fut 1997, 22: 945.

MCI-154

Treatment of Heart Failure

EN: 120907



.HCl

$C_{15}H_{14}N_4O.HCl$ **Mitsubishi-Tokyo Pharm.**

MCI-154 was tested using a new high-throughput technique to record real-time changes in sarcomere length in response to different pCa concentrations in skinned cardiomyocytes. Results showed that the compound increased Ca^{2+} sensitivity by increasing cooperativity of myofilaments, but did not have any effects at low Ca^{2+} concentration (1).

MCI-154 was demonstrated in animal experiments to exert a direct positive inotropic effect, as well as to be able to reverse isoflurane-depressed myocardial contractility and enhance the systemic and coronary vasodilating effects of isoflurane. Isoflurane-anesthetized dogs showed reductions in mean aortic pressure, left ventricular systolic pressure, systemic and coronary vascular resistance, myocardial contractility, segment shortening and dP/dt_{max} compared to conscious animals. In the presence or absence of autonomic nervous system activity, MCI-154 (0.5 and 1.0 μg/kg/min over 15 min) produced increases in heart rate, cardiac output and coronary blood flow and restored myocardial contractility, segment shortening and dP/dt_{max} reductions induced by isoflurane; it also dose-dependently enhanced the decreases in systemic and coronary vascular resistance seen following isoflurane administration (2).

Mitsubishi-Tokyo Pharmaceuticals is evaluating MCI-154 in phase II clinical trials for the treatment of heart failure (3).

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2. Takahashi, S., Cho, S., Tomiyasu, S., Sumikawa, K. *Interaction of MCI-154, a calcium sensitizer, and isoflurane on myocardial contractility and hemodynamics in chronically instrumented dogs.* Annu Meet Am Soc Anesthesiol (ASA) (Oct 14-18, San Francisco) 2000, Abst A-649.

3. Mitsubishi-Tokyo Pharmaceuticals Product Pipeline 2000, March 31.

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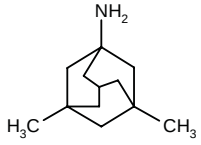
Memantine Hydrochloride
Akatinol®

Treatment of Alzheimer's Disease
Treatment of Diabetic Neuropathy

EN: 091101



.HCl

$C_{12}H_{21}N.HCl$ **Merz; Neurobiological Technologies; Lundbeck; Forest**

A meta-analysis has been performed on data from 2 placebo-controlled trials of memantine 20 mg/day for the treatment of vascular dementia with the goal of determining the impact of various subgroups on cognitive outcome. Subgroups identified in the randomized, double-blind trials included those with and without macrolesions, those with large vessel disease and those with small vessel disease. In a total of 836 evaluable patients, mean Alzheimer's Disease Assessment Scale cognitive subscale total scores were superior in the memantine treatment group *versus* the placebo group. Patients with macrolesions, however, had a smaller mean difference in change from baseline than those without macrolesions. Patients with small vessel disease had a greater difference between treatment groups in favor of memantine than patients with large vessel disease. While small vessel disease patients benefited most from memantine treatment, those with large vessel disease or macrolesions given placebo experienced less cognitive decline, suggesting that stroke or multiple infarctions may not be the primary cause of cognitive decline in patients with vascular dementia (1).

Memantine was the subject of a 6-month, placebo-controlled, double-blind efficacy and tolerability study conducted in multiple centers with 252 patients with advanced Alzheimer's disease. Patients were randomized to either memantine 10 mg b.i.d. or placebo. Though the status of both groups deteriorated over the course of the study, memantine-treated patients experienced smaller declines in various endpoints. Memantine treatment was found to be statistically superior to placebo in assessments of clinical global change, function and cognition. Resource Utilization in Dementia scale results revealed that memantine treatment was advantageous

with respect to caregiver time and total cost. The drug was safe and well tolerated (2).

At Forest Laboratories' meeting with the FDA to review a summary of the clinical data on memantine hydrochloride for the treatment of moderately severe to severe Alzheimer's disease, the agency agreed that the summary data of the phase III study conducted in the U.S., if confirmed in a full submission, provided evidence of efficacy for the drug in this indication. The FDA indicated that a second study performed in Europe would likely need to be reviewed by an advisory committee to determine whether the specific endpoints utilized were adequate to qualify it as a second study demonstrating efficacy. As a result, the company intends to prepare an NDA for submission around the end of year 2001, but will also begin additional phase III studies this spring in both mild to moderate and moderately severe to severe AD. These studies would be completed in the second half of 2002 and used as additional evidence of efficacy as needed. According to this timetable, memantine could be launched by the second half of 2003, or even sooner if the advisory committee recommends and the FDA accepts the European study for inclusion in the NDA (3).

Neurobiological Technologies has announced that Forest Laboratories will be conducting the second of two necessary trials for registration of memantine for the treatment of painful diabetic neuropathy. Neurobiological Technologies conducted the first trial with an enrollment of 400 patients and positive results were reported. Forest Laboratories is conducting an additional large-scale, multicenter, double-blind, placebo-controlled trial to assess the safety and efficacy of memantine in the treatment of diabetic neuropathy. Neurobiological Technologies has an agreement with Merz which involves milestone payments and a share of revenues from the sale of memantine through the collaborative efforts of Merz, Forest Laboratories and H. Lundbeck (4).

