Drugs of the Future 1998, 23(9): 1023-1050

CCC: 0377-8282/98

Information Update

Volume 1-22, Number 9

Estimated developmental phase for this month's updated products:

Phase I

BMS-181184 (antifungal; Bristol-Myers Squibb)
BOF-4272 (xanthine oxidase inhibitor; Otsuka)

Phase II

9-Aminocamptothecin (antineoplastic, DNA topoisomerase I inhibitor; Research Triangle Inst., Natl. Cancer Inst., IDEC)
AIT-082 (cognition enhancer; NeoTherapeutics)
Amonafide (antineoplastic; Knoll)
Bryostatin 1 (antineoplastic, protein kinase C activator; Arizona State Univ., Bristol-Myers Squibb, Natl. Cancer Inst.)
Idazoxan hydrochloride (α_2-adrenoceptor antagonist; Pierre Fabre)
NO-1886 (hypolipidemic; Otsuka)
OPC-31260 (vasopressin V_2 antagonist; Otsuka)
Xanomeline (cognition enhancer, muscarinic M_1 agonist; Lilly, Novo Nordisk)

Phase III

Brain-derived neurotrophic factor (neurotrophic factor, agent for ALS and neuropathies; Regeneron, Amgen, Sumitomo)
Edatrexate (antineoplastic; SRI Int., Sloan-Kettering Inst., Novartis)
Lafutidine (gastric antisecretory, H_2-receptor antagonist; Fujirebio, Taiho)
LC-9018 (immunostimulant; Yakult Honsha, Daiichi Pharm.)
MCI-154 (treatment of heart failure; Mitsubishi Chem., Hoechst Marion Roussel, Astra)
Osutidine (gastric secretory, H_2-receptor antagonist; Toyama, Kowa)
Pegylated recombinant megakaryocyte growth and development factor (hematopoietic; Amgen, Kirin Breweries)
Ranolazine (antianginal; Roche Bioscience, Kissei, CV Therapeutics)
Rasagiline (antiparkinsonian, MAO-B inhibitor; Teva, Lemmon)
RP-59500 (streptogramin; Rhône-Poulenc Rorer)
RS-25259-197 (antiemetic, 5-HT_3 receptor antagonist; Roche Bioscience)
Sitafloxacin (fluoroquinolone antibacterial; Daiichi Pharm.)

Registered/Year

Prednisolone farnesylate (corticosteroid; Taiho, Kuraray, Dainippon)/1998

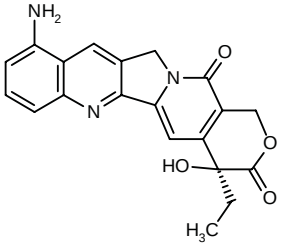
Launched/Year

Atorvastatin calcium (hypolipidemic, HMG-CoA reductase inhibitor; Warner-Lambert, Pfizer, Yamanouchi)/1997
Dexfenfluramine hydrochloride (antiobesity; Wyeth-Ayerst, Interneuron)/1985
Fluvastatin sodium (hypolipidemic, HMG-CoA reductase inhibitor; Novartis, Tanabe Seiyaku, Astra, Hoechst Marion Roussel)/1994
Imiquimod (immunomodulator, interferon inducer; 3M Pharm., Daiichi Pharm.)/1997
Mangafodipir trisodium (MRI contrast agent; Nycomed Amersham)/1997
Olopatadine hydrochloride (antiallergic/antiasthmatic; Kyowa Hakko, Alcon)/1997
Pegaspargase (antineoplastic; Enzon, Natl. Cancer Inst., Rhône-Poulenc Rorer, Medac)/1994
Tirofiban hydrochloride (platelet antiaggregatory, gpIIb/IIIa receptor antagonist; Merck & Co.)/1998
Troglitazone (antidiabetic; Sankyo, Warner-Lambert, Glaxo Wellcome)/1997
Venlafaxine (antidepressant, norepinephrine reuptake inhibitor, 5-HT reuptake inhibitor; Wyeth-Ayerst, Almirall Prodesfarma, Scios)/1994

9-Aminocamptothecin

Antineoplastic
Topoisomerase I Inhibitor

EN: 184764



$C_{20}H_{17}N_3O_4$

Research Triangle Inst. (US); Natl. Cancer Inst. (US); IDEC

An *in vitro* study demonstrated that while the sequence of administration of 9-AC and chemotherpeutic agents did not effect cell cytotoxic activity, distribution within the cell cycle was influenced. Bladder (MGHU1), breast (MCF7) and colon (HT-29 colon) cell lines were exposed to 9-AC, cisplatin (CDDP) or 5-fluorourcil (5-FU) for 24 h or 9-AC prior to, following or together with the chemotherapeutic agents. The order of potency was 9-AC (IC_{90} = 11-19 nM), CDDP (IC_{90} = 2.4 - 4.8 μM) and 5-FU (IC_{90} = 44-215 μM). Combination treatments resulted in additive cell kill when cells were treated with IC_{50} but not IC_{90} combinations. Accumulation of 9-AC, 5-FU and CDDP was observed in G2/M, G0/G1 and S phase of the cell cycle, respectively, and both CDDP and 9-AC but not 5-FU treatment resulted in damage to single stranded DNA (1).

A phase II study involving prolonged treatment with 9-AC for advanced colorectal carcinomas failed to demonstrate any antitumor activity in 18 patients administered daily continuous infusions (480 μg/m2/24 h) 5 days/week x 3 repeated every 4 weeks. Eight patients received dose escalation to 600 μg/m^2/24 h due to nadir granulocyte and platelet counts of greater than 1000 and 100,000, respectively and nonhematologic toxicity grades of 1. No partial or complete responses were observed and grade 3-4 toxicities observed included diarrhea, granulocytopenia, nausea and vomiting (2).

In a phase I pharmacokinetic trial, patients with several types of tumor malignancies were administered 9-AC (15 min infusion of 0.1, 0.3 or 0.4 mg/day x 5 for 2 weeks or 4 weeks with 2 days rest). Of 17 patients, 7 showed plasma 9-AC lactone clearance values ranging from 8.7 to 37.0 l/h/m^2. Mean C_{max} was 2.0, 9.9 and 15.5 mg/ml and mean lactone AUCs were 4.8, 23.8, and 32.8 ng/ml for doses of 0.1, 0.3 and 0.4 mg/m^2, respectively. No objective responses were observed while grade 3-4 toxicities were noted (*i.e.*, anemia, thrombocytopenia and neutropenia) with a dose of 0.4 mg/m^2/day x 5 (3).

In a phase I clinical trial, the efficacy of a lyophilized colloidal dispersion formulation of 9-AC in 20% dextrose and saline was examined when 25 cancer patients were administered continuous 72 h infusions of 9-AC (37.5 μg/m^2/h i.v.with escalation of doses to 4.65 mg/m^2 until grade 3-4 neutropenia toxicities were observed). No objective responses were observed and 9 patients had stable disease for 2-6 months. Pharmacokinetics showed a plasma clearance rate of 30.3 ± 4.5 l/h/m^2, a mean residence time of 9.7 ± 3.5 h and a half-life of 22.5 ± 8.5 h. The steady-state volume of distribution was 325 ± 145 l/m^2. The recommended doses for phase II trials was continuous infusion for 72 h of 54.2 μg/m^2/h every 3 weeks (4).

In a phase I pharmacological study, 20 patients received 24 h continuous infusions of 9-AC in a colloidal dispersion formulation (0.7, 1.4, 1.9 or 1.65 mg/m^2) once per week x 4 every 5 weeks. Dose-limiting toxicity was observed in 6 patients receiving a dose of 1.9 mg/m^2, with 3 patients exhibiting grade 4 neutropenia. Moderate nonhematologic toxicities were observed including greater than or equal to grade 3 diarrhea and lethargy. Steady state 9-AC concentrations greater than or equal to 10 nM were observed in 5/7 and 5/6 patients receiving 1.65 mg/m^2 and 1.9 mg/m^2, respectively. The appropriate dose for phase II was concluded to be continuous 24 h infusion of 1.65 mg/m^2/week x 4 every 5 weeks. (5).

Treatment of adults with newly diagnosed gliobastoma multiform (GBM) and recurrent high grade astrocytomas (HGA) with maximum tolerated doses of 9-AC (1776 and 1611 μg/m^2/24, respectively, i.v. for 72 h i.v. every 2 weeks) was found to be ineffective. Following treatment, 19/22 patients with new GBM had evaluable disease and no complete or partial responses were observed while 20/21 patients with recurrent HGA had evaluable disease with only one patient showing a partial response. After only 1-2 treatments, more than 50% of the patients displayed rapid tumor progression (6).

Idec Pharmaceuticals has initiated a phase I/II trial of 9-AC to identify an initial indication to pursue for marketing approval. Another objective of this study is to confirm a more convenient dosing schedule previously identified in a phase I study carried out by The Netherlands Cancer Institute. The trial will include patients with one of eight solid tumor types: non-small cell lung, colorectal, pancreatic, gastric, bladder, prostate, head and neck or kidney cancer (7).

1. Horn, L., Firby, P.S., Moore, M.J. *Cellular effects of 9-aminocamptothecin when combined with other chemotherapeutic agents*. Proc Amer Assoc Cancer Res 1998, Abst 3581.

2. Medgyesy, D., Pazdur, R., Dakhil, S., Moore, D., Scalzo, A., Hoff, P.M., Winn, R., Abbruzzese, J. *Phase II trial of 5-day continuous infusion of 9-amino camptothecin (9-AC) in advanced colorectal carcinomas (CRCS)*. Proc Amer Soc Clin Oncol 1998, Abst 1140.

3. Tran, H.T., Madden, T., Newman, R.A., Taebel, K., Abbruzzese, J. *Phase I pharmacokinetic trial of 9-aminocamptothecin given as a 15 minute infusion daily x 5 for 2 to 4 weeks*. Proc Amer Assoc Cancer Res 1998, Abst 3554.

4. Eder, J.P., Supko, J.G., Lynch, T., Bryant, M., Vosburgh, E., Shulman, L.N., Xu, G.X., Kufe, D.W. *Phase I trial of the colloidal dispersion formulation of 9-amino-20(S)-camptothecin adminis-*

tered as a 72-hour continuous intravenous infusion. Clin Cancer Res 1998, 4(2): 317.

5. Siu, L.L., Oza, A.M., Eisenhauer, E.A. et al. *Phase I and pharmacologic study of 9-aminocamptothecin colloidal dispersion formulation given as a 24-hour continuous infusion weekly times four every 5 weeks*. J Clin Oncol 1998, 16(3): 1122.

6. Hochberg, F., Grossman, S.A., Mikkelsen, T., Calabresi, P., Fisher, J., Piantadosi, S. *Efficacy of 9-aminocamptothecin (9-AC) in adults with newly diagnosed glioblastoma multiforme (GBM) and recurrent high grade astrocytomas (HGA)*. Proc Amer Soc Clin Oncol 1998, Abst 1494.

7. *Idec begins phase I/II trial for 9-AC*. Daily Essentials Nov 19, 1997.

Original monograph - Drugs Fut 1996, 21: 881.

Additional References

Beijnen, J.H. et al. *A phase I and pharmacokinetic (PK) study of a daily times 5 intravenous (IV) bolus schedule of 9-aminocamptothecin (9-AC[CD]) in patients with advanced solid tumors*. Proc Amer Soc Clin Oncol 1998, Abst 759.

Lad, T. et al. *Phase II trial of 9-aminocamptothecin (9AC/DMA) in patients with advanced squamous cell head and neck cancer*. Proc Amer Soc Clin Oncol 1998, Abst 1510.

Mani, S. et al. *Phase I clinical and pharmacokinetic study of oral 9-aminocamptothecin (NSC-603071)*. Cancer Chemother Pharmacol 1998, 42(1): 84.

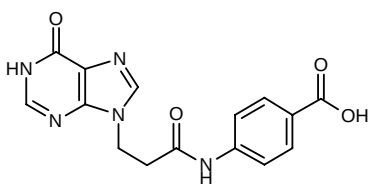
O'Leary, J.J. et al. *Anti-angiogenic effects of 9-amino-20(S)-camptothecin (9-AC), topotecan (TTN), and CPT-11 studied in the mouse cornea model*. Proc Amer Soc Clin Oncol 1998, Abst 953.

Punt, C.J.A. et al. *Phase I and pharmacologic study of the topoisomerase I inhibitor [PEG 1000] 9-aminocamptothecin (9-AC) given orally to patients (pts) with solid tumors*. Proc Amer Soc Clin Oncol 1998, Abst 760.

AIT-082
AIT0082
Neotrofin™

Cognition Enhancer

EN: 204883



$C_{15}H_{13}N_5O_4$

NeoTherapeutics

In rats with unilateral entorhinal cortex lesions, treatment with AIT-082 of hippocampal neurons caused nerve outgrowth and enhanced branching of the nerve processes after just 4 days of treatment (1).

Results from recent studies indicated that AIT-082 enhanced memory function in both young adult and aged mice within 2 h after oral administration. In addition, prophylactic treatment with the drug prevented or delayed the onset of age-induced memory deficits in mice when administered in the drinking water. When memory impairment was produced by specific brain lesions, AIT-082 restored memory performance and increased the genetic expression of neurotrophin-3 (NT-3), a natural protein growth factor associated with nerve cell function. In phase I trials with Alzheimer's patients, no serious side effects were observed at single oral doses ranging from 10-4000 mg. In addition, AIT-082 was rapidly absorbed and remained in the blood long enough to suggest that once-daily dosing may be possible (2).

In mice, AIT-082 (0.005-60 mg/kg) had no effect on exploratory behavior or hot plate latency, although the highest dose produced decreased locomotor activity. Performance in tests of motor coordination was improved at several dose levels. Furthermore, in a passive avoidance paradigm, AIT-082 reversed amnesia induced by scopolamine, L-NAME, NPC-15437, NBQX and MK-801 (3).

The effects of AIT-082 on the production of trophic factors following spinal cord hemisection were evaluated in male Wistar rats. Administration of 20 mg/kg/day of AIT-082 in the drinking water for 3 or 7 days increased CNTF levels as compared to controls. However, in the caudal section of lesioned animals, CNTF levels decreased, and no treatment-related effects were observed in lesioned or sham operated animals. Similar results were observed with respect to CNTF mRNA levels in animals following induction of sciatic nerve crush injuries distally to spinal cord hemisection (4).

AIT-082 was found to mimic or enhance the activity of endogenous nerve growth factor *in vivo* in rat models of nociception (5).

In a rat model of NMDA-induced striatal lesioning, the coinfusion with NMDA of AIT-082 or guanosine into the rat caudate nucleus was found to significantly reduce the extent of striatal lesions and to prevent the loss of GABAergic neurons induced by NMDA. Both guanosine and AIT-082 demonstrated neuroprotective activity, and the study drug was shown to cross the blood-brain barrier (6).

NeoTherapeutics will begin a phase I multidose pharmacokinetic study of AIT-082, in which 24 healthy elderly volunteers will be administered the drug once daily for 7 consecutive days at doses of 100-2000 mg (7).

A phase II trial of AIT-082 has been initiated in more than 60 patients with mild to moderate Alzheimer's disease. The is designed specifically to measure the biological activity of the drug in addition to dose range and safety parameters (8).

1. Ramirez, J.J., Glasky, A., Parakh, T., George, M.N., Becton, A. *The effects of AIT-082 on septodentate sprouting after unilateral entorhinal cortex lesions in rats*. Drug Dev Res 1998, 43(1): Abst 221.

2. *AIT-082 enhances memory function in preclinical model*. Daily Essentials April 23, 1998.

3. Ritzmann, R., Glasky, A.J. *Psychopharmacological actions of AIT-082*. Soc Neurosci Abst 1997, 23(Part 2): Abst 736.16.

4. Crocker, C.E., Clark, S.D., Urschel-Gysbers, B.A., Glasky,A.J., Rathbone, M.P. *Effect of AIT-082 on neurotrophin levels following spinal cord hemisection*. Soc Neurosci Abst 1997, 23(Part 2): Abst 458.1.

5. Diamond, J., Holmes, M., Pertens, E. *The effects of AIT-082 on nerve growth factor-dependent nociceptive functions*. Drug Dev Res 1998, 43(1): Abst 201.

6. Di Iorio, P., Ciccarelli, R., Ballerini, P., Battaglia, G., Bruno, V., Middlemiss, P.J., Rathbone, M.P., Caciagli, F. *Effect of guanosine and guanosine-like drugs on NMDA-induced unilateral lesion of rat striatum in vivo*. Drug Dev Res 1998, 43(1): Abst 202.

7. *AIT-082 enters multidose study*. Daily Essentials Feb 27, 1998.

8. *Phase II clinical trial initiated for Neotrofin*. Daily Essentials May 14, 1998

Original monograph - Drugs Fut 1997, 22: 945.

Additional References

Glasky, A.J. et al. *Neuroprotective effects of hypoxanthine derivatives*. Drug Dev Res 1998, 43(1): Abst 209.

Juurlink, B.H.J., Rathbone, M.P. *AIT-082 (a hypoxanthine derivative), guanosine and metabolites stimulate neurite formation in hippocampal neurons*. Drug Dev Res 1998, 43(1): Abst 210.

Rathbone, M.P. et al. *An overview of the neurotrophic effect of non-adenine based purines*. Drug Dev Res 1998, 43(1): Abst 222.

AIT-082 shows promise for spinal cord injury. Daily Essentials Oct 30, 1997.

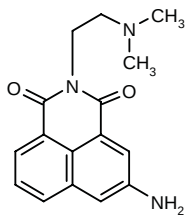
NeoTherapeutics begins U.S. clinical trials of AIT-082. Daily Essentials July 15, 1997

NeoTherapeutics reports AIT-082 interim phase I/II results. Daily Essentials June 3, 1997.

Amonafide

Antineoplastic

EN: 091280



$C_{16}H_{17}N_3O_2$ **Knoll**

The efficacy of amonafide (300 mg/m^2 i.v. for 5 consecutive days every 3 weeks) was evaluated in a phase II trial in 27 patients with nonsquamous cell carcinoma of the cervix. Twelve subjects had received prior chemotherapy and 22 had been treated with radiation therapy. Partial response to the therapy was observed in 1 patient and 13 patients had stable disease. Seven subjects developed lifethreatening thrombocytopenia and 1 had severe anemia, while nonhematologic toxicity was mild (1).

1. Asbury, R., Blessing, J.A., Look, K.Y., Buller, R., Lucci, J.A. *A phase II trial of amonafide in patients with nonsquamous cell carcinoma of the cervix: A gynecologic oncology group study*. Am J Clin Oncol Cancer Clin Trials 1997, 20(6): 626.

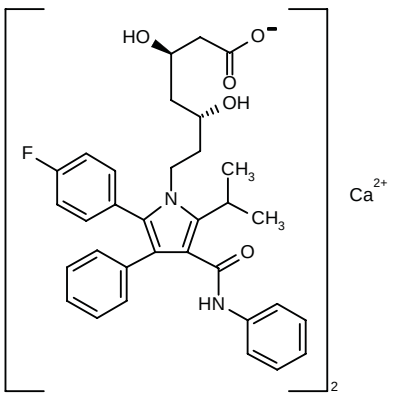
Original monograph - Drugs Fut 1990, 15: 879

Additional Reference

Asbury, R. et al. *A phase II trial of amonafide in patients with mixed mesodermal tumors of the uterus: A Gynecologic Oncology Group study*. Am J Clin Oncol Cancer Clin Trials 1998, 21(3): 306.

Atorvastatin Calcium *Hypolipidemic*
CI-981 *HMG-CoA Reductase Inhibitor*
YM-548
Lipitor™
Sortis™
Torvast™

EN: 180072



$C_{66}H_{68}CaF_2N_4O_{10}$ **Warner-Lambert; Pfizer; Yamanouchi**

In vitro and *in vivo* studies have demonstrated that when stimulated vascular smooth muscle cells (SMC) cultures with defects in G_1 and G_2/M compartments were exposed to atorvastatin (0.1-50 μM), cellular proliferation was significantly reduced dose-dependently at 24 h of incubation, followed by a stronger inhibition at 48 h and apoptosis at 72 h. Moreover, statin-induced apoptosis was reversed by mevalonate (100 μM). Similarly, pretreatment of rabbits with atorvastatin (5 mg/kg/day) prior to stimulation of SMC proliferation on the outer surface of carotid arteries, increased apoptosis as determined by TUNEL assay (1).

In a randomized, double-blind study involving 177 hypercholesterolemic patients, 1-year treatment with atorvastatin more potently and significantly reduced

LDL-cholesterol, total-cholesterol, VLDL-cholesterol, total triglycerides and apolipoprotein B levels as compared to simvastatin (10 mg/day); 46% of atorvastatin-treated patients achieved target LDL levels as compared to only 27% in the simvastatin group. No serious adverse effects were noted with either treatment group (2).

In a randomized, open-label, multicenter study, 84 combined hyperlipidemia patients received either atorvastatin at 10 mg/day for 12 weeks followed by 20 mg/day for another 12 weeks or fenofibrate (100 mg t.i.d.) for 24 weeks to compare the efficacy and safety of both treatments. Greater significant decreases in total cholesterol, LDL-cholesterol, apolipoprotein (apo)B, LDL-apoB and lipoprotein B were observed in patients treated with atorvastatin than those receiving fenofibrate. However, although atorvastatin treatment also significantly reduced triglycerides, VLDL-cholesterol, apoB, apoC-III and apoB/triglyceride in VLDL and increased HDL-cholesterol and apoA, fenofibrate treatment was more potent on these levels (3).

The long-term safety and efficacy of atorvastatin (10 mg) and lovastatin (20 mg) were compared in a multicenter, randomized, placebo-controlled study in 1049 patients with primary hypercholesterolemia. Safety profiles in terms of changes from baseline in laboratory evaluations, ophthalmologic parameters and adverse events were similar in both active treatment groups. Atorvastatin-treated patients maintained significantly greater reductions in LDL-cholesterol, triglyceride, total cholesterol and apoB. LDL-cholesterol target levels were achieved by 78% of atorvastatin-treated patients as compared to 63% of lovastatin patients (4).

A new international trial, the Treating to New Targets (TNT) study, is being launched to investigate whether lowering LDL cholesterol to levels below current clinical practice can further reduce the chances of death or heart attack in patients with coronary heart disease. This multicenter, 5-year study will involve about 8600 patients who will be treated with atorvastatin calcium (Lipitor™). Since the effect of atorvastatin on cardiovascular morbidity and mortality is unknown, this is one of the studies that has been designed to determine its effect (5).

Results of an 8-week, multicenter, randomized, open-label study in 534 hypercholesterolemic patients showed that atorvastatin (10, 20, and 40 mg) produced greater reductions in LDL-cholesterol and total cholesterol than equivalent doses of simvastatin, pravastatin, lovastatin and fluvastatin. All compounds had similar tolerability, and no persistent elevations in serum transaminases or myositis were observed (6).

The efficacy and safety of atorvastatin treatment was demonstrated in an open-label, parallel-design, active-controlled trial in which 108 combined hyperlipidemia patients were administered either atorvastatin (10 mg/day) or niacin (1 g t.i.d.) for 12 weeks. Total cholesterol, LDL-cholesterol and total triglycerides were reduced by 26, 30 and 17%, respectively, in atorvastatin-treated patients and by 7, 2 and 29% in niacin-treated patients; niacin also significantly increased HDL-cholesterol (25%) (7).

The effects of low doses of atorvastatin calcium have been evaluated in renal transplant patients with elevated cholesterol levels on maintenance therapy with ciclosporin or tacrolimus. After 3 months, the compound effectively lowered serum cholesterol levels by over 20%. No muscle soreness or weakness was reported and no significant elevations in liver function tests were observed, indicating the safety of atorvastatin for controlling hypercholesterolemia in renal transplant patients on maintenance immunosuppressants (8).

1. Baetta, R., Donetti, E., Comparato, C., Calore, M., Rossi, A., Teruzzi, C., Paoletti, R., Fumagalli, R., Soma, M.R. *Proapoptotic effect of atorvastatin on stimulated rabbit smooth muscle cells*. Pharmacol Res 1997, 36(2): 115.

2. Dart, A., Jerums, G., Nicholson, G. et al. *A multicenter, double-blind, one-year study comparing safety and efficacy of atorvastatin and simvastatin in patients with hypercholesterolemia*. Am J Cardiol 1997, 80(1): 39.

3. Ooi, T.C., Heinonen, T., Alaupovic, P. et al. *Efficacy and safety of a new hydroxymethylglutaryl-coenzyme A reductase inhibitor, atorvastatin, in patients with combined hyperlipidemia: Comparison with fenofibrate*. Arterioscler Thromb Vasc Biol 1997, 17(9): 1793.

4. Davidson, M., McKenney, J., Stein, E., Schrott, H., Bakker Arkema, R., Fayyad, R., Black, D. *Comparison of one-year efficacy and safety of atorvastatin versus lovastatin in primary hypercholesterolemia*. Perfusion 1997, 10(10): 344.

5. *TNT will assess further benefits of Lipitor*. Daily Essentials April 7, 1998

6. Jones, P., Kafonek, S., Laurora, I., Hunninghake, D. *Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin and fluvastatin in patients with hypercholesterolemia (the CURVES study)*. Perfusion 1998, 11(4): 202.

7. McKenney, J.M., McCormick, L.S., Weiss, S., Koren, M., Kafonek, S., Black, D.M. *A randomized trial of the effects of atorvastatin and niacin in patients with combined hyperlipidemia or isolated hypertriglyceridemia*. Am J Med 1998, 104(2): 137.

8. Greathouse, A., Winklhofer, F., Greathouse, J., Layes, D., Cowley, B., Chonko, A., Diederich, D. *Safety and efficacy of atorvastatin in renal transplant recipients*. Transplantation 1998, 65(8, Suppl.): Abst 581.

Original monograph - Drugs Fut 1997, 22: 956.

Additional References

Adeli, K. et al. *Effects of atorvastatin on intracellular levels and stability of apolipoprotein B and HMG-CoA reductase in Hep G2 cells*. Atherosclerosis 1997, 134(1-2): Abst 2.P.11.

Alaupovic, P. et al. *Effect of a new HMG-CoA reductase inhibitor, atorvastatin, on lipids, apolipoproteins and lipoprotein particles in patients with elevated serum cholesterol and triglyceride levels*. Atherosclerosis 1997, 133(1): 123.

Alegret, M. et al. *Effect of atorvastatin on key enzymes regulating lipid metabolism in cholesterol/coconut oil fed rabbits*. Eur Heart J 1997, 18(Suppl.): Abst P2146.

Bakker-Arkema, R.G. et al. *An overview of the clinical safety profile of atorvastatin a new, more effective HMG-CoA reductase inhibitor*. Atherosclerosis 1997, 134(1-2): Abst 2.P.14.

Bakker-Arkema, R.G. et al. *Two year safety of atorvastatin compared to lovastatin in patients with hypercholesterolemia*. 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 58.

Bakker-Arkema, R.G. et al. *An overview of the clinical safety profile of atorvastatin*. Eur Heart J 1998, 19(Suppl.): Abst P2801.

Bakker-Arkema, R.G. et al. *Safety profile of patients with low LDL-cholesterol on atorvastatin treatment*. 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 58.

Bakker-Arkema, R.G. et al. *Two-year comparison of safety and efficacy of atorvastatin and lovastatin*. Atherosclerosis 1997, 134(1-2): Abst 2.P.15.

Barter, P.J., O'Brien, R.C. *A primary care, treatment to target study comparing atorvastatin with simvastatin or with simvastatin plus cholestyramine*. 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 57.

Bergstrom, J.D. et al. *Responses to the inhibition of HMG-CoA reductase: A comparison of simvastatin and atorvastatin*. Atherosclerosis 1997, 134(1-2): Abst 2.P.24.

Bertolini, S. et al. *Efficacy and safety of atorvastatin compared to pravastatin in patients with hypercholesterolemia*. Perfusion 1997, 10(11): 407.

Black, D.M. et al. *Efficacy and safety of atorvastatin in hyperlipidemic patients with concurrent hypertension or non-insulin dependent diabetes mellitus*. J Hypertens 1998, 16(Suppl. 2): Abst P31.018.

Black, D.M. *Comparison of the efficacy and safety of atorvastatin with simvastatin in patients with primary hypercholesterolemia*. Atherosclerosis 1997, 134(1-2): Abst 2.P.18.

Bocan, T.M.A. et al. *HMG-CoA reductase and ACAT inhibitors act synergistically to lower plasma cholesterol and limit atherosclerotic lesion formation in the rabbit*. Atherosclerosis 1997, 134(1-2): Abst 2.P.20.

Bottazzo, S. et al. *Comparison of atorvastatin and bezafibrate treatment in dyslipidemic patients with metabolic syndrome (MS)*. 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 59.

Bourcier, T. et al. *The HMG-CoA reductase inhibitors atorvastatin and lovastatin reduce accumulation of collagenase and 92-kD gelatinase released by cultured human monocytic and vascular smooth muscle cells*. Atherosclerosis 1997, 134(1-2): Abst 2.P.21.

Burnett, J.R. et al. *The HMG-CoA reductase inhibitor, atorvastatin, increases the fractional clearance rate of postprandial triglyceride rich lipoproteins*. 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 78.

Burnett, J.R. et al. *Inhibition of HMG-CoA reductase by atorvastatin decreases both VLDL and LDL apolipoprotein B production in miniature pigs*. Arterioscler Thromb Vasc Biol 1997, 17(11): 2589.

Camera, M. et al. *Atorvastatin and its metabolite reduce the prothrombotic potential of activated endothelial cells*. 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 93.

Chong, P.H., Seeger, J.D. *Atorvastatin calcium: An addition to HMG-CoA reductase inhibitors*. Pharmacotherapy 1997, 17(6): 1157.

Couture, P. et al. *Effect of atorvastatin on serum levels of lipoproteins in French Canadians with homozygous or compound heterozygous familial hypercholesterolemia*. Atherosclerosis 1997, 134(1-2): Abst 1.P.178.

Dart, A. et al. *A multicenter double-blind, one-year study comparing safety and efficacy of atorvastatin versus simvastatin in patients with hypercholesteremia*. Perfusion 1997, 10(9): 296.

Davidson, M. et al. *Effect of atorvastatin and lovastatin on plasma levels of fibrinogen, lipoprotein(a) and PAI-1 in patients with elevated plasma LDL-C*. 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 58.

Davila, M. et al. *Efficacy and safety of long-term treatment with high-dose atorvastatin*. 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 58.

Desrumaux, C. et al. *Effect of atorvastatin on plasma cholesteryl ester transfer protein and plasma phospholipid transfer protein in hyperlipidemic patients*. 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 87.

Elkin, R.G. et al. *Reduction of egg yolk cholesterol content through inhibition of hepatic cholesterol biosynthesis and alteration of plasma VLDL composition in laying hens: Comparative effects of atorvastatin, lovastatin, and simvastatin*. Atherosclerosis 1997, 134(1-2): Abst 2.P.31.

Farnier, M. et al. *Efficacy of atorvastatin 10 mg compared to simvastatin 10 and 20 mg in patients with hypercholesterolemia*. 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 61.

Gaudet, D. et al. *Lipid-lowering effect of atorvastatin in homozygous familial hypercholesterolemia patients with portocaval anastomosis*. Atherosclerosis 1997, 134(1-2): Abst 2.P.35.

Heinonen, T., Black, D.M., Nawrocki, J.W. *An overview of the clinical efficacy profile of atorvastatin*. Atherosclerosis 1997, 134(1-2): Abst 2.P.42.

Heinonen, T. et al. *Two year treatment experience with high dose atorvastatin*. Atherosclerosis 1997, 134(1-2): Abst 2.P.41.

Heinonen, T. et al. *An evaluation of the clinical efficacy of atorvastatin, a novel 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitor*. Eur Heart J 1998, 19(Suppl.): Abst P2805.

Hernandez Perera, O. et al. *Effects of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, atorvastatin and simvastatin, on the expression of endothelin-1 and endothelial nitric oxide synthase in vascular endothelial cells*. J Infect 1998, 101(12): 2711.

Hoogerbrugge, N. *Effects of atorvastastin on serum lipids of patients with familial hypercholesterolemia*. 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 62.

Hyatt, P.J. *Atorvastatin*. Br J Hosp Med 1997, 58(7): 333.

Illingworth, D.R. et al. *The efficacy and safety of atorvastatin compared with simvastatin and gemfibrozil in patients with type III hyperlipidaemia*. Eur Heart J 1997, 18(Suppl.): Abst P2147.

Jones, P.H. *Comparison of the dose efficacy of atorvastatin with pravastatin, simvastatin, fluvastatin and lovastatin - The CURVES study*. Eur Heart J 1997, 18(Suppl.): Abst P2145.

Kafonek, S. *The CURVES study - A comparison of the dose efficacy of atorvastatin with pravastatin, simvastatin, fluvastatin and lovastatin*. J Hypertens 1998, 16(Suppl. 2): Abst P31.013.

Kobashigawa, J.A. et al. *Atorvastatin for refractory hypercholesterolemia in heart transplant patients*. J Am Coll Cardiol 1998, 31(2, Suppl. A): Abst 1071-53.

Koren, M. et al. *Cost of resource utilization of atorvastatin compared with fluvastatin, lovastatin and simvastatin in patients with risk factors for CHD*. Atherosclerosis 1997, 134(1-2): Abst 1.P.167.

Laguna, J.C. et al. *Effect of atorvastatin on key enzymes regulating lipid metabolism in the cholesterol/coconut oil fed rabbit*. Atherosclerosis 1997, 134(1-2): Abst 2.P.57.

Lahera, V. et al. *Effects of atorvastatin on endothelium-dependent relaxations and contractions in dyslipidemic rabbits*. Atherosclerosis 1997, 134(1-2): Abst 2.P.58.

Lamas, S. et al. *Effects of HMG-CoA reductase inhibitors (atorvastatin and simvastatin) on the vasoactive pathways mediated by endothelin-1 and nitric oxide in vascular endothelial cells*. Atherosclerosis 1997, 134(1-2): Abst 3.P.216.

Landray, M.J. et al. *The effect of atorvastatin on low density lipoprotein subfraction profile*. 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 65.

Maeso, R. et al. *Atorvastatin reduces endothelium-dependent contractions in rabbits*. Eur Heart J 1997, 18(Suppl.): Abst P2149.

Maeso, R. et al. *Consequences of atorvastatin treatment on endothelial dysfunction in dyslipidemic rabbits*. J Hypertens 1998, 16(Suppl. 2): Abst P10.19.

Marais, A.D. et al. *Atorvastatin: An effective lipid-modifying agent in familial hypercholesterolemia*. Arterioscler Thromb Vasc Biol 1997, 17(8): 1527.

Marais, A.D. et al. *Decreased production of low density lipoprotein by atorvastatin after apheresis in homozygous familial hypercholesterolemia*. J Lipid Res 1997, 38(10): 2071.

März, W. et al. *The Target Tangible Trial: A multicenter evaluation of atorvastatin versus simvastatin in 2902 German patients with coronary artery disease*. 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 66.

Matsuo, K. et al. *Antigenicity study of CI-981*. Jpn Pharmacol Ther 1998, 26(6): 71.

McKenney, J., McCormick, L. *The effect of atorvastatin and niacin on lipoprotein subclasses in patients with mixed hyperlipidemia*. Atherosclerosis 1997, 134(1-2): Abst 1.P.198.

Mikami, Y. et al. *Marked reduction of LDL-cholesterol by treatment with LDL-apheresis and atorvastatin in a case of homozygous familial hypercholesterolemia (FH*. 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 67.

Mikhailidis, D.P. et al. *Atorvastatin reduces LDL-cholesterol but has unpredictable effects on lipoprotein(a)*. 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 12.

Nakamura, H. *Dose-related reduction of LDL-cholesterol in patients with primary hypercholesterolemia by atorvastatin*. Atherosclerosis 1997, 134(1-2): Abst 2.P.66.

Naoumova, R.P. et al. *Prolonged inhibition of cholesterol synthesis explains the efficacy of atorvastatin*. Atherosclerosis 1997, 134(1-2): Abst 2.P.67.

Nawrocki, J. et al. *Effectiveness of atorvastatin in treating patients to LDL-C goals compared with lovastatin, pravastatin and simvastatin*. Atherosclerosis 1997, 134(1-2): Abst 2.P.17.

Nawrocki, J.W. et al. *A comparison of the efficacy and safety of atorvastatin with simvastatin, pravastatin and lovastatin in patients with hypercholesterolemia*. J Am Coll Cardiol 1998, 31(5, Suppl. C): Abst 2088.

Nemoto, H. et al. *Pharmacokinetic studies on CI-981 (1): Absorption, distribution and excretion in rats following single oral or intravenous administration*. Jpn Pharmacol Ther 1998, 26(7): 65.

Nemoto, H. et al. *Pharmacokinetic studies on CI-981 (2): Absorption, distribution and excretion following repeated oral administration, and placental transfer and transfer to milk and suckling pups following single oral administration*. Jpn Pharmacol Ther 1998, 26(7): 79.

Nemoto, H. et al. *Pharmacokinetic studies on CI-981 (3) - In vitro and in vivo plasma protein binding*. Jpn Pharmacol Ther 1998, 26(8): 55.

Neub, M. et al. *Influence of atorvastartin on the proliferation of human vascular smooth muscle cells from saphenous vein and coronary arteries*. Eur Heart J 1998, 19(Suppl.): Abst P2139.

Oishi, S. et al. *Atorvastatin (CI-981) clinical pharmacokinetic study (VI) - Bioequivalence of 5 mg and 10 mg atorvastatin tablets*. Jpn Pharmacol Ther 1998, 26(8): 133.

Oishi, S. et al. *Atorvastatin (CI-981) clinical pharmacokinetic study (I) - Relative bioavailability of amorphous and crystalline preparation of atorvastatin*. Jpn Pharmacol Ther 1998, 26(8): 67.