1. Wilcock, G., Stoeffler, A., Sahin, K., Moebius, H.J. *Neuro-radiological findings and the magnitude of cognitive benefit by memantine treatment. A subgroup analysis of two placebo-controlled clinical trials in vascular dementia.* Eur Neuropsychopharmacol 2000, 10(Suppl. 3): Abst P.4.013.

2. Reisberg, B., Ferris, S., Sahin, K., Windscheif, U., Möbius, H.J. *Results of a placebo-controlled 6-month trial with memantine in moderate to severe Alzheimer's disease (AD).* Eur Neuropsychopharmacol 2000, 10(Suppl. 3): Abst P.4.021.

3. *Product developments announced by Forest.* DailyDrugNews.com (Daily Essentials) Feb 2, 2001.

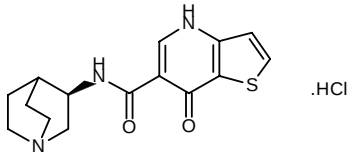
4. *Memantine to be evaluated in the treatment of diabetic neuropathy.* DailyDrugNews.com (Daily Essentials) Aug 3, 2001.

Original monograph - Drugs Fut 1976, 1: 427.

MKC-733

Treatment of GERD

EN: 219330



.HCl

$C_{15}H_{17}N_3O_2S.HCl$ **Mitsubishi-Tokyo Pharm.; Janssen**

The role of 5-HT_3 receptors in fasting and fed antral motility was investigated in a double-blind, randomized, placebo-controlled study of MKC-733 in 12 healthy male subjects. Fasting subjects were administered either single doses of MKC-733 (0.2, 1.0 or 4.0 mg) or placebo and fasting manometry was recorded for 8 h. A second dose of MKC-733 was followed by a mixed nutrient meal 30 min later. In the fasting manometry the number of MMCs emanating from the gastric antrum per hour were found to be significantly increased. The number of antral contractions during phase II of the MMC also increased significantly but the motility index did not. There was also a significant reduction in the duration of phase I of the MMC. During fed manometry there were no significant effects on the motility index, the number and amplitude of antral contractions or the time to onset of postprandial antral activity. Stimulation of 5-HT_3 receptors by MKC-733, therefore, appeared to have a significant effect on fasting, but not fed, antral motility (1).

Two randomized, double-blind, placebo-controlled, crossover studies were performed to evaluate the effects of MKC-733 on small bowel transit time, gastric fundal relaxation and antral motility. Single oral doses of MKC-733 (0.2, 1 or 4 mg) or placebo were administered to fasting healthy male volunteers. After 30 min, subjects consumed either a radiolabeled pancake and milkshake meal or a viscous drink. For the liquid meal, small bowel transit time was shown to dose-dependently decrease. The maximum cross-sectional area of the proximal stomach was significantly increased 30 min after the meal by the 4 mg dose as compared to placebo. No significant effects on antral contraction speed or frequency were seen. It was concluded that 5-HT_3 agonists relax the gastric fundus but do not inhibit antral motility and may have a stimulatory effect on small bowel secretion and motility, resulting in faster intestinal transit (2).

1. Coleman, N.S., Wright, J., Parker, M., Spiller, R.C. *MKC-733, a selective 5-HT_3 receptor agonist, stimulates fasting human antral motility.* Dig Dis Week (May 20-23, Atlanta) 2001, Abst 2343.

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Original monograph - Drugs Fut 1999, 24: 966.

Natalizumab
AN100226
Antegren®

Treatment of IBD
Treatment of Multiple Sclerosis

EN: 215926

Immunoglobulin G_4 (human-mouse monoclonal AN100226 γ-chain anti-human integrin 4), disulfide with human-mouse monoclonal AN100226 light chain, dimer

Athena Neurosciences; Biogen

Elan and Biogen have reported positive results from preliminary analyses of two large phase II trials with natalizumab (Antegren®) in multiple sclerosis (MS) and Crohn's disease. The first study, a double-blind, placebo-controlled phase II trial involving 213 MS patients, was conducted at 26 sites in the U.S., Canada and the U.K. Patients received monthly doses of natalizumab or placebo over a 6-month period. The primary endpoint of a reduction in new gadolinium-enhancing lesions compared to placebo over the 6-month treatment period was achieved with a high degree of statistical significance. A separate double-blind, placebo-controlled phase II trial conducted at 38 sites in 8 European countries included 240 patients with moderate to severe Crohn's disease. Patients received doses of natalizumab or placebo at week 0 and week 4. This study also demonstrated statistically positive results on multiple endpoints, including induction of remission as measured by the Crohn's Disease Activity Index. Based on these positive results, the companies expect to begin phase III evaluation in 2001 for both MS and Crohn's disease. These clinical studies are the result of an exclusive worldwide collaboration between Elan and Biogen established in August 2000 to develop, manufacture and commercialize Antegren® (1).

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

Original monograph - Drugs Fut 2000, 25: 917.

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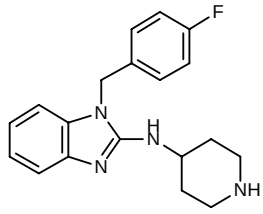
Norastemizole
Soltara®

Treatment of Allergic Rhinitis

EN: 209628



$C_{19}H_{21}FN_4$ **Sepracor**

Researchers have developed a descriptive pharmacokinetic model for norastemizole to estimate interindividual variability in pharmacokinetics. Nearly 2000 plasma norastemizole samples were collected during 4 studies including a total of 102 healthy volunteers. Subjects were administered oral norastemizole in capsules and aqueous solutions in doses of 6.4-300 mg. The pharmacokinetics of norastemizole were found to be independent of dose and to exhibit moderate variability (21, 38 and 41% for absorption rate, clearance and central compartment volume, respectively) (1).