Oishi, S. et al. *Atorvastatin (CI-981) clinical pharmacokinetic study (II) - Pharmacokinetics of single dose atorvastatin in healthy male volunteers*. Jpn Pharmacol Ther 1998, 26(8): 79.

Oishi, S. et al. *Atorvastatin (CI-981) clinical pharmacokinetic study (III) - Effect of food on bioavailability of atorvastatin*. Jpn Pharmacol Ther 1998, 26(8): 93.

Oishi, S. et al. *Atorvastatin (CI-981) clinical pharmacokinetic study (IV) - Pharmacokinetics of multiple dose atorvastatin in healthy male volunteers*. Jpn Pharmacol Ther 1998, 26(8): 105.

Oishi, S. et al. *Atorvastatin (CI-981) clinical pharmacokinetic study (V) - Pharmacokinetics of single dose atorvastatin in healthy young and elderly volunteers*. Jpn Pharmacol Ther 1998, 26(8): 121.

Ortego, M. et al. *Atorvastatin inhibition of NF-κB activation in vascular smooth muscle cells is mediated by protein isoprenylation blockade*. Atherosclerosis 1997, 134(1-2): Abst 2.P.72.

Reckless, J.P.D. et al. *Influence of atorvastatin [A] and simvastatin [S] on postprandial [PP] lipoprotein [LP] and APOB-48 metabolism*. Atherosclerosis 1997, 128(2): Abst 14.

Robertson, D.G. et al. *Atorvastatin is not cataractogenic in beagle dogs*. Curr Eye Res 1997, 16(12): 1229.

Roederer, G.O. et al. *Variability in the response to atorvastatin in two siblings homozygote for the same LDL-receptor gene mutation*. Atherosclerosis 1997, 134(1-2): Abst 1.P.207.

Roth, B.D. et al. *Inhibitors of cholesterol biosynthesis. 3. Tetrahydro-4-hydroxy-6-[2-(1H-pyrrol-1-yl)ethyl]-2H-pyran-2-one inhibitors of HMG-CoA reductase. 2. Effects of introducing sub-*

stituents at positions three and four of the pyrrole nucleus. J Med Chem 1991, 34(1): 357.

Rudy, D. et al. *Atorvastatin induces proteasome-mediated degradation of apolipoprotein B in HepG2 cells*. 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 25.

Satoh, K. et al. *Influence of atorvastatin and pravastatin, HMG-CoA reductase inhibitors, on myocardial stunning in dogs*. Jpn J Pharmacol 1998, 76(Suppl. 1): Abst O-151.

Satoh, K., Ichihara, K. *Effects of atorvastatin and pravastastin on myocardial contractile function during reperfusion after ischemia in dogs*. 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 52.

Schettler, V. et al. *Effect of atorvastatin vs. simvastatin in patients undergoing regular LDL-apheresis (ASLA I)*. Atherosclerosis 1997, 134(1-2): Abst 2.P.82.

Schinker, R. et al. *Effects of atorvastatin on the cholesterol homeostasis of cultured cells*. 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 52.

Schrott, H. et al. *The short-term effects of atorvastatin on lipid levels in patients with hyperlipidemia*. Atherosclerosis 1997, 134(1-2): Abst 2.P.19.

Shimada, A. et al. *Pharmacodynamic effects of CI-981*. Jpn Pharmacol Ther 1998, 26(6): 79.

Shum, Y.Y. et al. *Development, validation, and interlaboratory comparison of an HMG-CoA reductase inhibition assay for quantitation of atorvastatin in plasma matrices*. Ther Drug Monit 1998, 20(1): 41.

Simons, L.A. et al. *Effects of atorvastatin or simvastatin plus cholestyramine on arterial endothelial function in primary hypercholesterolaemia*. Atherosclerosis 1997, 134(1-2): Abst 3.P.190.

Simons, L.A. et al. *Effects of atorvastatin monotherapy and simvastatin plus cholestyramine on arterial endothelial function in patients with severe primary hypercholesterolaemia*. Atherosclerosis 1998, 137(1): 197.

Simons, L.A. *Comparison of atorvastatin alone versus simvastatin +- cholestyramine in the management of severe primary hypercholesterolaemia*. Aust New Zealand J Med 1998, 28(3): 327.

Sinzinger, H. et al. *Atorvastatin therapy for treatment of severe hypercholesterolemia in patients undergoing regular LDL-apheresis*. Atherosclerosis 1997, 134(1-2): Abst 1.P.212.

Sinzinger, H. et al. *Atorvastatin improves vascular thrombogenicity*. 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 24.

Stern, R. et al. *Atorvastatin does not alter the anticoagulant activity of warfarin*. J Clin Pharmacol 1997, 37(11): 1062.

Stern, R.H. et al. *Cimetidine does not alter atorvastatin pharmacokinetics or LDL-cholesterol reduction*. Eur J Clin Pharmacol 1998, 53(6): 475.

Stern, R.H. et al. *Renal dysfunction does not alter the pharmacokinetics or LDL-cholesterol reduction of atorvastatin*. J Clin Pharmacol 1997, 37(9): 816.

Wassmann, S. et al. *Atorvastatin down-regulates AT_1 receptor gene expression*. Eur Heart J 1998, 19(Suppl.): Abst 807.

Wolffenbuttel, B.H.R. et al. *Efficacy and safety of a new cholesterol synthesis inhibitor, atorvastatin in comparison with simastatin and pravastatin, in subjects with hypercholesterolemia*. Neth J Med 1998, 52(4): 131.

Yamamoto, A. *The effect of atorvastatin, a new HMG-CoA reductase inhibitor, and LDL-apheresis on homozygous familial hypercholesterolemia*. 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 130.

Yamamura, T. et al. *Effects of atorvastatin on serum lipoproteins and urinary excretion of mevalonic acid in patients with heterozygous familial hypercholesterolemia*. 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 130.

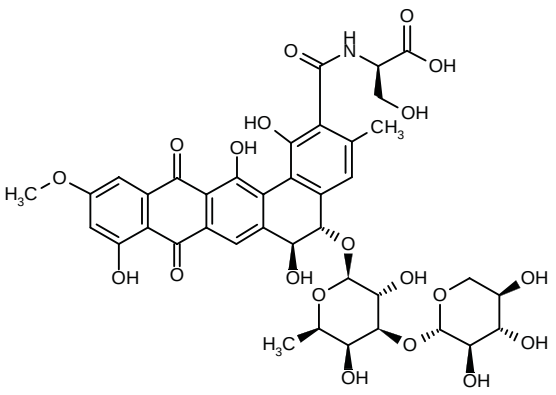
Atorvastatin approved in Canada. Daily Essentials March 11, 1997.

Clinical trial of Lipitor for the reduction of cholesterol in women. Daily Essentials July 31, 1997.

BMS-181184

Antifungal

EN: 189339



$C_{39}H_{41}NO_{20}$

Bristol-Myers Squibb

The pharmacokinetics of single and multiple doses of BMS-181184 (10-150 mg/kg/day) was evaluated in catheterized rabbits. Plasma concentration data was best fitted to a two-compartment open model, indicating non-linear disposition with increased plasma clearance at higher doses and extravascular accumulation. Repeated administration of 10, 25 and 50 mg/kg/day had no effect on AUC values, while the 150 mg/kg/day dose produced a 30% decrease as compared to baseline values, suggesting an inducible process of elimination. Tissue to plasma concentration ratios following the 16th dose were 0.20 for liver and lung, 0.15 for spleen, esophagus and choroid, and equal to or less than 0.05 for cerebrospinal fluid, brain and vitreous (1).

1. Groll, A., Gonzalez, C., Giri, N. et al. *Compartmental pharmacokinetics and tissue distribution of the pradimicin derivative*

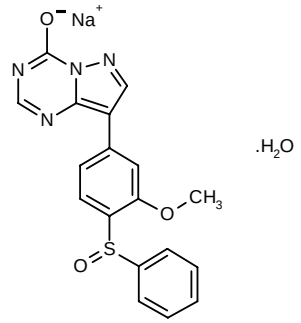
BMS 181184 in rabbits. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-96.

Original monograph - Drugs Fut 1995, 20: 876.

BOF-4272

Xanthine Oxidase Inhibitor

EN: 188399



$C_{18}H_{13}N_4NaO_3S.H_2O$ **Otsuka**

The enantioselectivity in the hepatic local disposition of BOF-4272 in the presence and in the absence of bovine serum albumin perfusate was evaluated in rat liver. At 37 °C, the hepatic extraction ratios of the *R*- and *S*-enantiomers were 75.6% and 71.7% in the absence of BSA and 31.7% and 19.6% in the presence of 4% BSA. At 4 °C, the extraction ratios for the two enantiomers did not differ significantly in the presence and in the absence of BSA (1).

1. Nishimura, M., Yamaoka, K., Naito, S., Nakagawa, T. *Influence of albumin on enantioselective local disposition of BOF-4272, a xanthine oxidase inhibitor with chiral sulfoxide, in rat liver*. Biol Pharm Bull 1997, 20(12): 1285.

Original monograph - Drugs Fut 1993, 18: 791.

Brain-Derived Neurotrophic Factor
BDNF
Neurotrophic Factor
rhBDNF
Agent for ALS and Neuropathies

EN: 198453

Regeneron; Amgen; Sumitomo

The potential therapeutic efficacy of brain-derived neurotrophic factor (BDNF) and ciliary-derived neurotrophic factor (CNTF) has been compared in a rat model of stroke, with special attention given to the respective abilities of these growth factors to limit infarct size in an *in vivo* model of permanent middle cerebral artery occlusion. BDNF, CNTF or vehicle was administered by osmotic minipump at a dose of 1 μg/h, with infusion beginning shortly after occlusion. Brains were removed 24 h later in order to determine infarct volume. BDNF-treated rats showed a 33% reduction in total infarct volume and a 37% decrease in cortical infarct volume as compared to vehicle-treated animals. Infarct volume decreased by approximately 20% in CNTF-treated animals, but this effect did not reach statistical significance. Thus, infarct size in this rat model could be reduced via administration of BDNF, but not CNTF (1).

Treatment of cultures of fetal rat ventral mesencephalon with BDNF or GDNF alone produced moderate increases in dopamine content of the culture medium, the number of tyrosine hydroxylase-immunoreactive neurons and culture volumes, while combination treatment with the two factors produced significant increases in the same parameters (6.8-, 3.2- and 2.4-fold, respectively). These results indicate that pretreatment of dopaminergic tissue with a combination of the two factors may improve the tissue prior to grafting in patients with Parkinson's disease (2).

Daily intramuscular injections of 20 mg/kg of brain-derived neurotrophic factor (BDNF) in wobbler mice resulted in enhanced BDNF immunoreactivity in anterior horn motor neurons as compared to control animals. Increments in immunoreactivity of 62% and 84% were observed after 4 and 8 weeks, respectively, in C5 but not in L3 spinal cord segments. The number of NADPH-d positive neurons per hemicord section was significantly reduced in BDNF-treated animals compared to untreated animals.The results indicate that BDNF may prevent the degeneration of spinal cord motor neurons possibly via nitric oxide synthase-mediated mechanisms (3).

Administration of exogenous brain-derived neurotrophic factor (BDNF) to galactose-fed rats attenuated motor nerve conduction velocity deficits in the sciatic nerve and myelin splitting of motor axons in the ventral root, whereas sensory nerve conduction velocity deficits in the sciatic nerve and myelin splitting in the central projections of sensory neurons were unaffected. Reduced axonal caliber in the sciatic nerve was not attenuated by BDNF, although the diminution of the caliber of central sensory projections in the dorsal root was ameliorated. These results indicate that BDNF may have beneficial therapeutic effects in the treatment of peripheral neuropathies (4).

Safety and tolerability of brain-derived neurotrophic factor (BDNF) were evaluated in 30 patients with amyotrophic lateral sclerosis. Blinded doses of BDNF (25, 60, 150, 400 and 1000 μg/day) were delivered intrathecally to the spinal subarachnoidal space for 12 weeks, followed by open-label drug for at least 1 year. Treatment-related abnormalities in cerebrospinal fluid or systematic side effects were not observed. Analysis of BDNF levels in cerebrospinal fluid suggest dose proportionality, with a lumbar to cervical concentration ratio of 3:1. Doses above 400 μg/day were associated with dry mouth, insomnia and agitation, and were severe enough in 3 patients to warrant dose reduction. Overall, BDNF appeared to be safe and well tolerated, although larger trials are necessary to evaluate the efficacy of the drug in this patient population (5).

1. Yamashita, K., Wiessner, C., Lindholm, D., Hossmann, K.-A. *BDNF and CNTF treatment of experimental stroke in rat*. Stroke 1998, 29(1): Abst P172.

2. Sautter, J., Meyer, M., Spenger, C., Seiler, R.W., Widmer, H.R. *Effects of combined BDNF and GDNF treatment on cultured dopaminergic midbrain neurons*. NeuroReport 1998, 9(6): 1093.

3. Ishiyama, T., Pioro, E.P., Tsuzaka, K., Mitsumoto, H. *Increase of brain-derived neurotrophic factor (BDNF) in motor neurons: Possible role in wobbler mouse motor neuron disease*. 50th Annu Meet Amer Assoc Neurol (April 25-May 2, Minneapolis) 1998, Abst S21.004.

4. Mizisin, A.P., Bache, M., DiStefano, P.S., Acheson, A., Lindsay, R.M., Calcutt, N.A. *BDNF attenuates functional and structural disorders in nerves of galactose-fed rats*. J Neuropathol Exp Neurol 1997, 56(12): 1290.

5. Ochs, G., Penn, R.D., Giess, R., Schrank, B., Sendtner, M., Toyka, K.V. *A trial of recombinant methionyl human brain-derived neurotrophic factor (BDNF) given by intrathecal (IT) infusion to patients with amyotrophic later sclerosis (ALS)*. 50th Annu Meet Amer Assoc Neurol (April 25-May 2, Minneapolis) 1998, Abst S21.005.

Original monograph - Drugs Fut 1997, 22: 969

Additional References

Bennett, D.L.H. et al. *The effects of BDNF on c-fos and NOS expression in dorsal horn neurones of the adult rat spinal cord*. Soc Neurosci Abst 1996, 22(Part 2): Abst 396.15.

Berninger, B., Thoenen, H. *Brain-derived neurotrophic factor potentiates dendritic Ca^{2+} transients in cultured hippocampal neurons*. Soc Neurosci Abst 1996, 22(Part 2): Abst 397.10.

Cheng, Y. et al. *BDNF protects the neonatal rat brain from hypoxic-ischemic insults*. Soc Neurosci Abst 1996, 22(Part 2): Abst 397.12.

Cik, M. et al. *BDNF increases survival of fetal mesencephalic dopaminergic neurons and enhances their recovery after treatment with 6-hydroxydopamine*. Soc Neurosci Abst 1996, 22(Part 2): Abst 397.2.

Drum, K. et al. *Treatment of BDNF does not prevent normal chick retinal ganglion cell death in ovo*. Soc Neurosci Abst 1996, 22(Part 2): Abst 397.25.

Erickson, J.T. et al. *BDNF-, but not NT4-knockout mice are deficient in dopaminergic visceral sensory neurons and display severe developmental deficits in control of breathing*. Soc Neurosci Abst 1996, 22(Part 2): Abst 396.3.

Felts, P.A. et al. *The effect of treatment with brain-derived neurotrophic factor on experimental allergic neuritis*. Soc Neurosci Abst 1997, 23(Part 2): Abst 877.6.

Fritzsch, B. et al. *The neurotrophic support of the developing ear: A comparison of BDNF/NT-3 with TrkB/C knockout mice*. Soc Neurosci Abst 1996, 22(Part 2): Abst 396.2.

Frost, D.O. et al. *BDNF injected into retinal targets reduces developmental ganglion cell death*. Soc Neurosci Abst 1997, 23(Part 1): Abst 247.2.

Giehl, K.M. et al. *BDNF is an autocrine-paracrine survival factor for axotomized adult rat corticospinal neurons (CSN) in vivo*. Soc Neurosci Abst 1997, 23(Part 1): Abst 247.6.

Ho, P. et al. *BDNF and CNTF can be simultaneously delivered to regenerating nerves by crosslinkage to collagen tubules*. J Invest Med 1997, 45(1): 108A.

Huhn, M. et al. *Effect of the neurotrophic factors NGF and BDNF on NG 108-15 cells*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 23.2.

Ikeda, K. et al. *BDNF (brain-derived neurotrophic factor) reduces retinal cell damage caused by chemically induced ex vivo hypoxia and hypoglycemia in rats*. Soc Neurosci Abst 1996, 22(Part 2): Abst 397.22.

Kimpinski, K. et al. *Effects of the neurotrophins nerve growth factor, neurotrophin-3, and brain-derived neurotrophic factor (BDNF) on neurite growth from adult sensory neurons in compartmented cultures*. J Neurobiol 1997, 33(4): 395.

Li, Y.-X. et al. *Presynaptic modulation of neurotransmitter release by BDNF in cultured hippocampal neurons*. Soc Neurosci Abst 1997, 23(Part 2): Abst 457.5.

Lyons, W.E. et al. *BDNF infusion stimulates activity of TrkB receptors and the sprouting of serotonin axons in the rat brain with a similar dose response*. Soc Neurosci Abst 1996, 22(Part 2): Abst 397.16.

Ma, Y.T. et al. *BDNF injected into the superior colliculus reduces developmental retinal ganglion cell death*. J Neurosci 1998, 18(6): 2097.

Mamounas, L.A. et al. *BDNF stimulated sprouting of serotonergic axons is impaired in the aged rat brain*. Soc Neurosci Abst 1996, 22(Part 2): Abst 397.17.

Messaoudi, E. et al. *Acute intrahippocampal infusion of BDNF induces lasting potentiation of synaptic transmission in the rat dentate gyrus*. Soc Neurosci Abst 1997, 23(Part 1): Abst 47.12.

Nakatani, M., Linden, R. *TrkB-mediated blockade of retinal apoptosis by NT-4, BDNF and intraretinal neurotrophic factors*. Soc Neurosci Abst 1997, 23(Part 1): Abst 247.3.

Osehobo, P. et al. *Effects of in vivo BDNF infusion on amygdala kindling, sprouting, and hilar area*. Soc Neurosci Abst 1996, 22(Part 2): Abst 397.6.

Patterson, S.L. et al. *Recombinant BDNF rescues deficits in hippocampal LTP and basal synaptic transmission in BDNF knockout mice*. Soc Neurosci Abst 1996, 22(Part 2): Abst 397.13.

Qiao, X. et al. *Correlation of BDNF expression deficit and delayed granule cell migration in the cerebellum of stargazer mutant mouse*. Soc Neurosci Abst 1996, 22(Part 2): Abst 396.17.

Reibel, S. et al. *Protective effects of brain-derived neurotrophic factor in two models of epilepsy in the rat*. Soc Neurosci Abst 1996, 22(Part 2): Abst 397.11.

Schabitz, W.R. et al. *Intraventricular brain-derived neurotrophic factor reduces infarct size following focal cerebral ischemia in rats*. J Cereb Blood Flow Metab 1997, 17(Suppl. 1): S378.