Sepracor's NDA for norastemizole (Soltara®) has been accepted for formal review by the FDA. The company submitted the NDA on March 9, 2001 seeking clearance for the use of norastemizole in the treatment of allergic rhinitis as capsules of 15 and 30 mg. The NDA was supported by data from 7 large-scale allergic rhinitis studies, over 30 smaller clinical trials and numerous preclinical studies. The clinical studies included over 3700 subjects with seasonal and perennial allergic rhinitis administered norastemizole at doses of 2-300 mg. Sepracor is also developing a norastemizole/pseudoephedrine combination for the treatment of allergic rhinitis, as well as syrup and rapidly dissolving tablet formulations (2).

1. Bachman, W.J., Maier, G., Koch, P., Amato, D., Tripp, K., Degraw, S., Baumgartner, R. *Population pharmacokinetics of norastemizole (NORA) in healthy volunteers.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 2332.

2. *Soltara moves into formal review at the FDA.* DailyDrugNews.com (Daily Essentials) May 10, 2001.

Original monograph - Drugs Fut 1998, 23: 966.

  CCC: 0377-8282/2001

OM-89 Subreum®

Immunomodulator

EN: 122672

OM Pharma

The *Escherichia coli* extract subreum has demonstrated efficacy and excellent safety in clinical trials in rheumatoid arthritis and has been postulated to act by inducing oral tolerance and a switch from Th1 to Th2 responses. It has now been assessed for its clinical effects in patients with different forms of spondyloarthropathy (ankylosing spondylitis, psoriatic arthritis, reactive arthritis and undifferentiated spondyloarthropathy) in a double-blind trial in which patients were administered a dose of 24 mg/day for 48 weeks or placebo. Although no significant difference from placebo was seen in the ankylosing spondylitis or psoriatic arthritis patients, those with undifferentiated spondyloarthropathy showed significant improvement in all clinical parameters evaluated. Moreover, 6 of 8 patients receiving subreum in this subgroup, compared to only 1 of 7 placebo patients, had clinical remission at 24-36 weeks. It is suggested that this immunoactive preparation may prevent the progression to ankylosing spondylitis in such patients (1).

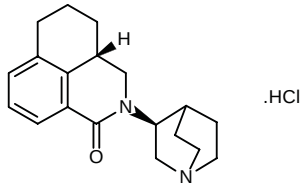
1. Mielants, H., Goemaere, S., Van den Bosch, F., Goethals, K., de Vlam, K., Vanneuville, B. *The effect of subreum (OM 8980) on the peripheral manifestations in spondyloartropathy patients.* 64th Annu Meet Am Coll Rheumatol (Oct 29-Nov 2, Philadelphia) 2000, Abst 216.

Original monograph - Drugs Fut 1994, 19: 845.

Palonosetron Hydrochloride

Antiemetic

EN: 223772



.HCl

$C_{19}H_{24}N_2O.HCl$ **Roche Bioscience; Helsinn; MGI**

MGI Pharma and Helsinn have signed a definitive agreement granting MGI Pharma exclusive North American license and distribution rights to palonosetron hydrochloride, currently in phase III development for the prevention of chemotherapy-induced nausea and vomiting. Based on positive results from a U.S. phase II trial, Helsinn initiated a phase III clinical trial program that is intended to enroll more than 1900 patients in several well-controlled, double-blind trials comparing palonosetron to currently available 5-HT_3 antagonists. Completion of the phase III trials could allow for the NDA submission in the first half of 2002. Under the terms of the exclusive license agreement, MGI Pharma will make USD 11 million in upfront payments, including the initial USD 5 million made upon signature of the letter of intent, and will make additional payments based on the achievement of certain milestones through the approval of palonosetron in the U.S. Helsinn will continue to fund and conduct all development of palonosetron and MGI Pharma will also pay royalties and product supply fees based upon net sales (1).

1. *MGI Pharma and Helsinn sign definitive agreement for palonosetron.* DailyDrugNews.com (Daily Essentials) April 11, 2001.

Original monograph - Drugs Fut 1996, 21: 906.

Additional Reference

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Pegvisomant Trovert® Somavert®

Treatment of Acromegaly

EN: 253947

18-L-Aspartic acid-21-L-asparagine-120-L-lysine-167-L-asparagine-168-L-alanine-171-L-serine-172-L-arginine-174-L-serine-179-L-threonine-growth hormone (human), reaction product with polyethylene glycol

Genentech; Sensus

Pegvisomant has been shown to reduce circulating IGF-1 and to be efficacious in the treatment of acromegaly. Transgenic mice constitutively expressing a growth hormone (GH) antagonist and nontransgenic mice were studied with the DMBA model of breast carcinogenesis to evaluate tumor incidence. The transgenic mice had lower IGF-1 levels, altered body weight and reduced tumor incidence as compared with controls. At 39 weeks, 31.6% of transgenic animals were without tumor as compared to 68.2% of controls (p <0.001). Pegvisomant and other GH antagonists, therefore, may be clinically useful in the prevention of cancer (1).

The therapeutic potential of downregulating the GH/IGF-I axis in the management of colon cancer has been investigated using pegvisomant and a syngeneic mouse model of colon cancer and hepatic metastasis. BALB/c mice injected with colon carcinoma CT-26 cells were treated with saline, pegvisomant 5 mg/day s.c., the topoisomerase I inhibitor irinotecan 100 mg/kg s.c. on days 7, 14 and 21, or a pegvisomant-irinotecan combination. The results showed significant reductions in both primary tumor size in the spleen and hepatic metastases in pegvisomant-treated animals. The GH antagonist was effective alone and potentiated the effects of irinotecan.

Further studies of pegvisomant in colon cancer appear warranted (2).

The GH receptor antagonist pegvisomant (0, 1.25, 2.5, 5 and 10 mg/kg/day x 7) was administered to mice in order to study the effects of GH in regulating the expression of the hepatic and renal GH and insulin-like growth factor (IGF) system. While body weight, food consumption and blood glucose were not changed, all doses decreased circulating IGF-1 levels dose-dependently, and the highest doses decreased hepatic and renal IGF-1 levels, also in a dose-dependent manner. All doses significantly increased hepatic GH receptor and GH binding protein mRNA levels. At 2.5 and 5 mg/kg/day, pegvisomant significantly increased endogenous circulatory GH and all doses resulted in increased circulating IGF binding protein-4 and hepatic IGF binding protein-4 mRNA levels. At high pegvisomant doses, renal GH receptor and GH binding protein mRNA levels were not changed and in most groups, renal IGF binding protein-3 mRNA levels were not changed. The highest doses, however, significantly increased IGF binding protein-1, -4 and -5 (3).

Pegvisomant was evaluated for its efficacy as an antineoplastic agent in *in vivo* models of 3 GH-responsive tumor types. Doses of pegvisomant which reduced circulating IGF-1 levels by 20-50% decreased the tumor volume of T-47D, MCF-7 and MDA-MB-231 xenografts by 42-62% as compared with controls. The effect was dose-dependent and an increase in apoptotic cells was seen in the pegvisomant group. The drug showed potent anticancer activity in syngeneic and xenograft models of colon cancer. The development of liver metastases was reduced and the drug potentiated the action of a standard chemotherapeutic agent. Mice bearing xenografts of human meningioma developed significantly smaller tumors when treated with pegvisomant as compared with vehicle. Benign, atypical and malignant tumors responded to treatment (4).

Pegvisomant was studied in 109 patients with active acromegaly and soft-tissue swelling. Patients included those who took part in a previous 12-week, double-blind, placebo-controlled study of pegvisomant 10-20 mg/day and 6 additional patients receiving 5-40 mg pegvisomant in an open-label study. In the initial study, pegvisomant 20 mg/day normalized serum IGF-I in 89% of patients and resulted in improvements in perspiration, fatigue, soft-tissue swelling and total symptom scores. These changes were maintained for a median 12 months. A dose-dependent reduction in ring size was found in the first study which was maintained at last visit in the second study. The fall in serum IGF-I was positively correlated with the fall in total symptom score and the scores for perspiration and soft-tissue swelling (5).

Patients with active acromegaly (n = 16) were administered pegvisomant 10-40 mg/day to study the effects of serum IGF-I normalization on serum IGF-11, IGF binding protein (IGFBP)-1, IGFBP-2 and the molar ratio of IGF-I and II to IGFBP-3. Treatment with pegvisomant reduced serum IGF-I to normal ranges in all patients and the decrease was correlated with a fall in fasting plasma insulin. Serum IGF-II was not changed. The IGF-I/IGFBP-3 molar ratio decreased and the IGF-II/IGFBP-3 molar ratio increased. The HOMA equation, which was used to calculate insulin, and the fall in IGFBP-1 indicated that improved insulin sensitivity caused the reduction of fasting plasma insulin and that IGF-II is independent of growth hormone (6).

In February 2001, Sensus submitted an NDA to the FDA for Somavert® (pegvisomant for injection), the first in a new class of GH receptor antagonists under investigation for the treatment of acromegaly. Somavert® has been granted orphan drug designation in the U.S., the E.U. and Japan. The product has been designated for priority review by the FDA. Additional regulatory filings are expected later this year (7).

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  CCC: 0377-8282/2001

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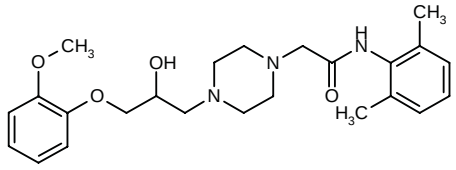
Ranolazine

Antianginal
Treatment of Heart Failure

EN: 101796



$C_{24}H_{33}N_3O_4$

Roche Bioscience; CV Therapeutics; Innovex

Ranolazine significantly reduced infarct size and cardiac troponin T release in a rat model of anterior descending coronary artery occlusion. Male Wistar rats were subjected to left anterior descending coronary artery occlusion for 25 min and a 2-h reperfusion 30 min after administration of saline or a ranolazine bolus injection (10 mg/kg + infusion of 9.6 mg/kg/h). Myocardial infarct size in ranolazine-treated rats was reduced by approximately 33% compared with controls (p <0.05). Release of cardiac troponin T into the plasma was also reduced from 65 ± 14 to 12 ± 2 ng/ml with ranolazine treatment (1).