Scharfman, H.E. *Potentiation of hyperexcitability in entorhinal/hippocampal slices of adult rat after exposure to brain-derived neurotrophic factor (BDNF)*. Soc Neurosci Abst 1997, 23(Part 2): Abst 457.7.

Schmidt-Kastner, R. et al. *Role of brain-derived neurotrophic factor (BDNF) in global and focal brain ischemia in rat*. J Cereb Blood Flow Metab 1997, 17(Suppl. 1): S375.

Shoji, F. et al. *The prevention of noise-induced deafness with growth factors: GDNF, BDNF, NT-3*. Soc Neurosci Abst 1997, 23(Part 1): Abst 248.2.

Shu, X.-Q. et al. *Sensitization of nociceptors to noxious heat by NT-4 and BDNF but not by NT-3*. Soc Neurosci Abst 1997, 23(Part 2): Abst 877.1.

Siuciak, J.A. et al. *Brain-derived neurotrophic factor (BDNF) increases opioid receptor mRNA expression in the PAG*. Soc Neurosci Abst 1996, 22(Part 2): Abst 396.16.

Spranger, M. et al. *BDNF improves long-term potentiation and cognitive functions after global cerebral ischemia*. J Cereb Blood Flow Metab 1997, 17(Suppl. 1): S370.

Tang, N.J., Lo, D.C. *Short- and long-term regulation of hippocampal synaptic transmission by BDNF*. Soc Neurosci Abst 1996, 22(Part 2): Abst 397.9.

Wang, J., Yan, Q. *Glial cell line-derived neurotrophic factor (GDNF) is a neurotrophic factor for retinal ganglion cells in adult rats*. Soc Neurosci Abst 1997, 23(Part 1): Abst 248.1.

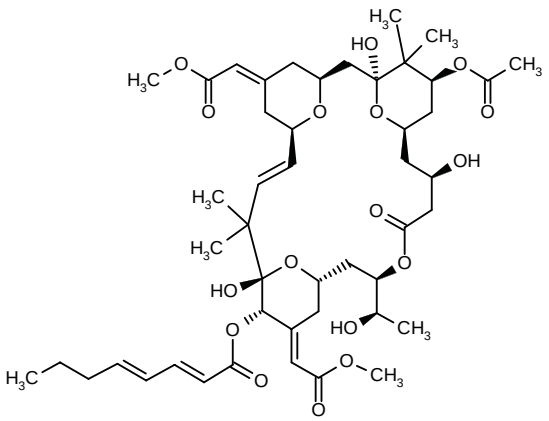
Yanamoto, H. et al. *Brain protection by direct cerebral injection of brain-derived neurotrophic factor against focal temporary ischemia*. Soc Neurosci Abst 1997, 23(Part 2): Abst 948.1.

Yang, B. et al. *Brain derived neurotrophic factor induces a transient calcium increase in cortical neurons*. Soc Neurosci Abst 1996, 22(Part 2): Abst 397.21.

Bryostatin 1

Antineoplastic
Protein Kinase C Activator

EN: 165188



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

Arizona State Univ. (US); Bristol-Myers Squibb; Natl. Cancer Inst. (US)

An *in vitro* study has demonstrated that bryostatin-1 can selectively activate PKCε under certain conditions. Treatment with bryostatin-1 for 72 hours resulted in increased τ phosphorylation and suppression of neuritogenesis in human neuroblastoma cells while treatment with staurosporine or TPA induced neuritogenesis and had no effect on τ phosphorylation; moreover, bryostatin-1 blocked staurosporine-induced neurite elaboration (1).

In an *in vitro* study using RT-PCR for mdr-1 mRNA and immunoassay confirmation, 72 h exposure of human prostate cancer cells (DU-145 prostate carcinoma #ATTCC HTB 81) to 10 nM bryostatin-1 resulted in a 14 fold reduction in mdr-1 gene overexpression. Further studies demonstrated that when bryostatin-1-treated cells were exposed to adriamycin (10 ng/ml), adriamycin-induced cytotoxicity was increased indicating that bryostatin-1 may be a potential adjunct to chemotherapy for cancers involving overexpression of mdr-1 such as prostate cancer (2).

In vitro exposure of a mature B-cell line (WSU-DLCL2) established from a patient with diffuse large cell lymphoma with bryostatin-1 resulted in reversal of multidrug resistance phenotype at 24 h and a 3 fold increase in [^{3}H]vincristine accumulation. Although bryostatin-1, vincristine, doxorubicin and 1-β-D-arabinofuranosylcytosine administration to WSU-DLCL2-tumor bearing immune deficient mice had no effect, if bryostatin-1 was administered 24 h prior to vincristine, antitumor activity of vincristine was enhanced. In addition, β-glycoprotein expression was significantly reduced in tumors from bryostatin-1-treated mice and a decrease in mdr-1 RNA expression was observed *in vivo* 24 h following treatment (3).

When LIF-deprived murine embryonic stem cells were treated with bryostatin-1, CFU formation was enhanced and developing embryoid bodies increased in number and were larger in size. Bryostatin-1 also induced a 5 times greater number of CD34$^+$ progenitor cells as compared to control cells. Moreover, expression of PKCα, ε and ζ/ι expression was detected in bryostatin-treated embryonic stem cells. A 2 times greater number of total cells resulted from embryonic stem cells treated with bryostatin-1 indicating a potential use for this agent in stem cell transplantation (4).

In an ongoing phase I/II *in vitro* trial, human monocytic leukemia cells (U937) preincubated with taxol (500 nM for 6 h) and then exposed to bryostatin-1 (10 nM for 6-18 h) resulted in a significantly increased percentage of apoptotic cells with a decrease in the fraction of cells arrested in G_2M phase as compared to cells first pretreated with bryostatin-l and subsequently exposed to taxol. Although bryostatin-1 treatment did not increase taxol-induced tubulin stabilization or [^{3}H]taxol retention, slight changes in Bcl-2 protein mobilization were observed and free Bax values were higher. Moreover, PD988059 also increased taxol-induced antiproliferative activity in a manner similar to bryostatin-1 suggesting that enhancement of taxol activity by bryostatin-1 could be due to possible interactions of Bcl-2 proteins and interferences in cell survival cycles (5).

A phase I study was undertaken to determine the maximum dose and infusion time of bryostatin-1 treatment for patients with advanced cancer. A range of 8 μg/m^2/day x 96 h to 24 μg/m^2/day x 144 h was administered to 20 patients with incurable, advanced cancer. No responses were observed and *in vitro* experiments showed no PKC or MAPK protein modulation or alterations in MMP-2 or -9 activation states. However, modulations of MEK/MEK-p and PKCη were observed in tumor samples (6).

A phase I study has demonstrated that when 26 pediatric patients with various types of refractory solid tumors were given bryostatin-1 (20, 26, 34, 44 or 55 μg/m^2 over 1 h per week x 3), 3/5 patients receiving 55 μg/m^2 displayed dose limiting toxicities including greater than or equal to grade 3 myalgia and photophobia with a duration of less than 7 days. In addition, grade 1-2 toxicities such as fever, headache, hypotension, thrombocytopenia and elevated transaminases were also observed. A dose of 44 μg/m^2/week x 3 was concluded to be an appropriate dose for phase II trials in pediatric patients (7).

1. Ekinci, F.J., Shea, T.B. *Selective activation by bryostatin-1 demonstrates unique roles for PKCε in neurite extension and τ phosphorylation*. Int J Dev Neurosci 1997, 15(7): 867.

2. Kamanda, W.S., Leece, C.M. *Bryostatin-1 down regulates MDR-1 and enhances adriamycin-induced cytotoxicity in human prostate cancer cells*. Proc Amer Soc Clin Oncol 1998, Abst 940.

3. Al Katib, A.M., Smith, M.R., Kamanda, W.S., Pettit, G.R., Hamdan, M., Mohamed, A.N., Chelladurai, B., Mohammad, R.M. *Bryostatin 1 down-regulates mdr1 and potentiates vincristine cytotoxicity in diffuse large cell lymphoma xenografts*. Clin Cancer Res 1998, 4(5): 1305.

4. Kalmaz, G., Ruvolo, P., May, W.S. *Bryostatin 1 promotes the proliferation and differentiation of CD34$^+$ progenitor cells derived from murine embryonic stem (ES) cells*. Blood 1997, 90(10, Suppl. 1, Part 2): Abst 3371.

5. Grant, S., Wang, Z., Dent, P. *Potentiation of Taxol-induced apoptosis in human monocytic leukemia cells (U937) by the PKC activator bryostatin 1*. Blood 1997, 90(10, Suppl. 1, Part 1): Abst 2209.

6. Marshall, J.L., Johnson, M., Rizvi, M., Dahut, N., Oberst, M., Norris, B.M., VanUmmerson, L., Hawkins, M.J. *Phase 1 trial of prolonged infusion bryostatin-I in patients with advanced cancer*. Proc Amer Assoc Cancer Res 1998, Abst 4092.

7. Langevin, A.M., Bernstein, M., Kraft, A.S., Berkow, R.L., Weitman, S. *Phase I trial of bryostatin-1 in childhood solid tumors. A Pediatric Oncology Group (POG) study*. Proc Amer Soc Clin Oncol 1998, Abst 825.

Original monograph - Drugs Fut 1983, 8: 757.

Additional References

Ali-Sadat, S. et al. *Interactions of bryostatin 1 with tamoxifen, paclitaxel and doxorubicin in human breast cancer cells*. Proc Amer Assoc Cancer Res 1998, Abst 2115.

Grant, S. et al. *Phase Ib trial of bryostatin 1 in patients with refractory malignancies*. Clin Cancer Res 1998, 4(3): 611.

Mohammad, R.M. et al. *Synergistic interaction of selected marine animal anticancer drugs against human diffuse large cell lymphoma*. Anti-Cancer Drugs 1998, 9(2): 149.

Mohammad, R.M. et al. *The role of bryostatin 1 in 2-CdA resistant B-CLL line: Mechanism of resistance and response*. Blood 1997, 90(10, Suppl. 1, Part 1): Abst 2364.

Varterasian, M.L. et al. *Phase I study of bryostatin 1 in patients with relapsed non-Hodgkin's lymphoma and chronic lymphocytic leukemia*. J Clin Oncol 1998, 16(1): 56.

Vrana, J.A. et al. *Effects of bryostatin 1 and calcium ionophore (A23187) on apoptosis and differentiation in human myeloid leukemia cells (HL-60) following 1-β-D-arabinofuranosylcytosine exposure*. Int J Oncol 1998, 12(4): 927.

Zellner, A. et al. *Bryostatin 1: In vitro effects on human glioblastoma cell lines and protein kinase C expression*. Proc Amer Soc Clin Oncol 1998, Abst 1590.

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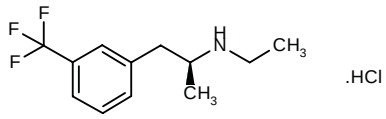
Redux®

EN: 090977



$C_{12}H_{16}F_3N.HCl$ **Wyeth-Ayerst; Interneuron**

Wyeth-Ayerst and Interneuron have announced that the U.S. FDA has advised that the companies may proceed with a phase IV clinical study in humans to investigate whether any cognitive, behavioral or psychological changes occur in patients taking dexfenfluramine (Redux™). This multicenter, 2-year, double-blind, randomized, placebo-controlled study will address issues raised by animal studies which indicate that administration of high doses of dexfenfluramine leads to changes in brain serotonin levels (1).

Interneuron and Wyeth-Ayerst have voluntarily withdrawn dexfenfluramine hydrochloride from the U.S. market, as requested by the FDA based on new, preliminary evidence of heart valve abnormalities in subjects taking the weight-loss medication, most often in combination with phentermine (2).

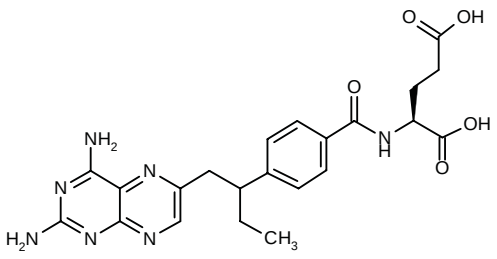
1. *Phase IV trial of Redux*. Daily Essentials Aug 21, 1997.

2. *Fenfluramine, dexfenfluramine voluntarily withdrawn*. Daily Essentials Sept 16, 1997.

Original monograph - Drugs Fut 1987, 12: 845.

Edatrexate *Antineoplastic*

EN: 108334



$C_{22}H_{25}N_7O_5$ **SRI Int.; Sloan-Kettering Inst. (US); Novartis**

Edatrexate was evaluated in a phase II trial for the treatment of metastatic soft tissue carcinoma. Thirty-three patients received edatrexate 80 mg/m^2 i.v. for 5 weeks, followed by 1 week of administration with dose modification. Three patients had a partial response, 2 patients had a < 50% response, 3 had stable disease and 16 progressed. Neutropenia and mucositis were the dose-limiting toxicities observed (1).

1. Wasserheit, C., Blum, R.H., Ryan, L. *Phase II trial of edatrexate in adult patients with metastatic soft tissue sarcomas, an ECOG phase II trial*. Proc Amer Soc Clin Oncol 1998, Abst 1978.

Original monograph - Drugs Fut 1989, 14: 849.

Fluvastatin Sodium

Hypolipidemic

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HMG-CoA Reductase Inhibitor

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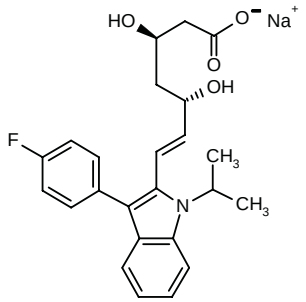

$C_{24}H_{25}FNNaO_4$

Novartis; Tanabe Seiyaku; Astra; Hoechst Marion Roussel

Fluvastatin sodium (Lescol®), previously available for the treatment of primary hypercholesterolemia unresponsive to diet, has been approved in the U.K. for slowing the progression of coronary atherosclerosis in patients with primary hypercholesterolemia and concomitant heart disease not adequately responding to diet (1).

Information about two new studies evaluating the ability of fluvastatin sodium (Lescol®) to improve event-free survival times in special patient groups has been presented. The LIPS (Lescol® Intervention Prevention Study) trial is examining the activity of the compound in patients who have undergone coronary angioplasty, and the ALERT (Assessment of Lescol® in Renal Transplantation) study is examining the long-term effects of the compound on survival time in renal transplant recipients (2).

1. *New use approved for Lescol*. Daily Essentials Jan 14, 1998.

2. *Two new international trials will further explore the therapeutic benefits of Lescol*. Daily Essentials April 29, 1998.

Original monograph - Drugs Fut 1991, 16: 804.

Additional References

Ballantyne, C.M. et al. *Lesion progression, regression, and stability with fluvastatin in the lipoprotein and coronary atherosclerosis study*. J Am Coll Cardiol 1998, 31(2, Suppl. A): Abst 1116-8.

Gerö, L. et al. *One-year follow-up of fluvastatin treatment in kidney transplant recipients with posttransplant diabetes*. 8th Cong Eur Soc Organ Transplant (Sept 2-6, Budapest) 1997, Abst 62.

Herd, J.A. et al. *Effects of fluvastatin on coronary atherosclerosis in patients with mild to moderate cholesterol elevations (lipoprotein and coronary atherosclerosis study (LCAS))*. Am J Cardiol 1997, 80(3): 278.

Locsey, L. et al. *Efficacy and safety long-term effect of fluvastatin (Lescol) therapy in hypertonic, hyperlipidaemic transplanted patients*. J Hypertens 1998, 16(Suppl. 2): Abst P27.120.

Locsey, L. et al. *Efficacy and safety of fluvastatin long-term treatment on hyperlipidemia after renal transplantation*. 13th Int Symp Drugs Affect Lipid Metab (May 30-June 3, Florence) 1998, 66.

Schrama, Y.C. et al. *The efficacy and safety of fluvastatin (a HMG-CoA reductase inhibitor) in renal and cardiac transplant patients; an exercise provocation test*. 8th Cong Eur Soc Organ Transplant (Sept 2-6, Budapest) 1997, Abst 63.

Idazoxan Hydrochloride

α_2-Adrenoceptor Antagonist

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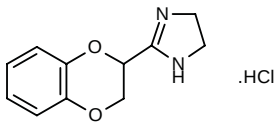

$C_{11}H_{12}N_2O_2.HCl$

Pierre Fabre

Administration of idazoxan (0.25 mg/kg i.p.) in rats significantly increased extracellular dopamine levels, with a maximum facilitatory effect of 241.5% observed 80 min after drug administration. Idazoxan-induced increases in dopamine levels were blocked by diazepam and tropisetron, as well as by 5-HT, indicating that the interaction between dopaminergic and serotonergic neuronal systems in rat prefrontal cortex may be involved in anxiety or fear (1).

1. Matsumoto, M., Yoshioka, M., Togashi, H., Mori, K., Ueno, K., Saito, H. *Effects of idazoxan on dopamine release in the prefrontal cortex of freely moving rats*. Eur J Pharmacol 1998, 343(2-3): 165.

Original monograph - Drugs Fut 1983, 8: 778

Additional References

Arborelius, L. et al. *Enhanced activation of locus coeruleus neurones by idazoxan in rats chronically treated with imipramine*. Soc Neurosci Abst 1997, 23(Part 2): Abst 435.1.

Fara-On, M. et al. *In vivo release of noradrenaline by idazoxan activates glycogenolysis in rat neocortex and hippocampus*. Soc Neurosci Abst 1996, 22(Part 2): Abst 357.6.

Gintautas, J. et al. *Vasoconstrictor effects of clonidine, yohimbine and idazoxan on isolated dog carotid arteries*. 11th World Cong Anaesthesiol (April 14-20, Sydney) 1996, Abst P67.

Gross, C.E. et al. *Dose effect relationship of the α_2 antagonist, idazoxan, in MPTP-treated monkeys*. Soc Neurosci Abst 1997, 23(Part 2): Abst 738.15.

Middleton, H.C. et al. *Idazoxan potentiates rather than antagonises the psychological effects of clonidine*. J Psychopharmacol 1997, 11(3, Suppl.): Abst 231.

Schmidt, M.E. et al. *Acute α_2 blockade by idazoxan increases insulin and lowers plasma glucose during positron emission tomography*. Psychopharmacol Bull 1997, 33(2): 253.

Imiquimod
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Interferon Inducer

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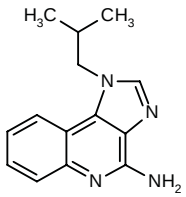

$C_{14}H_{16}N_4$ **3M Pharm.; Daiichi Pharm.**

In vitro studies using RT-PCR have demonstrated that imiquimod treatment upregulates interferon-α gene expression in human keratinocytes 2 and 3 fold with doses of 1 and 10 μg/ml, respectively. In addition, IL-8 message and protein and IL-1α protein were increased as well as a 1.4 fold increase in IL-1α gene expression with 10 μg/ml imiquimod. In *in vivo* studies, interferon-α message was induced 1 h after hairless mice were treated with 5% imiquimod cream with peak induction occurring at 4 h. Increases in interferon-α RNA, interferon protein and TNF protein were also observed with imiquimod treatment (1).