Dogs with chronic left ventricular dysfunction and heart failure were given dobutamine (2-4 μg/kg/min over 30 min) or ranolazine (0.5 mg/kg by bolus plus 1.0 mg/kg/h over 30 min). Both treatments produced a significant and similar increase in ejection fraction and stroke volume without effects on heart rate or systemic pressure. However, in contrast to dobutamine, ranolazine improved left ventricular function without increasing coronary blood flow or myocardial oxygen consumption, and it significantly increased left ventricular efficiency. Ranolazine thus appears to partly inhibit the use of fatty acids to generate energy to pump blood, switching back to the use of the more oxygen-efficient carbohydrates or sugars (2).

A randomized, double-blind, placebo-controlled, multicenter phase II trial of orally administered ranolazine has been initiated in patients with New York Heart Association class III and IV CHF. The study is evaluating the pharmacokinetics, safety and tolerability of ranolazine in patients with severe CHF (3).

Results reported from the MARISA (Monotherapy Assessment of Ranolazine In Stable Angina) study demonstrate that patients with both chronic angina and a history of CHF tolerated and responded to ranolazine at least as well as angina patients without CHF. The phase III MARISA trial was a double-blind, placebo-controlled, crossover study of ranolazine in patients not receiving any other antianginal drugs. These chronic angina patients received ranolazine at doses of 500, 1000 or 1500 mg b.i.d. and placebo for 1 week each, and exercise tests at the time of trough and peak drug levels were evaluated in 146 patients without a history of CHF and 29 with NYHA class I or II CHF. At trough plasma concentrations, ranolazine produced significant increases in exercise duration, time to angina and time to 1-mm S-T segment depression compared to placebo in both groups of patients. At peak plasma levels, patients with CHF had increases in exercise duration and time to 1-mm S-T segment depression compared to placebo which were significantly greater than those observed in the patients without CHF. Adverse event rates were generally not greater in the CHF subgroup than in those without CHF. No clinically relevant changes in resting or exercise heart rate or systolic blood pressure were seen in either group of patients, an important finding considering that many patients with chronic angina and CHF also have low heart rate and blood pressure (4).

The last patient has completed treatment in the second pivotal phase III trial of ranolazine for chronic angina. CARISA (Combination Assessment of Ranolazine In Stable Angina) is a randomized, double-blind, placebo-controlled, multinational trial comparing the safety and efficacy of two dose regimens of ranolazine (750 mg twice daily and 1000 mg twice daily) together with background antianginal medications in over 700 chronic angina patients. Results from the second phase III trial are expected during the fourth quarter of 2001 (5).

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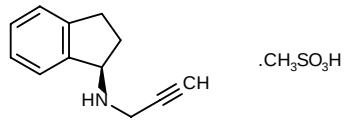
Rasagiline Mesilate

Antiparkinsonian
Treatment of Alzheimer's Disease

EN: 174550



$C_{12}H_{13}N.CH_4O_3S$ **Teva; Lundbeck**

The neuroprotective activity of rasagiline was assessed in an *in vitro* oxygen-glucose deprivation (OGD) model of time-course dependent neuronal cell death in nerve growth factor-differentiated PC12 cultures. Rasagiline was found to substantially reduce cell death induced by OGD, independently of monoamine oxidase B (MAO-B) inhibition. OGD-induced cell death was also reduced when rasagiline was added after the OGD insult. OGD-induced prostaglandin E_2 release was also inhibited by rasagiline in a dose-dependent manner. The metabolism of rasagiline does not involve the production of neurotoxic metabolites and therefore it may have an advantage over the MAO-B inhibitor selegiline in the treatment of Parkinson's disease (1).

The effects of rasagiline mesilate, its (*S*)-(–)-enantiomer TVP-1022, the racemic compound AGN-1135 and selegiline on monoamine oxidase (MAO-A and MAO-B) have been examined in a series of *in vitro*, *ex vivo* and *in vivo* experiments. Rasagiline is an analogue of selegiline but is associated with a reduced liability for amphetamine-like effects compared to the latter due to its metabolism to aminoindan instead of 1-methamphetamine. Both rasagiline and the racemate displayed highly potent, selective and irreversible inhibition of MAO-B *in vitro* and *in vivo*, whereas TVP-1022 showed little activity. Against rat brain MAO-B and MAO-A, rasagiline gave respective IC_{50} values of 4.43 ± 0.92 nM and 412 ± 123 nM, and against human brain enzymes respective IC_{50}s were 14 ± 3.5 nM and 710 ± 93 nM; similar potency was seen for selegiline (IC_{50} = 3.63 ± 0.59 nM, 944 ± 52 nM, 6.8 ± 1.4 nM and 1700 ± 444 nM, respectively, against rat brain MAO-B, rat brain MAO-A, human brain MAO-B and human brain MAO-A). As evaluated *ex vivo* following single oral doses, rasagiline inhibited brain and liver MAO-B with ED_{50} values of 0.1 and 0.042 mg/kg, respectively, and MAO-A in these tissues was inhibited with respective ED_{50} values of 6.48 and 2.38 mg/kg. Moreover, the compound selectively inhibited MAO-B in liver and brain in rats treated orally for 21 days, with respective ED_{50} values of 0.014 and 0.013 mg/kg. Although rasagiline had similar potency to selegiline *in vitro* for inhibition of MAO-B, it was at least 3 times more potent than selegiline *in vivo* against rat brain and liver MAO-B, and it maintained the selectivity of selegiline for MAO-B *versus* MAO-A. Based on these and other data, including reports of neuroprotective and antiapoptotic properties, it is suggested that rasagiline may have advantages over selegiline in the treatment of Parkinson's disease (2).