In a randomized, double-blind, placebo-controlled study, 20 patients with ano-HPV/genital warts self-applied either 5% imiquimod cream or a vehicle cream 3 times per week for up to 16 weeks. Correlations were detected between responses of imiquimod-treated patients and keratinocyte markers of proliferation, differentiation, apoptosis, cellular infiltration and cellular activation and in levels of HPV, DNA, HPV early and late proteins, chemokines, Th1- and Th2-promoting cytokines and IFN inducible gene products (2).

The safety of imiquimod treatment was examined in 3 trials. In the first trial, 40 healthy subjects received either topical Hill Top chambers® imiquimod 5% cream, vehicle cream or Vaseline Intensive Care Lotion® (VICL) for 21 days with results showing that imiquimod and vehicle creams were significantly less irritating than VICL. Imiquimod cream and the vehicle were also shown to have the same sensitization potential in the second trial in which 139 healthy subjects applied either Hill Top chambers® imiquimod 5% cream or the vehicle cream to the upper arm 3 times per week for 3 weeks followed by a 14 day rest period and subsequent challenge with either cream. The percutaneous penetration of imiquimod was assessed and found to be less than 0.9% of the dose in the third trial in which 6 healthy subjects were given a single 8 h application of radiolabeled imiquimod 5% cream; no radioactivity was found in serum over the 48 h sampling period (3).

Two double-blind, vehicle-controlled, multicenter, parallel trials examined different imiquimod (5% or 1% cream) regimens as a treatment for genital/perianal warts. In the first trial, 279 patients were treated daily for up to 16 weeks with a 5% or 1% imiquimod or vehicle cream and in the second, 311 were treated with the same creams 3 times/week for up to 16 weeks. The first trial resulted in a greater wart clearance rate in all patients although both trials demonstrated a higher total wart clearance for woman as compared to men. In addition, both trials showed that the 5% cream had a higher clearance rate than the 1% and vehicle creams and reoccurrence rates were low. Although no significant differences were observed in side effects, patients from trial 1 experienced greater incidence and severity of local skin reactions (4).

The immunostimulatory effects of topically applied imiquimod 5% cream (3 times weekly up to 16 weeks) were evaluated in a double-blind, placebo-controlled study in 19 patients with genital/perianal warts. All 16 imiquimod-treated patients demonstrated a (75% reduction in wart area, which was strongly correlated with decreases in virally infected cells and mRNA expression for cellular proliferation, as well as increases in local cytokines (5).

The safety and efficacy of imiquimod topical cream were evaluated in a placebo-controlled, randomized, double-blind trial in 311 patients with external anogenital warts. Patients applied imiquimod 5%, imiquimod 1% or placebo cream overnight to all external warts 3 times weekly for 16 weeks or until all warts disappeared. The rate of eradication of all baseline warts was 50%, 21% and 11% in the imiquimod 5%, imiquimod 1% and placebo groups, respectively. Of the patients in whom baseline warts were totally eradicated with 5% imiquimod cream, 13% experienced recurrence of at least one wart; recurrence rates were 0% and 10% in the imiquimod 1% and placebo groups, respectively. The most common adverse effect was local erythema, although most patients had no or only mild adverse inflammatory reactions (6).

1. Tomai, M.A., Miller, R.L., Fujisawa, H., Shivji, G.M., Wang, B., Sauder, D.N. *A novel topical immune response enhancer induces cytokine production in human keratinocytes and skin*. Australas J Dermatol 1997, 38(Suppl. 2): Abst 2040.

2. Chopra, K., Lee, P., Tyring, S.K., Arany, I., McDermott, D. *Vehicle-controlled study investigating the mechanism of action of 5% imiquimod cream applied three times a week for the treatment of patients with genital/perianal warts*. Australas J Dermatol 1997, 38(Suppl. 2): Abst 1320.

3. Owens, M.L., Tygum, K.I., Senta, T.A., Myers, J.A., Fox, T.L., Smith, M.H. *Safety assessment of topical imiquimod*. Australas J Dermatol 1997, 38(Suppl. 2): Abst 5151.

4. Tyring, S., Trofatter, K., Beutner, K. et al. *Two vehicle-controlled clinical trials of topical imiquimod for the treatment of genital/perianal warts*. Australas J Dermatol 1997, 38(Suppl. 2): Abst 5159.

5. Slade, I.H.B., Tyring, S.K., Arany, I., Stanley, M.A., Tomai, M.A., Parrish, S.L., Smith, M.H., McDermott, D.J., Millers, R.L. *Stimulation of local cytokine and cell mediated immune responses in human papillomavirus (HPV) patients receiving imiquimod*. J Eur Acad Dermatol Venereol 1997, 9(Suppl. 1): Abst FC142.

6. Edwards, L., Ferenczy, A., Eron, L. et al. *Self-administered topical 5% imiquimod cream for external anogenital warts*. Arch Dermatol 1998, 134(1): 25.

Original monograph - Drugs Fut 1989, 14: 870.

Additional References

Arany, I. et al. *Molecular effects of imiquimod and S-28463 in human papillomavirus-containing cell lines*. Australas J Dermatol 1997, 38(Suppl. 2): Abst 5212.

Beutner, K.R. et al. *Treatment of genital warts with an immune-response modifier (imiquimod)*. J Am Acad Dermatol 1998, 38(2): 230.

Beutner, K.R. et al. *Imiquimod, a patient-applied immune-response modifier for treatment of external genital warts*. Antimicrob Agents Chemother 1998, 42(4): 789.

Edwards, L. *Immune response modification: Imiquimod. Imiquimod in clinical practice*. Australas J Dermatol 1997, 38(Suppl. 2): 14.

Imbertson, L.M. et al. *Cytokine induction in hairless mouse and rat skin after topical application of the immune response modifiers imiquimod and S-28463*. J Invest Dermatol 1998, 110(5): 734.

Maw, R.D. *Genital warts: A recurring problem - Imiquimod a new approach to treatment*. J Eur Acad Dermatol Venereol 1997, 9(Suppl. 1): Abst ST004.

Owens, M.L. et al. *A safety assessment of topical imiquimod*. J Eur Acad Dermatol Venereol 1997, 9(Suppl. 1): Abst P333.

Tomai, M.A. et al. *A novel topical immune response modifier induces cytokine production in human keratinocytes and skin*. J Eur Acad Dermatol Venereol 1997, 9(Suppl. 1): Abst P336.

Trofatter, K. et al. *Two vehicle-controlled trials of topical imiquimod for the treatment of genital/perianal condylomata acuminata*. J Eur Acad Dermatol Venereol 1997, 9(Suppl. 1): Abst P335.

Tyring, S. *Immune response modification: Imiquimod. Immune response in vitro*. Australas J Dermatol 1997, 38(Suppl. 2): 14.

Tyring, S.K. et al. *A randomized, controlled, molecular study of condylomata acuminata clearance during treatment with imiquimod*. J Infec Dis 1998, 178(2): 551.

Wagner, T.L. et al. *Induction of cytokines in cynomolgus monkeys by the immune response modifiers, imiquimod, S-27609 and S-28463*. Cytokine 1997, 9(11): 837.

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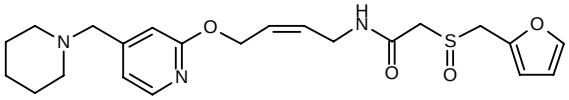

$C_{22}H_{29}N_3O_4S$

Fujirebio; Taiho

In rats with experimentally induced gastric and intestinal lesions, lafutidine (3-30 mg/kg in fasted animals and 1-10 mg/kg in nonfasted animals), but not cimetidine, was shown to have a significant, dose-dependent cytoprotective action against both types of lesions. This action was suggested to be mediated mainly via capsaicin-sensitive sensory neurons and calcitonin gene-related peptide, rather than endogenous prostaglandins or nitric oxide (1).

1. Tashima, K., Konaka, A., Sugawa, Y., Kato, S., Takeuchi, K. *Effects of lafutidine, a novel histamine H_2-receptor antagonist, on gastrointestinal lesions in rats: Relation to capsaicin sensitive sensory neurons*. Dig Dis Week (May 17-20, New Orleans) 1998, Abst 342.

Original monograph - Drugs Fut 1994, 19: 835.

Additional References

Hirakawa, N. et al. Y. *A novel histamine 2(H_2) receptor antagonist with gastroprotective activity. II. Synthesis and pharmacological evaluation of 2-furfuryl-thio and 2-furfurylsulfinyl acetamide derivatives with heteroaromatic rings*. Chem Pharm Bull 1998, 46(4): 616.

Onodera, S. et al. *Effect of lafutidine, a novel antiulcer agent, on healing and relapse of acetic acid-induced gastric ulcer in rats*. Folia Pharmacol Jpn 1998, 111(3): 167.

Sekine, Y. et al. *A novel histamine 2(H_2) receptor antagonist with gastroprotective activity. I. Synthesis and pharmacological evaluation of N-phenoxypropylacetamide derivatives with thioether function*. Chem Pharm Bull 1998, 46(4): 610.

LC-9018
Lemonal®

Immunostimulant

EN: 101738

Yakult Honsha; Daiichi Pharm.

The results from a study in mice bearing Meth A tumors administered LC-9018 intrapleurally indicated that the antitumor activity of the compound is closely related to tumor necrosis factor-α production (1).

1. Matsuzaki, T., Kimura, K., Hashimoto, S., Yokokura, T., Yoshikai, Y. *Antitumor activity and cytokine production by intrapleural administration of Lactobacillus casei in mice*. 56th Annu Meet Jpn Soc Cancer Res (Sept 25-27, Kyoto) 1997, Abst VAP-184.

Original monograph - Drugs Fut 1990, 15: 895.

Mangafodipir Trisodium *MRI Contrast Agent*
MnDPDP
S-095
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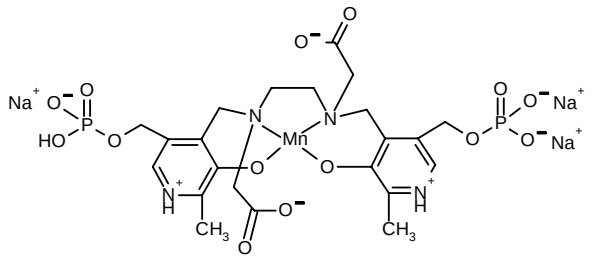
EN: 172203



$C_{22}H_{27}MnN_4Na_3O_{14}P_2$ **Nycomed Amersham**

Nycomed's mangafodipir (Teslascan®) has been approved by the FDA for use as an adjunct to MRI to enhance T1-weighted images in the detection, localization, characterization and evaluation of liver lesions (1).

Mangafodipir (Teslascan®) has been introduced in the U.K., Germany, Austria and Sweden by Nycomed for use in the diagnosis of liver diseases; supplied as vials containing solution for i.v. infusion (50 ml), 0.01 mmol/ml (2, 3).

1. *FDA clears Teslascan for detection of liver diseases*. Daily Essentials Dec 10, 1997.

2. *New MRI contrast agent available in Europe*. Daily Essentials Oct 28, 1997.

3. *Mangafodipir trisodium*. Drug Data Rep 1998, 20(1): 92.

Original monograph - Drugs Fut 1997, 22: 974.

Additional References

Ahlstrom, H., Gehl, H.B. *Overview of MnDPDP as a pancreas-specific contrast agent for MR imaging*. Acta Radiol 1997, 38(4, Part 2): 660.

Ni, Y., Marchal, G. *Clinical implications of studies with MnDPDP in animal models of hepatic abnormalities*. Acta Radiol 1997, 38(4, Part 2): 724.

Ni, Y., et al. *Comparison of manganese biodistribution and MR contrast enhancement in rats after intravenous injection of MnDPDP and $MnCl_2$*. Acta Radiol 1997, 38(4, Part 2): 700.

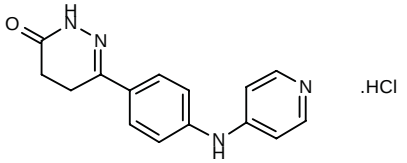
Southon, T.E. et al. *NMR relaxation studies with MnDPDP*. Acta Radiol 1997, 38(4, Part 2): 708.

Tirkkonen, B. et al. *Physicochemical characterisation of mangafodipir trisodium*. Acta Radiol 1997, 38(4, Part 2): 780.

Wang, C. et al. *Diagnostic efficacy of MnDPDP in MR imaging of the liver - A phase III multicentre study*. Acta Radiol 1997, 38(4, Part 2): 643.

MCI-154 *Treatment of Heart Failure*

EN: 120907



$C_{15}H_{14}N_4O.HCl$ **Mitsubishi Chem.; Hoechst Marion Roussel; Astra**

Evaluation of the effects of MCI-154 on the contractile properties of skinned rabbit skeletal muscle fibers showed that the drug, as in cardiac muscle, potentiated isometric tension and improved isometric tension cost during full Ca^{2+} activation. However, in contrast to its effect on cardiac muscle, in skeletal muscle MCI-154 reduced the shortening velocity, rate of rise of tension and actomyosin ATPase activity (1).

1. Iwamoto, H. *Effect of a cardiotonic agent, MCI-154, on the contractile properties of skinned skeletal muscle fibers*. Eur J Pharmacol 1998, 341(2-3): 243.

Original monograph - Drugs Fut 1987, 12: 856.

Additional References

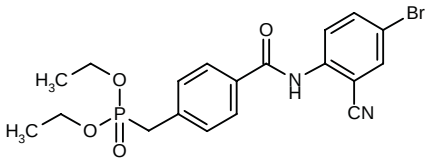
Kitada, Y. *MCI-154, a cardiac Ca^{2+} sensitizer, reverses the depression in maximal Ca^{2+}-activated force by inorganic phosphate and acidic pH in skinned fiber of guinea pig heart*. Cardiovasc Drugs Ther 1997, 11(5): 611.

Okamoto, H. et al. *Beneficial effects of a new Ca^{2+} sensitizer, MCI-154, on microvascular remodeling and myocardial performance in dilated cardiomyopathy*. Circulation 1997, 96(8, Suppl.): Abst 770.

Mitsubishi Chemical R&D status in Japan and overseas. Daily Essentials July 22, 1997.

NO-1886 *Hypolipidemic*

EN: 168363



$C_{19}H_{20}BrN_2O_4P$ **Otsuka**

The effect of NO-1886 on fat accumulation in rats fed a high-fat diet was studied. FA volume increased 3.3 times more in rats fed a high-fat diet than in controls, while rats treated with NO-1886 (50 mg/kg for 3 months) increased their FA volume by only 1.5 times the control values. NO-1886 also suppressed subcutaneous fat accumulation and decreased the respiratory quotient (1).

1. Kusunoki, M., Hara, T., Sakakibara, F., Chikada, K., Usui, K., Yamanouchi, K., Nakaya, Y., Koremu, S. *Inhibitory effect of NO-1886, an LPL activator, on accumulation of fat in rats fed a high-fat diet*. J Jpn Diabetes Soc 1997, 40(Suppl. 1): Abst 1V 09.

Original monograph - Drugs Fut 1996, 21: 901.

Additional References

Hagi, A. et al. *The novel compound NO-1886 activates lipoprotein lipase in primary cultured adipose and skeletal muscle cells*. Biol Pharm Bull 1997, 20(10): 1108.

Hara, T. et al. *The actions of a novel lipoprotein lipase activator, NO-1886, in hypertriglyceridemic fructose-fed rats*. Metab Clin Exp 1998, 47(2): 149.

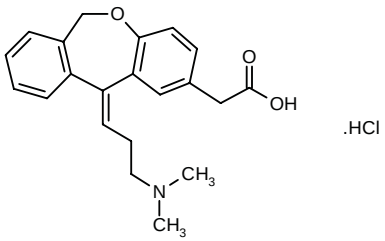
Hara, T. et al. *A lipoprotein lipase activator, NO-1886, improves endothelium-dependent relaxation of rat aorta associated with aging*. Eur J Pharmacol 1998, 350(1): 75.

Ohara, M. et al. *Suppression of carcass weight loss in cachexia in rats bearing Leydig cell tumor by the novel compound NO-1886, a lipoprotein lipase activator*. Metabolism 1998, 47(1): 101.

Olopatadine Hydrochloride
Patanol®

Antiallergic/Antiasthmatic

EN: 141324



$C_{21}H_{23}NO_3.HCl$ **Kyowa Hakko; Alcon**

Unique pocket binding of KW-4679 to the histamine H_1 receptor was demonstrated in a binding study. [^{3}H]KW-4679 was shown to have high affinity (K_d = 2.5 ± 0.12 nM) for the wild-type human histamine H_1 receptor. Moreover, when Asp^{107} of the H_1 receptor was replaced by alanine, a 280-2100 fold reduction in tri- and tetracyclic compounds affinities was noted in contrast to only a 14 fold reduction in KW-4679 affinity (1).

The pharmacokinetics of single (10 mg) and multiple (10 mg x 6 days) doses of KW-4697 was compared in elderly and young male subjects. C_{max} and AUC after single doses were significantly greater in the elderly subjects, while total body clearance was greater in the young subjects. Renal clearance was lower in elderly subjects and correlated to creatinine clearance. Pharmacokinetic parameters, except for C_{max} values, did not change between first and last doses in the multiple-dose trial, and accumulation of the drug was not observed (2).

1. Nonaka, H., Otaki, S., Ohshima, E., Kono, M., Kase, H., Ohta, K., Fukui, H., Ichimura, M. *Unique binding pocket for KW-4679 in the histamine H-1 receptor*. Eur J Pharmacol 1998, 345(1): 111.

2. Tateishi, T., Kobayashi, S., Shigeyama, C., Nakamura, T., Kobayashi, H. *Pharmacokinetics of KW-4679 in the elderly: Single-dose and multiple-dose trials*. Drugs Exp Clin Res 1998, 24(1): 1.

Original monograph - Drugs Fut 1993, 18: 794.

Additional References

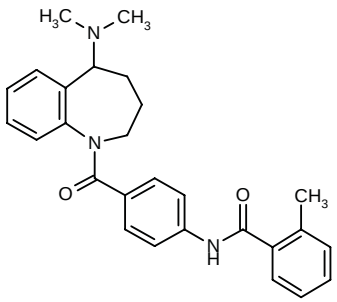
Sasaki, Y. et al. *Influence of KW-4679, an antiallergic agent, on increase of chemical mediator concentrations in bronchial alveolar lavage fluid (BALF) in actively sensitized guinea pigs with asthma*. Jpn J Allergol 1997, 46(2-3): 266.

Olopatadine still under regulatory review in Japan. Daily Essentials Feb 18, 1998.

OPC-31260

Vasopressin V_2 Antagonist

EN: 172879



$C_{27}H_{29}N_3O_2$ **Otsuka**

The diuretic and antivasopressin efficacy of OPC-31260 has been evaluated after acute and chronic administration in rats. In animals treated chronically with OPC-31260 (2 mg s.c. b.i.d. for 4 weeks), the peak and cumulative (12-h) diuretic responses to an acute dose (2 mg s.c.) were significantly attenuated compared to after acute treatment only. In addition, the antidiuretic response to vasopressin was preserved after an acute dose in animals treated chronically with OPC-31260, whereas this response was abolished in controls receiving an acute dose of the drug (1).