A 12-week, multicenter, parallel-group, double-blind, randomized, placebo-controlled trial has evaluated the efficacy, safety and tolerability of rasagiline mesilate (0.5, 1 and 2 mg/day) as adjunctive treatment to levodopa in 70 Parkinson's disease patients. A decrease of 23% in the total Unified Parkinson's Disease Rating Scale score was achieved in fluctuating patients as compared to an 8.5% decrease in the placebo patients. The treatment effect of all doses lasted at least 6 weeks after discontinuation. The drug was well tolerated and safe, with adverse events similar to those in the placebo group. All doses induced almost complete platelet MAO-B inhibition (3).

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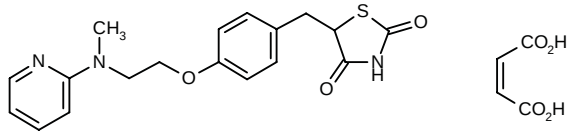
Rosiglitazone Maleate
Avandia®

Antidiabetic

EN: 210057



$C_{18}H_{19}N_3O_3S.C_4H_4O_4$ **GlaxoSmithKline; Bristol-Myers Squibb**

SmithKline Beecham has claimed the use of PPARγ agonists for delaying or preventing the development of type 1 diabetes by reducing insulin resistance. This method is particularly indicated in prepubescent persons with elevated levels of antibodies to glutamate decarboxylase, an indication of predisposition to develop

type 1 diabetes. Suitable PPARγ agonists included in the invention are thiazolidinediones, preferably rosiglitazone or its salts as well as pioglitazone, troglitazone or ciglitazone (1).

The safety and efficacy of combination therapy with rosiglitazone and an HMG-CoA reductase inhibitor were evaluated in patients with type 2 diabetes. Following 8 weeks of single-blind rosiglitazone therapy (4 mg b.i.d.), patients with LDL cholesterol below 160 mg/dl and triglycerides below 500 mg/dl were randomized to receive add-on placebo or atorvastatin 10 mg or 20 mg once daily for 16 further weeks. The majority of patients treated with rosiglitazone + atorvastatin achieved ADA targets for LDL cholesterol. Significant decreases in mean total cholesterol (27% and 32%, respectively), triglycerides (19% and 28%, respectively) and LDL cholesterol (33% and 40%, respectively) were achieved on atorvastatin 10 and 20 mg, and HDL cholesterol significantly increased in these groups compared to placebo. Adverse events were similar across all treatment groups, with no rhabdomyolysis or liver abnormalities (2).

The FDA has issued an approvable letter for the combination of Avandia® (rosiglitazone maleate) and insulin for the treatment of type 2 diabetes. Avandia® is currently approved in the U.S. as monotherapy or in combination with a sulfonylurea or metformin for patients with type 2 diabetes (3).

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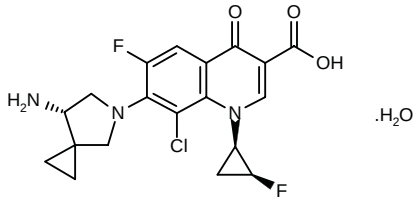
Sitafloxacin Hydrate *Quinolone Antibacterial*

EN: 176447



$C_{19}H_{18}ClF_2N_3O_3.H_2O$ **Daiichi Pharm.; Beijing General**

The MICs of sitafloxacin, gatifloxacin, moxifloxacin, sparfloxacin, levofloxacin and ciprofloxacin against 10 strains of *Mycobacterium ulcerans* were determined, with rifampicin, ethambutol, isoniazid and clarithromycin as comparators. All of the quinolones demonstrated high anti-*M. ulcerans* activity, with MIC_{90}s of 0.125, 0.25, 0.25, 0.5, 0.5 and 1 μg/ml for sitafloxacin, gatifloxacin, moxifloxacin, sparfloxacin, ciprofloxacin and levofloxacin, respectively. These values were 1, 8, >16 and 1 μg/ml for rifampicin, ethambutol, isoniazid and clarithromycin, respectively. The MIC_{90}s for the quinolones were within the range of achievable peak plasma levels (1).

The effects of DU-6859a, CS-834 and L-084 on rat and mouse caecal microflora have been assessed in conventional mice and caecum-skin fistula-implanted rats. Rats were administered the antimicrobials at oral doses of 30 mg/kg b.i.d. for 5 days. Results showed that DU-6859a greatly decreased caecal flora except for enterococci, CS-834 greatly reduced mouse caecal flora but had little influence on rat caecal flora, and L-084 had little impact on either rat or mouse caecal flora. *In vitro* studies indicated that the difference in antimicrobial activity on caecal flora was due to varying inactivation of the agents by caecum contents (2).

A phase I trial conducted in 12 male and 12 female volunteers evaluated the pharmacokinetics of a new capsule formulation of DU-6859. The new formulation was safe and well tolerated. By comparing the $AUC_{0-\infty}$ values following i.v. (400 mg 1-h infusion) and p.o. administration (500 mg), an absolute bioavailability of 89% was found. Pharmacokinetics were gender-independent and approximately 60% of unchanged DU-6859 was excreted in urine within 48 h (3).