1. Jonasen, T.E.N., Christensen, S., Petersen, J.S. *Tolerance during chronic treatment with the vasopressin type-2 receptor antagonist OPC-31260*. J Am Soc Nephrol 1997, 8: Abst A0089.

Original monograph - Drugs Fut 1993, 18: 802.

Additional References

Bosch-Marcé, M. et al. *The aquaretic effect of niravoline is more intense and long-lasting than that of OPC 31260 in cirrhotic rats with ascites*. J Hepatol 1997, 26(Suppl. 1): Abst P/C03/05.

Edwards, R.M. et al. *Inhibition of vasopressin-induced cAMP formation by OPC-31260 in rat renal tubules*. Pharmacol Rev Commun 1997, 9(3): 165.

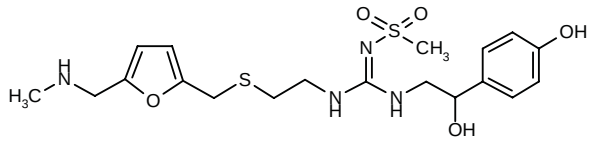
Kawachi, A. et al. *Studies of arginine^8-vasopressin- and endothelin-1-induced barrel rotation in rats*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 35.20.

Takeuchi, M. et al. *Influence of long-term oral administration of a selective vasopressin V_2 receptor antagonist (V_2A) in rats administered adriamycin*. Jpn Circ J 1997, 61(Suppl. 1): Abst 1073.

Osutidine
T-593

Gastric Antisecretory Drugs
H_2 Receptor Antagonist

EN: 159328



$C_{19}H_{28}N_4O_5S_2$ **Toyama; Kowa**

T-593 has been examined for its effects on the healing of chronic gastric ulcers in rats. The compound was administered at a dose of 30 mg/kg p.o. twice daily for 8 weeks. Macroscopic examination indicated significant acceleration of ulcer healing with T-593, and histological evaluation indicated that the compound facilitated mucosal regeneration and collagen fiber proliferation, increased the number of regenerated microvessels in the ulcer bed and decreased inflammatory cell infiltration into the connective tissue (1).

1. Doi, Y., Mori, Y., Mizuo, M., Urata, N., Sanzen, T., Arai, H. *Effects of T-593, a novel anti-ulcer agent, on healing process of chronic gastric ulcers in rats*. Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-645.

Original monograph - Drugs Fut 1993, 18: 809.

Additional References

Arai, H. et al. *Characteristics of T-593, a novel antiulcer agent, and each of its enantiomers on pharmacodynamics*. Folia Pharmacol Jpn 1998, 112(2): 107.

Arai, H. et al. *Effect of T-593 on gastric bleeding and lesions induced by indomethacin and water-immersion stress in rats: Improving effect of T-593 on reduced gastric mucosal blood flow in rats*. Folia Pharmacol Jpn 1998, 112(2): 117.

Inoue, M. et al. *Osutidine (T-593), a new H_2-receptor antagonist, versus famotidine, the strongest H_2-receptor antagonist: Effect on intragastric pH*. Digestion 1998, 59(Suppl. 3): Abst FoNO2159.

Iwai, N. et al. *Antigenicity study of osutidine (T-593), a novel antiulcer agent*. Pharmacometrics 1998, 55(5): 273.

Komae, N. et al. *Reproductive and developmental toxicity study of osutidine (T-593), a novel antiulcer agent, in rabbits administered orally during the period of organogenesis*. Pharmacometrics 1998, 55(5): 249.

Komae, N. et al. *Reproductive and developmental toxicity study of osutidine (T-593), a novel antiulcer agent, in rats administered orally prior to and in the early stages of pregnancy*. Pharmacometrics 1998, 55(5): 223.

Komae, N. et al. *Reproductive and developmental toxicity study of osutidine (T-593), a novel antiulcer agent, in rats administered orally during the period of organogenesis*. Pharmacometrics 1998, 55(5): 233.

Komae, N. et al. *Reproductive and developmental toxicity study of osutidine (T-593), a novel antiulcer agent, in rats administered orally during the perinatal and lactation periods*. Pharmacometrics 1998, 55(5): 257.

Naito, Y. et al. *Effect of the histamine H_2-receptor antagonist (±)-(E)-1-[2-hydroxy-2-(4-hydroxyphenyl)ethyl]-3'-[2-[[[5-(methylamino)methyl-2-furyl]methyl]thio]ethyl]-2''-(methylsulfonyl)guanidine on acute gastric mucosal injury in rats and its free-radical scavenging activities*. Arzneim-Forsch Drug Res 1997, 47(7): 845.

Nakamura, S. et al. *Mutagenicity studies of osutidine (T-593), a novel antiulcer agent*. Pharmacometrics 1998, 55(5): 279.

Ogihara, T. et al. *Effect of a novel H_2 blocker osutidine on human gastric mucosal hemodynamic change induced by ethanol*. Digestion 1998, 59(Suppl. 3): Abst FoNO2133.

Shibata, H. et al. *Synthesis and antiulcer activity of N-2-(2-hydroxy-2-phenyl)ethyl-N''-(methanesulfonyl)guanidine analogue of ranitidine. Development of a new antiulcer agent T-593*. Yakugaku Zasshi 1998, 118(3): 88.

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Enzon; Natl. Cancer Inst. (US); Rhône-Poulenc Rorer; Medac

Enzon and Rhône-Poulenc Rorer have expanded their licensing agreement, giving RPR rights to sell Enzon's Oncaspar® (pegaspargase) in the Pacific Rim. Rhône-Poulenc Rorer currently sells the drug in the U.S. and Canada and holds exclusive rights for Mexico. Oncaspar® is approved in West Germany and Russia and will be registered and marketed throughout Europe under an agreement with Medac. Enzon has also granted a license to Tzamal Pharma to market the product in Israel and is pursuing agreements with other companies for the remaining unlicensed territories, primarily South America (1).

1. *Rhône-Poulenc Rorer expands licensing agreement with Enzon for Oncaspar*. Daily Essentials May 18, 1998.

Original monograph - Drugs Fut 1994, 19: 838.

Additional References

Douer, D. et al. *PEG L-asparaginase (PEG-ASP): Pharmacokinetics (PK) and clinical response in newly diagnosed*

adults with acute lymphoblastic leukemia (ALL) treated with multiagent chemotherapy. Blood 1997, 90(10, Suppl. 1, Part 1): Abst 1490.

Frankel, S.R. et al. *Toxicity and pharmacokinetics of PEG-asparaginase (PEG-asn) in newly diagnosed adult acute lymphoblastic leukemia (ALL): CALGB 9511*. Blood 1997, 90(10, Suppl. 1, Part 1): Abst 1491.

Graham, M.L. et al. *Toxicity, pharmacology and feasibility of administration of PEG-L-asparaginase as consolidation therapy in patients undergoing bone marrow transplantation for acute lymphoblastic leukemia*. Bone Marrow Transplant 1998, 21(9): 879.

Homans, A. et al. *Comparison of polyethylene glycol conjugated (PEG) L-asparaginase (ASP) with native E. coli ASP for induction therapy of relapsed childhood acute lymphoblastic leukemia (ALL): A pediatric oncology group study*. Proc Amer Soc Clin Oncol 1998, Abst 851.

Malogolowkin, M. et al. *Successful CSF asparaginase (Asn) depletion following administration of PEG-asparaginase (PEG-ASNase) in children with acute lymphoblastic leukemia (ALL) and isolated CNS relapse*. Proc Amer Soc Clin Oncol 1998, Abst 2035.

Poddubnaja, I. et al. *The role of L-asparaginase-containing regimen in the treatment of relapsed and primary refractory non-Hodgkin's lymphoma*. 8th Int Cong Anti-Cancer Treat (Feb 3-6, Paris) 1998, Abst P 169 bis.

Silverman, L.B. et al. *PEG-asparaginase is less toxic than E. coli L-asparaginase in children with acute lymphoblastic leukemia (ALL): Results from the Dana-Farber Cancer Institute ALL Consortium*. Proc Amer Soc Clin Oncol 1998, Abst 2034.

Oncaspar approved in Canada. Daily Essentials Dec 5, 1997.

Pegylated Recombinant Megakaryocyte Growth and Development Factor

PEG-rHuMGDF *Hematopoietic*
MGDF™

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Amgen; Kirin Breweries

Results from studies in mice have shown that PEG-rHuMGDF was effective in improving thrombocytopenia and anemia induced by chemotherapeutic agents or by combined radiotherapy and carboplatin (1).

Results of studies in mice indicated that PEG-rmMGDF (100 μg/kg i.v.) administered as a single dose was more effective than daily dosing for 5 days in stimulating platelet production, suggesting that daily administration of the cytokine may not be necessary in future clinical trials (2).

Administration of PEG-rHuMGDF (300 μg/kg s.c.) in rhesus monkeys following myeloablation and autologous bone marrow transplantation significantly improved the duration of thrombocytopenia and shortened the time to recovery to baseline levels, without improving platelet nadir. The duration of neutropenia was also significantly shortened and the absolute neutrophil count was improved (3).

Pharmacokinetic and pharmacodynamic modeling of PEG-rHuMGDF in normal and myeloablated rhesus monkeys yielded estimated EC_{50} values of 0.4-0.5 ng/ml and a platelet life span of 7 days. In patients with advanced solid tumors, the EC_{50} was estimated to be 1.7 ng/ml, with a platelet life span of 9 days (4).

The effects of PEG-rHuMGDF on megakaryopoiesis were evaluated in bone marrow of normal subjects and patients with myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). In bone marrow from normal patients, the addition of PEG-rHuMGDF (10 ng/ml) resulted in a 3-fold increase in megakaryocyte colony growth and an 8- to 10-fold increase in $CD61^+$ cells. The results indicate that PEG-rHuMGDF may be useful in the treatment of thrombocytopenia in patients with AML and MDS by enhancing megakaryocyte proliferation (5).

The safety and efficacy of PEG-rHuMGDF were evaluated in a randomized, placebo-controlled, double-blind study in 8 patients with acute myeloid leukemia receiving induction and consolidation chemotherapy. Patients treated with 5 μg/kg/day demonstrated significantly higher peak values in progenitor cell mobilization compared to placebo-treated patients. Median increases of progenitor cell numbers in patients receiving chemotherapy or chemotherapy in combination with PEG-rHuMGDF were 2- to 45-fold higher than in normal individuals with steady-state hematopoiesis. A 15-fold increment in megakaryocyte proliferation was also observed following concomitant administration of PEG-rHuMGDF with chemotherapy. Thus, PEG-rHuMGDF may facilitate the harvest of progenitor cells by leukapheresis in patients with acute myeloid leukemia (6).

The effects of PEG-rHuMGDF after dose-intensive multiple cycles of chemotherapy were evaluated in 22 patients with advanced cancers. Patients were administered PEG-rHuMGDF (1 μg/kg s.c. for 1, 3 or 7 days) starting14 days prior to chemotherapy with carboplatin (600 mg/m^2) and cyclophosphamide (1200 mg/m^2). After the first cycle, patients were administered filgrastim alone, and after the second and subsequent cycles they received filgrastim plus PEG-rHuMGDF (5 μg/kg s.c.). The results showed that PEG-rHuMGDF was effective in reducing thrombocytopenia and was well tolerated in all schedules, with no patients developing inhibitory antibodies (7).

A randomized, double-blind, placebo-controlled, dose-finding trial evaluating the efficacy and safety of PEG-rHuMGDF (2.5 and 5 μg/kg/day) was conducted in 18 patients with non-Hodgkin's lymphoma. Every 14 days patients received chemotherapy consisting of ifosfamide, carboplatin and etoposide. Administration of PEG-rHuMGDF following chemotherapy resulted in improved platelet recovery and enabled chemotherapy to be administered as planned on a 14-day schedule (8).

Administration of PEG-rHuMGDF at doses of 1, 3, 10 and 30 μg/kg/day prior to high-dose chemotherapy in 53 patients with breast cancer significantly improved platelet counts on the day of transplant, without having any effects on platelet recovery or platelet transfusion requirements (9).

1. Akabori, H., Shibuya, K., Kobayashi, M., Ida, M., Katon, N., Miyazaki, H. *Effect of PEG-rHuMGDF in a mouse model of thrombocytopenia induced by administration of agents for cancer chemotherapy*. Jpn J Chemother 1998, 46(Suppl. A): Abst 71.

2. Daw, N.C., Arnold, J.T., Abushullaih, B.A., Stenberg, P.E., White, M.M., Jayawardene, D., Srivastava, D.K., Jackson, C.W. *A single intravenous dose of murine megakaryocyte growth and development factor potently stimulates platelet production, challenging the necessity for daily administration*. Blood 1998, 91(2): 466.

3. Farese, A.M., MacVittie, T.J., Lind, L.B., Stead, R.B. *Hematopoietic recovery following autologous bone marrow transplantation: Effect of an abbreviated, high dosage administration schedule of PEG-rHuMGDF*. Blood 1997, 90(10, Suppl. 1, Part 1): Abst 411.

4. Roskos, L., Stead, R., Harker, L. et al. *A cytokinetic model of platelet (PLT) production and destruction following administration of PEG-rHuMGDF*. Blood 1997, 90(10, Suppl. 1, Part 1): Abst 755.

5. Adams, J.A., Yin, J.A.L., Brereton, M.L., Briggs, M., Burgess, R., Hyde, K. *The in vitro effect of pegylated recombinant human megakaryocyte growth and development factor (PEG rHuMGDF) on megakaryopoiesis in normal subjects and patients with myelodysplasia and acute myeloid leukaemia*. Br J Haematol 1997, 99(1): 139.

6. Geissler, K., Kabrna, E., Stengg, S., Schwarzinger, I., Knöbl, P., Valent, P., Eichinger, S., Barge, A., Lechner, K. *Recombinant human megakaroycyte growth and development factor augments mobilization of hematopoietic progenitor cells post chemotherapy in patients with acute myeloid leukemia*. Blood 1997, 90(10, Suppl. 1, Part 1): Abst 431.

7. Szer, J., Basser, R., Underhill, C. et al. *Reduction of thrombocytopenia (TCP) after multicycle, intensive chemotherapy by megakaryocyte growth and development factor (PEG-rHuMGDF)*. Proc Amer Soc Clin Oncol 1998, Abst 294.

8. Moskowitz, C., Nimer, S., Gabrielove, J., Gencarelli, A., Tomita, D., Petrarca, M., Allen, C., O'Byrne, J., Zelenetzi, A. *A randomized, double-blind, placebo-controlled, dose finding, efficacy and safety study of PEG-rHuMGDF (M) in non-Hodgkin's lymphoma (NHL) patients (pts) treated with ICE (ifosfamide, carboplatin and etoposide)*. Proc Amer Soc Clin Oncol 1998, Abst 295.

9. Glaspy, J., Vredenburgh, J., Demetri, G.D. et al. *Effects of PEGylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) before high dose chemotherapy (HDC) with peripheral blood progenitor cell (PBPC) support*. Blood 1997, 90(10, Suppl. 1, Part 1): Abst 2582.

Original monograph - Drugs Fut 1997, 22: 987.

Additional References

Bolwell, B. et al. *Safety and biological effect of pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) in breast cancer patients following autologous peripheral blood progenitor cell transplantation (PBPC)*. Blood 1997, 90(10, Suppl. 1, Part 1): Abst 756.

Crawford, J. et al. *A randomized, placebo-controlled, blinded, dose scheduling trial of pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) with filgrastim support in non-small cell lung cancer (NSCLC) patients treated with paclitaxel and carboplatin during multiple cycles of chemotherapy*. Proc Amer Soc Clin Oncol 1998, Abst 285.

Harker, L.A. et al. *Treatment of thrombocytopenia in chimpanzees infected with human immunodeficiency virus by pegylated recombinant human megakaryocyte growth and development factor*. Blood 1997, 90(10, Suppl. 1, Part 1): Abst 754.

Kubota, Y. et al. *Response of platelets from patients with myeloproliferative disorders of thrombopoietin*. 56th Annu Meet Jpn Soc Cancer Res (Sept 25-27, Kyoto) 1997, Abst WAP-030.

Kuter, D. et al. *Treatment of platelet (PLT) donors with pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) increases circulating PLT counts (CTS) and PLT apheresis yields and increases platelet increments in recipients of PLT transfusions*. Blood 1997, 90(10, Suppl. 1, Part 1): Abst 2579.

McCullough, J. et al. *Donors' willingness to participate in a trial of pegylated megakaryocyte growth and development factor (PEG-rHuMGDF) for platelet apheresis*. Blood 1997, 90(10, Suppl. 1, Part 2): Abst 3318.

Nichol, J.L. et al. *Multicycle single-day dosing of normal BALB-C mice with PEG-rHuMGDF or PEG-rMuMGDF, implication in the platelet donor setting*. Blood 1997, 90(10, Suppl. 1, Part 2): Abst 3322.

Shibuya, K. et al. *PEGylated recombinat human megakaryocyte growth and development factor suppresses the development of megakaryoblastic leukemia in mice*. Blood 1997, 90(10, Suppl. 1, Part 1): Abst 757.

Shibuya, K. et al. *The effect of a single injection of PEG-rHuMGDF on hematopoietic recovery after irradiation in mice*. Int J Hematol 1997, 65(Suppl. 1): Abst 577.

Snyder, E.L. et al. *In vitro effect of PEG-rHu megakaryocyte growth and development factor (MGDF) on the platelet storage lesion*. Blood 1997, 90(10, Suppl. 1, Part 2): Abst 3536.

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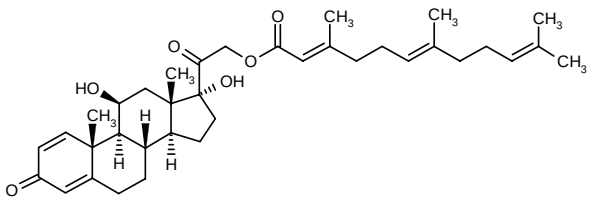


$C_{36}H_{50}O_6$

Taiho; Kuraray; Dainippon

Prednisolone farnesylate has been approved for marketing in Japan, where it is indicated for the topical treatment of pain caused by rheumatoid arthritis. The compound was codeveloped by Kuraray and Taiho, and will be marketed by Dainippon under the trade name Farnerate Gel in 25- and 50-g tubes containing 14 mg prednisolone farnesylate/g (1).

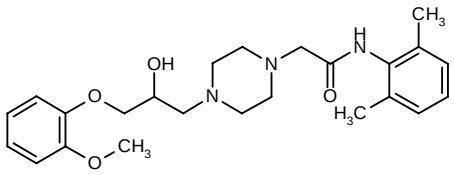
1. *Topical antiinflammatory corticosteroid approved for marketing in Japan*. Daily Essentials June 17, 1998.

Original monograph - Drugs Fut 1993, 18: 805.