An open phase II trial has been conducted to assess the efficacy and safety of sitafloxacin hydrate in the treatment of severe systemic infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecalis* (VRE). Nineteen patients were enrolled in the study with 10 infections caused by MRSA, 8 by VRE and 1 by both MRSA and VRE, and they received sitafloxacin at a dose of 400 mg i.v. once daily for a mean of 7 days. All but 1 patient had failed previous antibiotics. Clinical cure was obtained in 4 of 11 patients with MRSA infections, while 6 failed therapy and 1 was indeterminate; bacteriological cure was determined in 4 of these patients. In those with VRE infections, 5 cures were obtained and 4 treatment failures, and 6 patients had bacteriological cure. Possibly drug-related adverse events were observed in 12 patients and consisted mainly of diarrhea and rash. One case of seizures resulting in withdrawal from the study was reported but could have been due to concurrent propofol. Sitafloxacin may thus be a useful treatment option in certain severe, treatment-resistant infections due to these organisms (4).

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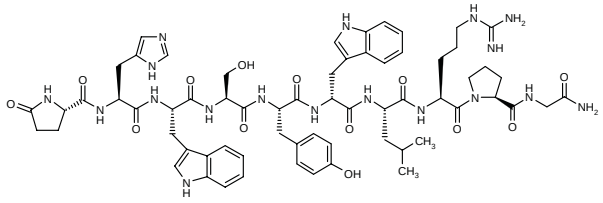
Triptorelin
Trelstar™

Treatment of Prostate Cancer

EN: 090485



$C_{64}H_{82}N_{18}O_{13}$

Debio RP

The FDA has granted marketing authorization for Debiopharm's Trelstar™ LA to treat advanced-stage prostate cancer. Trelstar™ LA is a controlled-release formulation of triptorelin which delivers the drug continuously over a period of 3 months after intramuscular injection. Extensive clinical studies comparing the effectiveness of the already approved 1-month controlled-release formulation of triptorelin (Trelstar™ Depot 3.75 mg) and the new 3-month formulation (Trelstar™ LA 11.25 mg) in men with advanced-stage prostate cancer have proven that administration of triptorelin every 3 months induces and maintains castration levels of serum testosterone as effectively as monthly injections. During the pivotal clinical trial, which proved that the 3-month formulation of triptorelin pamoate is as effective as the monthly formulation, secondary objectives included regression of pain, mean change in quality-of-life scales throughout the treatment period and testosterone pharmacodynamics. Patients treated with triptorelin pamoate used fewer analgesics after the start of treatment, and overall patients gained on average 5 kg of body weight. The local tolerance of the injections was excellent and Trelstar™ LA was well tolerated. Trelstar™ LA is approved in two different presentations: as a vial containing triptorelin pamoate to be reconstituted in sterile water for injection, and as Trelstar™ LA DebioClip™, a single-dose delivery system consisting of a vial containing triptorelin pamoate and a prefilled syringe containing 2 ml sterile water for injection (1).

1. *FDA grants approval for Debiopharm's Trelstar LA for use in advanced prostate cancer.* DailyDrugNews.com (Daily Essentials) July 6, 2001.

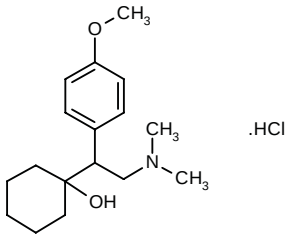
Original monograph - Drugs Fut 1978, 3: 645.