Ranolazine

Antianginal

EN: 101796



$C_{24}H_{33}N_3O_4$ **Roche Bioscience; Kissei; CV Therapeutics**

In studies in isolated rat heart, ranolazine (10 or 20 μM) significantly attenuated hydrogen peroxide-induced reductions in left ventricular developed pressure and ATP tissue levels, as well as the increments in left ventricular end-diastolic pressure, but did not modify the increased tissue levels of malondialdehyde. In contrast, dichloroacetate had no effect on these parameters. These results suggest that the protective properties of ranolazine against hydrogen-peroxide induced mechanical and metabolic derangements are not mediated via energy-sparing or antioxidant mechanisms (1).

Administration of ranolazine (32.7 mg i.v. bolus followed by continuous infusion) to male patients with coronary artery disease relieved angina pectoris in 2/9 patients, but had no effect on pacing time to pain in the remaining 7 patients. Coronary sinus blood flow, cardiac oxygen consumption, blood pressure and heart rate were not affected by drug treatment. Reductions in cardiac uptake of free fatty acids and net uptakes of glucose and lactate were also observed in ranolazine-treated patients. Minimal clinical effects were observed in this particular study group (2).

CV Therapeutics has initiated a phase III trial of ranolazine for the treatment of angina (3).

1. Matsumura, H., Hara, A., Hashizume, H., Maruyama, K., Abiko, Y. *Protective effects of ranolazine, a novel anti-ischemic drug, on the hydrogen peroxide-induced derangements in isolated, perfused rat heart: Comparison with dichloroacetate*. Jpn J Pharmacol 1998, 77(1): 31.

2. Bagger, J.P., Botker, H.E., Thomassen, A., Nielsen, T.T. *Effects of ranolazine on ischemic threshold, coronary sinus blood flow, and myocardial metabolism in coronary artery disease*. Cardiovasc Drugs Ther 1997, 11(3): 479.

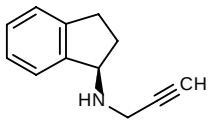
3. *CV Therapeutics moves ranolazine to phase III*. Daily Essentials Oct 13, 1997.

Original monograph - Drugs Fut 1988, 13: 837.

Rasagiline

Antiparkinsonian
MAO-B Inhibitor

EN: 174550



$C_{12}H_{13}N$ **Teva; Lemmon**

Rasagiline mesilate was evaluated *in vitro* as a potential neuroprotective agent for the treatment of Parkinson's disease. Survival of rat E14 mesencephalic dopaminergic neurons primed with serum increased after exposure to 1-10 μM rasagiline or deprenyl. When evaluated under serum-free conditions, only rasagiline preserved its neuroprotective effect on dopaminergic neurons. Rasagiline also increased total survival of MAP2-positive neurons, an effect not observed with deprenyl. Neither compound had any effect on GABAergic neurons. In comparison, the monoamine oxidase A inhibitor clorgyline did not produce any of the effects observed with rasagiline (1).

The efficacy and selectivity of action of TV-1012 (0.1-10 mg/kg for 7 days s.c.) was examined in the brain of the common marmoset. Monoamine oxidase (MAO)-B activity was irreversibly inhibited 80% in the prefrontal and occipital cortex, cerebellum, caudate nucleus, putamen, and nucleus accumbens of animals treated with 0.1 mg/kg. Although MAO-A activity was not inhibited in the putamen and nucleus accumbens at this dose, treatment with 0.5 mg/kg resulted in significant MAO-A and complete MAO-B suppression (2).

1. Finberg, J.P.M., Takeshima, T., Johnston, J.M., Commissiong, J.W. *Increased survival of dopaminergic neurons by rasagiline, a monoamine oxidase B inhibitor*. NeuroReport 1998, 9(4): 703.

2. Gotz, M.E., Breithaupt, W., Sautter, J., Kupsch, A., Schwarz, J., Oerte, W.H., Youdim, M.B.H., Riederer, P., Gerlach, M. *Chronic TVP-1012 (rasagiline) dose - Activity response of monoamine oxidases A and B in the brain of the common marmoset*. J Neural Transm Suppl 1998, 271.

Original monograph - Drugs Fut 1996, 21: 903.

Additional Reference

Speiser, Z., Katzir, O., Rehavi, M., Zabarski, T., Cohen, S. *Sparing by rasagiline (TVP-1012) of cholinergic functions and behavior in the postnatal anoxia rat*. Pharmacol Biochem Behav 1998, 60(2): 387.

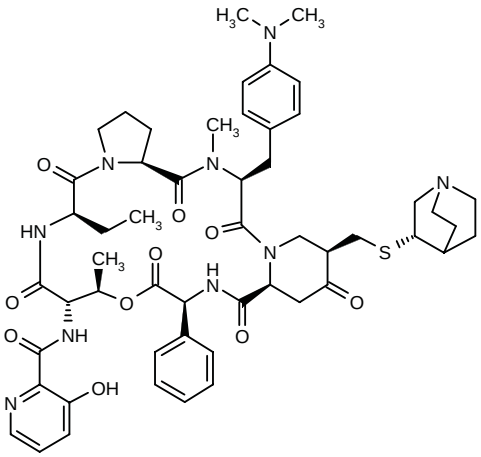
RP-59500
Synercid®

Streptogramin

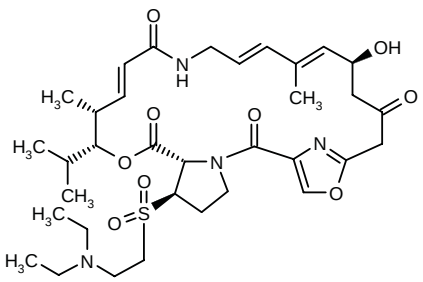
EN: 166760

Defined mixture of pure and synergistic quinupristin and daldopristin in a ratio 30/70 in %, w:w.

Quinupristin
EN: 138965



Dalfopristin
EN: 166761



Rhône-Poulenc Rorer

Rhône-Poulenc Rorer has filed an NDA with the FDA for Synercid® for the treatment of a variety of infections, including pneumonia, bacteremia and skin infections caused by Gram-positive bacteria (1).

Rhône-Poulenc Rorer has submitted a Marketing Authorization Application for Synercid® in the U.K. for the treatment of a variety of infections, including pneumonia, bacteremia and skin infections caused by Gram-positive bacteria (2).

1. *RPR submits NDA for novel antibiotic*. Daily Essentials Sept 9, 1997.

2. *RPR seeks U.K. approval for Synercid*. Daily Essentials Oct 1, 1997.

Original monograph - Drugs Fut 1993, 18: 833.

Additional References

Aeschlimann, J.R. et al. *Pharmacodynamic analysis of quinupristin/dalfopristin (Q/D, Synercid) versus vancomycin-resistant Enterococcus faecium (VREF) with differing MBCs using time kill curve (KC) and post-antibiotic effect (PAE) methods*. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst E-136.

Andrews, J. et al. *Study to determine the effect of various media and carbon dioxide on the in vitro activity of Synercid*. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst E-39.

Beal, J., Lefebvre, D. *Randomized, comparative, multicenter, open study of quinupristin/dalfopristin (Q/D, Synercid®) versus standard therapy (cefazolin or vancomycin) in the treatment of complicated Gram-positive skin and skin structure infections (C-SSSI)*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 3.31.

Bergeron, M.G. et al. *A phase I, open-label, single-dose study of blood and blister fluid pharmacokinetics of quinupristin/dalfopristin (Q/D, RP59500, Synercid)*. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst A-117.

Bompart, F. et al. *Overview of the safety and tolerability of quinupristin/dalfopristin (Synercid®) in the global development program*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 3.28.

Bozdogan, B. et al. *Intrinsic and acquired resistance to dalfopristin (streptogramin A) in Enterococcus spp.*. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst C-79.

Brown, S.D. et al. *Ten lab survey of quinupristin/dalfopristin (Q/D) and Rp106,972 against recent clinical bacterial isolates*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 2.06.

Caron, F. et al. *Influence of erythromycin resistance, inoculum growth phase, and incubation time on assessment of the bactericidal activity of RP 59500 (quinupristin-dalfopristin) against vancomycin-resistant Enterococcus faecium*. Antimicrob Agents Chemother 1997, 41(12): 2749.

De Azavedo, J.C. et al. *In vitro activity of new drugs against multi-drug resistant streptococci of the viridans group collected from across Canada*. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst E-54.

Dever, L.L. et al. *Bactericidal activity of quinupristin/dalfopristin (RP 59500) against Streptococcus pneumoniae in the rabbit model of meningitis*. 35th Annu Meet Infect Dis Soc Amer (Sept 13-16, San Francisco) 1997, Abst 267.

Dowzicky, M. et al. *In vitro activity of quinupristin/dalfopristin (Q/D) against worldwide clinical trial and other laboratory isolates*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 3.03.

Dowzicky, M. et al. *Correlation of clinical data with MICs of selected targeted pathogens from worldwide quinupristin/dalfopristin (Q/D) clinical trials*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 2.13.

Elsner, H.-A. et al. *In vitro susceptibilities of enterococcal blood culture isolates against erythromycin and quinupristin/dalfopristin*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 2.04.

Frank, U. et al. *Susceptibility of Staphylococcus aureus and Staphylococcus epidermidis growing on fibronectin-coated catheter surfaces to RP 59500*. 97th Gen Meet Amer Soc Microbiol (May 4-8, Miami Beach) 1997, Abst A-40.

Fuchs, P. et al. *Provisional quality control parameters and interpretive criteria for testing susceptibility of Streptococcus pneumoniae and Haemophilus influenzae to quinupristin/dalfopristin (RP59500)*. Eur J Clin Microbiol Infect Dis 1998, 17(3): 197.

Gazagne, L. et al. *In vitro activity of streptogramins against 45 methicillin resistant Staphylococcus aureus with decreased susceptibility to dalfopristin*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 3.23.

Grossi, P. et al. *Quinupristin/dalfopristin (Q/D) for treatment of severe multidrug resistant Staphylococcus infection*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 3.29.

Hara, T. et al. *A lipoprotein lipase activator, NO-1886, improves endothelium-dependent relaxation of rat aorta associated with aging*. Eur J Pharmacol 1998, 350(1): 75.

Hoban, D. et al. *Activity of quinupristin/dalfopristin (Q/D) against Enterococcus spp. isolated from stools of hospitalized patients in Canada*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 2.05.

Johnson, A.P. et al. *In-vitro activity of quinupristin/dalfopristin (Synercid) against isolates of Streptococcus pneumoniae, Staphylococcus aureus and Enterococcus spp.*. J Antimicrob Chemother, 1997, 40(4): 604 (Letters to the Editor).

Johnson, C.A., Taylor, C.A., Zimmerman, S.W., Chevalier, P., Pasquier, O., Baybutt, R.I. *Pharmacokinetics of quinupristin/dalfopristin (Synercid® RP 59500) in patients receiving continuous ambulatory peritoneal dialysis (CAPD)*. J Am Soc Nephrol 1997, Abst A1217.

Jones, R.N. et al. *Streptogramin combination (quinupristin/dalfopristin) activity and spectrum from a 1997 study in over 200 medical centers: Analysis for regional variations, co-resistances and validity of proposed susceptible breakpoints*. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst E-134.

Jones, R.N. et al. *Antimicrobial activity of quinupristin-dalfopristin (RP 59500, Synercid®) tested against over 28,000 recent clinical isolates from 200 medical centers in the United States and Canada*. Diagn Microbiol Infect Dis 1998, 31(3): 437.

Jones, R.N. et al. *Preliminary results from the Synercid (quinupristin/dalfopristin) microbiological assessment of resistance trends study - Multicenter analysis of nearly 4,000 clinical strains*. 97th Gen Meet Amer Soc Microbiol (May 4-8, Miami Beach) 1997, Abst A-141.

Kaku, M. et al. *In vitro activity of streptogramin (RP 59500 and RP 106972) and other 5 antimicrobial agents against Mycoplasma pneumoniae*. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-50.

Kenny, G.E., Cartwright, F.D. *Susceptibilites of human mycoplasmas to streptogramins: Dalfopristin (RP-54476) and Synercid (RP-59500)*. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst E-160.

Larkin, J. et al. *Staphylococcus epidermidis endocarditis treated with RP59500*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 3.32.

Linden, P. et al. *Liver histopathology in liver transplant recipients with hyperbilirubinemia during quinupristin/dalfopristin therapy*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 2.17.

Linden, P.K., Moellering, R.C. *Efficacy and safety of quinupristin/dalfopristin (RP59500, Synercid®) for the treatment of vancomycin-resistant Enterococcus faecium (VREF) infections in an ongoing emergency use program*. 8th Int Cong Infect Dis (May 15-18, Boston) 1998, Abst 59.017.

Linden, P.K. et al. *Effect of quinupristin/dalfopristin on FK-506 (tacrolimus) blood levels in liver transplant recipients*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 2.16.

Low, D.E. et al. *The effect of changes in media, length of incubation and incubation environment on the determination of quinupristin/dalfopristin minimum inhibitory concentrations (MIC)*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 3.01.

Moellering, R.C. Jr., Linden, P.K. *Efficacy and safety of quinupristin/dalfopristin (Synercid®) in the treatment of vancomycin-resistant Enterococcus faecium (VREF) infections*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 2.14.

Nadler, H. et al. *Low rates of emerging resistance and superinfection in Synercid (quinupristin/dalfopristin; Q/D) treated patients during worldwide clinical program*. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst E-136b.

Nakashio, S. et al. *Comparative antimicrobial activity of RP 59500 (quinupristin-dalfopristin), the first semisynthetic injectable streptogramin, against Gram-positive cocci and other recent clinical pathogens*. Jpn J Antibiot 1997, 50(10): 38.

Pankuch, G. et al. *Postantibiotic effect (PAE) and postantibiotic subMIC effect (P-SME) of RP 59500*. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst A-84b.

Piper, J. et al. *Quinupristin/dalfopristin (Syncercid) resistant vancomycin resistant Enterococcus faecium (SRVRE)*. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst C-80.

Raad, I. *Dose-ranging, randomized, multicenter, open phase II study of quinupristin/dalfopristin (Q/D, Synercid®) versus vancomycin in the treatment of catheter-related, Gram-positive bacteremia (CRGPB)*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 3.30.

Ridgway, G.L. et al. *The in vitro activity of quinupristin/dalfopristin (Synercid®), RPR 106972, erythromycin and doxycycline against isolates of Chlamydia trachomatis, Chlamydia pneumoniae, Mycoplasma pneumoniae, Mycoplasma hominis and Ureaplasma urealyticum*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 8.02.

Ridgway, G.L. et al. *The in vitro activity of Synercid (RP 59500) and RP 106972 against Chlamydia spp. Mycoplasma spp and*

Ureaplasma urealyticum. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst E-158.

Sambatakou, H. et al. *In-vitro activity and killing effect of quinupristin/dalfopristin (RP59500) on nosocomial Staphylococcus aureus and interactions with rifampicin and ciprofloxacin against methicillin-resistant isolates*. J Antimicrob Chemother 1998, 41(3): 349.

Schouten, M.A., Hoogkamp-Korstanje, J.A.A. *Comparative in-vitro activities of quinupristin-dalfopristin against Gram-positive bloodstream isolates*. J Antimicrob Chemother 1997, 40(2): 213.

Schülin, T. et al. *Susceptibilities of Legionella spp. to newer antimicrobials in vitro*. Antimicrob Agents Chemother 1998, 42(6): 1520.

Schwalbe, R.S., Qaiyumi, S. *Increased resistance of Enterococcus faecium veterinary isolates to quinupristin/dalfopristin*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 2.11.

Stout, J.E. et al. *Activity of azithromycin, clarithromycin, roxithromycin, dirithromycin, quinupristin/dalfopristin and erythromycin against Legionella species by intracellular susceptibility testing in HL-60 cells*. J Antimicrob Chemother 1998, 41(2): 289.

Stuertz, K. et al. *Differential release of lipoteichoic and teichoic acids from Streptococcus pneumoniae as a result of exposure to β-lactam antibiotics, rifamycins, trovafloxacin, and quinupristin-dalfopristin*. Antimicrob Agents Chemother 1998, 42(2): 277.

Talbot, G.H. et al. *Efficacy of quinupristin/dalfopristin (Synercid®) in the treatment of patients with positive blood cultures in global phase III studies*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 2.15.

Torres, A., Fagon, J.Y. *Randomized, comparative, multicenter, open study of quinupristin/dalfopristin (Q/D, Synercid®) plus aztreonam versus vancomycin plus aztreonam in the treatment of Gram-positive nosocomial pneumonia (NP)*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 10.24.

Trostdorf, F. et al. *RP 59500 for experimental pneumococcal meningitis*. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst B-78.

Von Eiff, C. et al. *In vitro-activity of quinupristin/dalfopristin (Q/D) in comparison to other antibiotics against staphylococci from patients with bacteremia - First results of a German multicenter study*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 3.24.

Vouillamoz, J. et al. *Synercid (Syn) alone or combined to cefamandole (Cef) in the treatment (Rx) of experimental endocarditis (EE) due to methicillin-resistant Staphylococcus aureus (MRSA) constitutively resistant to erythromycin (Ery-R)*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 3.27.

Werner, G. et al. *Resistance to quinupristin-dalfopristin in Enterococcus faecium - The link to animal husbandry*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 2.12.

Willey, B.M., Low, D.E. *Simple approach to the correct species identification of Enterococcus faecium and E. faecalis for epidemiological and quinupristin/dalfopristin treatment purposes*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 2.01.

Witte, W. et al. *Susceptibility to quinupristin-dalfopristin in MRSA from nationwide surveillance in Germany*. 4th Int Conf Macrolides Azalides Streptogramins Ketolides (Jan 21-23, Barcelona) 1998, Abst 3.21.

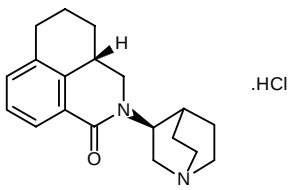
Zaoutis, T. et al. *In vitro activity of quinupristin/dalfopristin (RP 59500) against vancomycin tolerant isolates of group C,G and F streptococci obtained from sterile clinical sites*. 35th Annu Meet Infect Dis Soc Amer (Sept 13-16, San Francisco) 1997, Abst 724.

Advisory panel recommends approval of Synercid. Daily Essentials Feb 20, 1998.

Synercid scheduled for FDA committee review next week. Daily Essentials Feb 12, 1998.

RS-25259-197 *5-HT$_3$ Receptor Antagonist*
Palonosetron Hydrochloride *Antiemetic*

EN: 223772



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

The antiemetic properties of RS-25259 (0.1, 0.3, 1.0, 3.0 or 30 μg/kg i.v.) were evaluated in 218 healthy women after abdominal or vaginal hysterectomy. Only the 30 μg dose significantly decreased the incidence of postoperative vomiting and the requirement for rescue medication, prolonged the time to the first emetic episode, and significantly reduced the frequency of treatment failures (1).

Palonosetron hydrochloride is the new proposed international nonproprietary name for RS-25259-197 (2).