Venlafaxine Hydrochloride

Antidepressant
Anxiolytic
Treatment of Diabetic Neuropathy

Efexor®
Effexor®

EN: 100721



$C_{17}H_{27}NO_2.HCl$ **Wyeth-Ayerst; Almirall Prodesfarma**

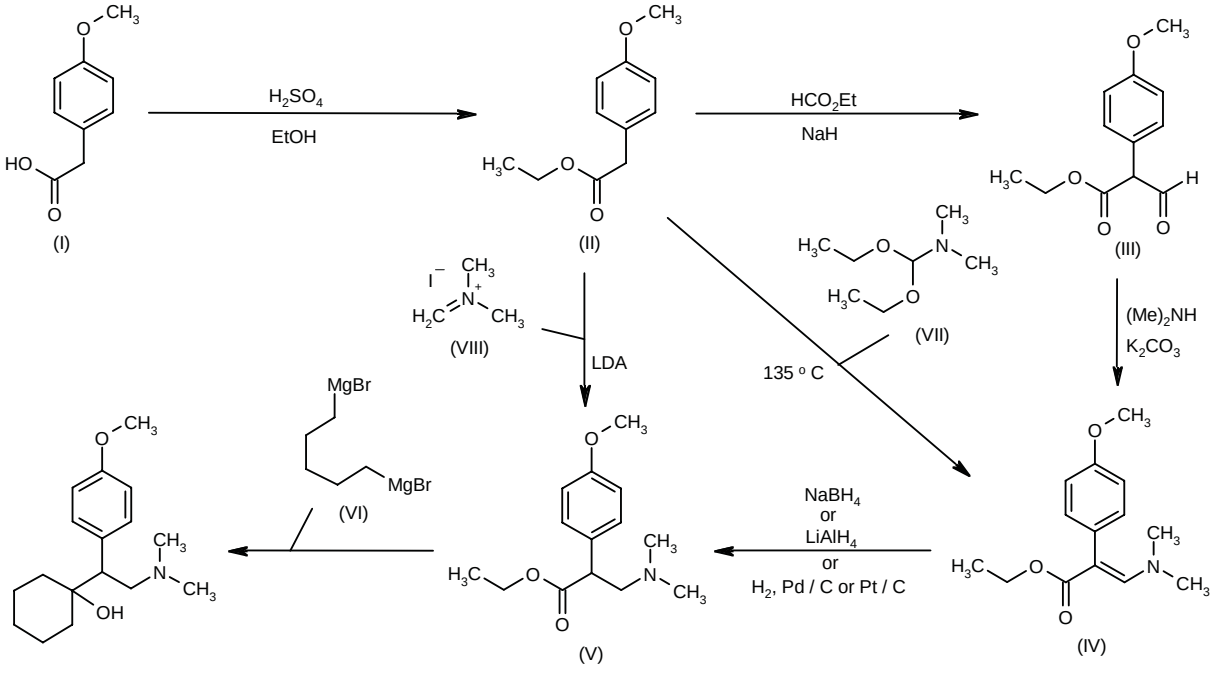
A new process for the production of venlafaxine has been reported: Esterification of 2-(4-methoxyphenyl)-acetic acid (I) with ethanol and sulfuric acid gives the corresponding ethyl ester (II), which is condensed with ethyl formate by means of NaH to yield 2-formyl-3-(4-methoxyphenyl)acetic acid ethyl ester (III). Reaction of (III) with dimethylamine and K_2CO_3 in ethanol affords 3-(dimethylamino)-2-(4-methoxyphenyl)acrylic acid ethyl ester (IV), which is reduced with either $NaBH_4$, $LiAlH_4$ or H_2 over Pd/C or Pt/C in ethanol to provide the corresponding propionic ester (V). Finally, this compound is cyclized with the bismagnesiane (VI) in THF.

Alternatively, acrylic ester (IV) can be obtained directly by condensation of acetate (II) with dimethylformamide diethylacetal (VII) at 135 °C.

Alternatively, propionic ester (V) can be obtained by condensation of acetate (II) with *N,N*-dimethylmethyleneiminium iodide (VIII) by means of LDA in THF/heptane/ethylbenzene (1) Scheme 2.

Anecdotal reports of the alleviation of hot flashes during treatment with venlafaxine hydrochloride for depression and the positive results from a pilot study led a Mayo Clinic-based group to conduct a double-blind, randomized, placebo-controlled trial evaluating the efficacy of venlafaxine in women with a history or fear of breast cancer. The subjects were randomized to placebo (n = 56) or extended-release venlafaxine at doses of 37.5 mg/day (n = 56), 75 mg/day (n = 55) or 150 mg/day (n = 54) for 4 weeks; all venlafaxine subjects started on the lowest dose and gradually increased up to the higher doses. At the end of the treatment period, hot flash scores were reduced from baseline by 27, 37, 61 and 61% on placebo, venlafaxine 37.5, 75 and 150 mg, respectively. The optimal dosing regimen appeared to be 37.5 mg/day for 1 week followed by an increase to 75 mg/day, which was more effective than the lower dose and better tolerated than the higher dose. Side effects included dry mouth, appetite suppression and nausea. Investigators also noted improvements in patients' quality of life on venlafaxine and no negative effect on libido. The results of ongoing randomized trials evaluating the effects of other

Scheme 2: Synthesis of Venlafaxine



related antidepressants are awaited to confirm these findings, but these results suggest that venlafaxine can be recommended for the alleviation of hot flashes in women in whom hormonal therapy is not desirable (2).

A recent study assessed the efficacy and safety of venlafaxine (Effexor®) extended release (ER) capsules in 541 outpatients between 18 and 86 years of age with generalized anxiety disorder (GAD). In this placebo-controlled, double-blind, dose-ranging study, patients received placebo or one of three doses of venlafaxine (37.5, 75 or 150 mg) daily for a period of 24 weeks. Efficacy was determined using the Hamilton Rating Scale for Anxiety (HRSA) total score, HRSA psychic anxiety factor, Hospital Anxiety and Depression (HAD) anxiety subscale and the Clinical Global Impression-Improvement (CGI-I) rating. At 6 months, patients receiving the 75 and 150 mg doses of venlafaxine ER showed significantly greater improvements in HRSA total score as compared to placebo (mean change of 15.5, 16.4 and 11.0, respectively). Both efficacy and onset of anxiolytic activity were dose-related. Overall discontinuation rates and discontinuation due to adverse effects were similar among groups. Based on these findings, venlafaxine ER appears to be a safe and effective treatment for GAD. The optimal clinical dose of venlafaxine ER is 75 mg/day, but it may be increased to 150 mg/day in some patients. Use of higher doses of this product requires dose tapering before discontinuing the medication (3).

The FDA has approved a new labeling change for the two versions of venlafaxine hydrochloride (Effexor® and Effexor® XR) for the prevention of major depressive disorder relapse. The agency's action was based on new clinical data demonstrating that venlafaxine was superior to placebo in preventing relapse and significantly reduced recurrent episodes (4).

Venlafaxine (Efexor® XR) is now available throughout the European Union for controlling the persistent, excessive anxiety that is characteristic of GAD. Its use provides a long-term alternative to benzodiazepines, which should only be used for 2-4 weeks. This drug has also demonstrated improved social functioning (5).

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