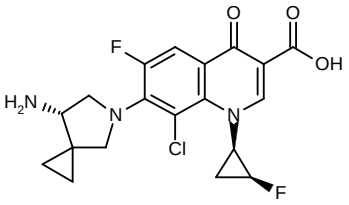
1. Tang, J., Angelo, R.D., White, P.F., Scuderi, P.E. *Efficacy of RS-25259, a novel 5-HT$_3$ antagonist, in the prevention of postoperative nausea and vomiting after major gynecologic surgery*. Anesthesiology 1997, 87(3A, Suppl.): Abst A329.

2. *Proposed international nonproprietary names (Prop. INN): List 77*. WHO Drug Inf 1997, 11(2): 107.

Original monograph - Drugs Fut 1996, 21: 906.

Sitafloxacin *Fluoroquinolone Antibacterial*
DU-6859

EN: 176447



$C_{19}H_{18}ClF_2N_3O_3$ **Daiichi Pharm.**

The postantibiotic effect of DU-6859a on methicilin-resistant *S. aureus* with an MIC of 0.03-1 μg/ml was < 1 h when evaluated at concentrations of 1 times the MIC. At 4 times the MIC, however, the drug exhibited a postantibiotic effect of > 5 h (1).

MIC values for DU-6859a in 18 *Klebsiella pneumoniae* and 21 *Enterobacter cloacae* isolates with mutated GyrA or mutated GyrA and ParC were ≤ 0.025-6.25 μg/ml and 0.1-3.13 μg/ml, respectively, demonstrating a 16- to 256-fold greater MIC_{90} activity than other fluoroquinolones currently in clinical use (2).

In a new model of rat uterine endometritis, caused by infection with mixed inocula of *Escherichia coli* and *Bacteroides fragilis*, DU-6859a had MICs of 0.025 mg/l and 0.20 mg/l against *E. coli* and *B. fragilis*. Viable cell counts of the two bacteria were significantly lower in druth-treated rats, as compared to those from untreated rats (3).

1. Grecka, P., Sambatakou, H., Giamarellos-Bourboulis, E.J., Chryssouli, Z., Giamarellou, H. *Post-antibiotic effect (PAE) of DU-6859a (DU) and trovafloxacin (TR) on methicillin-resistant Staphylococcus aureus (MRSA)*. 37th Interscі Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst A-81.

2. Deguchi, T., Yasuda, M., Kawamura, T., Nakano, M., Ozeki, S., Kanematsu, E., Nishino, Y., Kawada, Y. *Improved antimicrobial activity of DU-6859a, a new fluoroquinolone, against quinolone-resistant Klebsiella pneumoniae and Enterobacter cloacae isolates with alterations in GyrA and ParC proteins*. Antimicrob Agents Chemother 1997, 41(11): 2544.

3. Mikamo, H., Kawazoe, K., Sato, Y., Izumi, K., Tamaya, T. *Therapeutic effects of a new quinolone, DU-6859a, on polymicrobial infections in a newly designed model of rat uterine endometritis*. J Antimicrob Chemother 1998, 41(1): 131.

Original monograph - Drugs Fut 1994, 19: 827

Additional References

Doi, N. et al. *Therapeutic efficacy of three quinolone derivatives against murine tuberculosis*. Rev Esp Quimioter 1997, 10(Suppl. 2): 103.

Gerardo, S.H. et al. *Comparative in vitro activity of DU-6859a, levofloxacin, ofloxacin, sparfloxacin, and ciprofloxacin against 375 aerobic and anaerobic bite wound isolates*. 97th Gen Meet Amer Soc Microbiol (May 4-8, Miami Beach) 1997, Abst A-137.

Giamarellos-Bourboulis, E.J. et al. *In vitro bactericidal activity of trovafloxacin (TR) and DU-6859A (DU) and interactions with rifampin (RIF) on methicillin-resistant Staphylococcus aureus (MRSA)*. 8th Int Cong Infect Dis (May 15-18, Boston) 1998, Abst 12.028.

Kawazoe, K. et al. *Therapeutic effects of injectable new quinolone DU-6859a against polymicrobial infections in the uterine endometritis model*. 37th Interscі Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst B-89.

Nakano, M. et al. *Study of the antibiotic activity of DU-6859a against quinolone-resistant clinical isolates from complicated urinary tract infections*. Jpn J Chemother 1997, 45(Suppl. B): Abst 60.

Niki, Y. et al. *Effects of DU-6859a, a new quinolone antimicrobial, on theophylline metabolism in in vitro and in vivo studies*. Antimicrob Agents Chemother 1998, 42(7): 1751.

Ohara, A. et al. *Therapeutic effect of DU-6859a on hydroxyapatite concentration in a rat model of Bacteroides fragilis-induced osteomyelitis*. Jpn J Chemother 1997, 45(Suppl. A): Abst 31.

Park, C. et al. *The antimycobacterial activity of Du6859a and SynPhar 1193 against Mycobacterium avium complex (MAC)*. 37th Interscі Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-172.

Saito, H. et al. *In vitro and in vivo activities of various new quinolones against Mycobacterium leprae*. 37th Interscі Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst E-161.

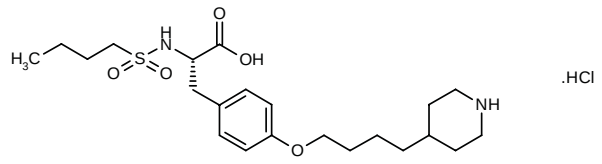
Satoh, K. et al. *An efficient synthesis of a key intermediate of DU-6859a via asymmetric microbial reduction*. Chem Pharm Bull 1998, 46(4): 587.

Taba, H. et al. *In vitro antimicrobial activities of new fluoroquinolones against clinical isolates of Streptococcus pneumoniae*. 37th Interscі Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst E-60.

Thomson, K.S., Sanders, C.C. *The effects of increasing levels of quinolone resistance on in-vitro activity of four quinolones*. J Antimicrob Chemother 1998, 42(2): 179.

Tirofiban Hydrochloride *Platelet Antiaggregatory*
Aggrastat® *gpIIb/IIIa Receptor Antagonist*

EN: 183737



$C_{22}H_{36}N_2O_5S.HCl$ **Merck & Co.**

Tirofiban (10-300 nmol/l) added to platelet-rich plasma collected from healthy volunteers blocked platelet aggregation (EC_{50} = 75-150 nmol/l) stimulated by the mouse monoclonal antibody, P256, which recognizes an epitope on the IIb component of the IIb/IIIa complex of human platelets (1).

Tirofiban (10 μg/kg i.v. bolus over 3 min followed by a 36-h infusion of 0.15 μg/kg/min) was evaluated in a ran-

domized, double-blind, placebo-controlled study in 2139 patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty and treated with aspirin or heparin. Relative reductions in the composite endpoint on days 2, 7 and 30 following angioplasty were 38%, 27% and 16%, respectively. A 24% reduction was observed on day 30 when repeat angioplasty or coronary artery bypass surgery procedures were included in the composite. The frequency of bleeding was not statistically different between tirofiban- and placebo-treated groups. Thus, tirofiban appeared to protect against early adverse cardiac events, although the reduction in adverse cardiac events after 30 days was not statistically significant (2).

Tirofiban in combination with aspirin reduced platelet aggregation in patients with acute myocardial ischemia, whereas this effect was not observed after administration of heparin with aspirin (3).

The efficacy of tirofiban on outcome and restenosis was evaluated in patients with acute ischemic syndromes undergoing angioplasty. Tirofiban therapy resulted in a 30% risk reduction in the composite endpoint of death, myocardial infarction and repeat procedures at 7 and 30 days posttreatment (4).

A cost substudy of tirofiban conducted in 818 of the 2141 patients participating in the RESTORE trial (Randomized Efficacy of Study of Tirofiban for Outcomes and Restenosis) showed that hospital costs tended to be lower in both stented and unstented patients receiving tirofiban compared to patients not given the drug (5).

Two NDAs have been filed by Merck & Co. for tirofiban hydrochloride (Aggrastat®): for use in combination with heparin in patients with unstable angina or non-Q wave myocardial infarction to prevent cardiac ischemic events, and for patients with coronary ischemic syndromes undergoing percutaneous transluminal coronary angioplasty or atherectomy to prevent cardiac ischemic complications related to abrupt closure of the treated coronary artery (6).

Merck & Co.'s tirofiban hydrochloride (Aggrastat®) was launched in the U.S. just after its approval by the FDA on May 14, 1998. The drug, in combination with heparin, is indicated for reducing the risk of death, new heart attack or refractory ischemia/repeat cardiac procedures in patients presenting with acute coronary syndrome, *i.e.*, unstable angina or non-Q-wave myocardial infarction. It is available in single-dose vials for i.v. infusion (50 ml), each ml containing 0.281 mg of tirofiban hydrochloride monohydrate equivalent to 0.25 mg of tirofiban (7-9).

1. Fisher, I., Robinson, P., Ritter, J.M. *Dose-dependent inhibition by tirofiban of platelet aggregation in response to an antibody (P256) directed against glycoprotein IIb/IIIa receptors of human platelets*. Br J Clin Pharmacol 1998, 45(2): 196P.

2. The RESTORE Investigators. *Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty*. Circulation 1997, 96(5): 1445.

3. Mattsson, E., Martinsson, A., Nyqvist, O., Rasmanis, G., Sylven, C., Karlberg, C. *The glycoprotein IIb/IIIa platelet receptor blocker tirofiban not heparin, counteracts platelet aggregation in unstable angina pectoris*. Am J Cardiol 1997, 80(7): 938.

4. Boccuzzi, S.J., Roehm, J.B., Cook, J.R., Burnette, J.C., Culler, S., Weintraub, W.S. *Clinical, resource and cost benefits of the RESTORE study applied to US population*. J Am Coll Cardiol 1998, 31(2, Suppl. A): Abst 1027-51.

5. Culler, S., Boccuzzi, S.J., Roehm, J., Cook, J., Burnette, J., Weintraub, W.S. *The contribution of adjunctive stent use to in-patient cost with and without GPIIa/IIIb blockade in the RESTORE trial*. J Am Coll Cardiol 1998, 31(2, Suppl. A): Abst 1190-103.

6. *FDA advisory committee will discuss Aggrastat NDA later this week*. Daily Essentials April 7, 1998.

7. *FDA advisory committee recommends approval of Aggrastat*. Daily Essentials May 4, 1998.

8. *FDA approves Aggrastat, the first platelet blocker for unstable angina*. Daily Essentials May 22, 1998.

9. *First launch for Aggrastat, a new antiplatelet agent for acute coronary syndrome*. Daily Essentials May 26, 1998.

Original monograph - Drugs Fut 1995, 20: 897.

Additional References

Barr, E. et al. *Improved long-term clinical outcomes in unstable angina-patients undergoing coronary angioplasty following therapy with tirofiban and heparin*. J Am Coll Cardiol 1998, 31(2, Suppl. A): Abst 802-6.

Bednar, R.A. et al. *Identification of low molecular weight GP IIb/IIIa antagonists that bind preferentially to activated platelets*. J Pharmacol Exp Ther 1998, 285(3): 1317.

Depré, M. et al. *Mild to moderate hepatic isufficiency does not affect pharmacokinetics and pharmacodynamics of tirofiban*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 47.11.

Giugliano, R.P., Hyatt, R.R. Jr. *Thrombocytopenia with GP IIb/IIIa inhibitors: A meta-analysis*. J Am Coll Cardiol 1998, 31(2, Suppl. A): Abst 837-5.

Moliterno, D.J., Topol, E.J. *Meta-analysis of platelet GP IIb/IIIa antagonist randomized clinical trials in ischemic heart disease: Consistent, durable, salutary effects*. Circulation 1997, 96(8, Suppl.): Abst 2652.

Troglitazone *Antidiabetic*

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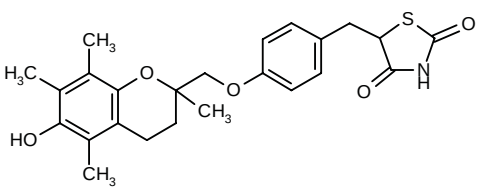

$C_{24}H_{27}NO_5S$

Sankyo; Warner-Lambert; Glaxo Wellcome

In vivo experiments in beagle dogs showed that when cholestyramine (1 g) was administered with troglitazone (200 mg), the AUC of troglitazone was reduced by 42% and the mean C_{max} was 49% of control values. In a clinical study in 12 healthy volunteers coadministered troglitazone (400 mg) and cholestyramine (12 g), the AUCs for troglitazone and its sulphate and quinone metabolites were reducted by 71, 80 and 86%, respectively. The C_{max} for the sulphate metabolite was also significantly reduced. These results indicate that cholestyramine alters the extent of absorption of troglitazone and that coadministration of the two drugs may severely reduce the antihyperglycemic activity of troglitazone (1).

The combination of troglitazone and metformin was evaluated in 29 type II diabetic patients. The study participants were randomized to treatment with either metformin or troglitazone monotherapy for 3 months, at which time the other drug was added for the following 3 months. Fasting and postprandial glucose concentrations decreased by 20% and 25%, respectively, during metformin monotherapy; the corresponding decreases on troglitazone monotherapy were also 20% and 25%. Endogenous glucose production decreased by 19% during metformin monotherapy, but was unchanged with troglitazone monotherapy. Mean glucose disposal rate increased by 54% and 13%, respectively, during troglitazone and metformin monotherapy. During the combination treatment stage of the study, fasting and postprandial plasma glucose concentrations decreased by a further 18% and 21%, respectively, and mean glycosylated hemoglobin value decreased by 1.2%. Based on the results obtained in this small group of patients, it appears that metformin and troglitazone have equal and additive beneficial effects on glycemic control in (2).

The effects of troglitazone (200 mg/day) on the resistance of LDL to oxidation were evaluated in 29 patients with NIDDM. Treatment was associated with a 23% increase in the lag phase of fluorescence development, a reduction in LDL hydroperoxide concentration and a decrease in plasma E-selectin levels. The observations indicate that troglitazone may retard the development of atherosclerosis by modifying LDL-related atherogenic events (3).

Administration of troglitazone (400 mg/day for 4 weeks) plus a sulphonylurea in a study group of 33 patients with NIDDM was associated with significant reductions in insulin concentrations both under fasting conditions and 2 h following a meal. Patients treated with troglitazone also demonstrated reduced triglyceride levels, but had no change in total and HDL cholesterol and free fatty acids. LDL cholesterol and lipoprotein(a) levels increased in troglitazone-treated patients. Troglitazone-associated increases in insulin sensitivity, as assessed by the K index of the insulin tolerance test, indicate that the drug may improve insulin resistance in patients with NIDDM (4).

The efficacy of troglitazone has been compared to placebo in 350 patients with non-insulin-dependent (type II) diabetes mellitus in whom disease was poorly controlled in spite of daily insulin treatment (at least 30 U/day). Patients were randomly assigned to treatment with 1 of 2 doses of troglitazone (200 or 600 mg/day) or placebo for 26 weeks. Doses of insulin were reduced only in order to prevent hypoglycemia. The study was completed by 90% of the 350 patients enrolled. Adjusted mean glycosylated hemoglobin values decreased by 0.8% and 1.4% in patients on 200 and 600 mg/day troglitazone, respectively, and concentrations of fasting serum glucose also decreased by 35 and 49 mg/dl, respectively. This was in spite of 11% and 29% decreases in insulin dose in the respective active treatment groups. Patients treated with placebo, in contrast, required a 1% increase in insulin doses by the end of the study period. Serum total cholesterol, LDL and HDL cholesterol increased somewhat, and serum triglyceride concentrations decreased slightly in patients administered troglitazone (5).

Evaluation of troglitazone (200 mg/day for 8 weeks) in a randomized, double-blind study in 40 patients with NIDDM indicated modest antihyperglycemic effects, with no notable changes on cardiovascular risk factors such as heart rate, serum triglycerides, and total, HDL and LDL cholesterol (6).

In a study in 135 Japanese subjects with type 2 diabetes, treatment with troglitazone (400 mg/day) for 6 months resulted in significant reductions in common carotid arterial intimal and medial complex thickness at 3 and 6 months, compared to placebo-treated patients. A reduction in HbA1c and postprandial serum triglycerides was also observed, but was not statistically related to the observed changes in physical parameters (7).

The effect of multiple doses of troglitazone (400 mg/day p.o.) on the steady-state pharmacokinetics of digoxin (0.25 mg/day p.o.) were evaluated in 12 healthy subjects. Mean C_{max}, t_{max} and AUC values for digoxin on day 10 were similar to the values obtained on day 20, as was the case for C_{min}, Cl/F, total urinary excretion and renal clearance.Thus, it appears that coadministration of troglitazone does not affect the steady-state pharmacokinetics of digoxin (8).

Troglitazone is available in the U.K. from Glaxo Wellcome/Sankyo under the tradename Romozin® for use as monotherapy in patients inadequately controlled on diet, or in combination with sulfonylureas or insulin, in the treatment of type II (non-insulin-dependent) diabetes mellitus. It is available as tablets of 200, 300 and 400 mg (9, 10).

Parke-Davis/Warner-Lambert is changing the prescribing information for the antidiabetic drug troglitazone (Rezulin®) to add new warning information regarding liver injury possibly associated with the use of the drug (11).

1. Young, M.A., Lettis, S., Eastmond, R. *Concomitant administration of cholestyramine influences the absorption of troglitazone*. Br J Clin Pharmacol 1998, 45(1): 37.

2. Inzucchi, S.E., Maggs, D.G., Spollett, G.R., Page, S.L., Rife, F.S., Walton, V., Shulman, G.I. *Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus*. New Engl J Med 1998, 338(13): 867.

3. Cominacini, L., Garbin, U., Pasini, A.F., Campagnola, M., Davoli, A., Foot, E., Sighieri, G., Sironi, A.M., Lo Cascio, V., Ferrannini, E. *Troglitazone reduces LDL oxidation and lowers plasma E-selectin concentration in NIDDM patients*. Diabetes 1998, 47(1): 130.

4. Matsumoto, K., Miyake, S., Yano, M., Ueki, Y., Tominaga, Y. *Increase of lipoprotein(a) with troglitazone*. Lancet 1997, 350(9093): 1748.

5. Schwartz, S., Raskin, P., Fonseca, V., Graveline, J.F. *Effect of troglitazone in insulin-treated patients with type II diabetes mellitus*. New Engl J Med 1998, 338(13): 861.

6. Sironi, A.M., Vichi, S., Gastaldelli, A., Pecori, N., Anichini, R., Foot, E., Seghieri, G., Ferrannini, E. *Effects of troglitazone on insulin action and cardiovascular risk factors in patients with non-insulin-dependent diabetes*. Clin Pharmacol Ther 1997, 62(2): 194.

7. Minamikawa, J., Tanaka, S., Yamauchi, M., Inoue, D., Koshiyama, H. *Potent inhibitory effect of troglitazone on carotid arterial wall thickness in type 2 diabetes*. J Clin Endocrinol Metab 1998, 83(5): 1818.

8. Loi, C.-M., Knowlton, P.W., Stern, R., Randinitis, E.J., Vassos, A.B., Koup, J.R., Sedman, A.J. *Effect of troglitazone on steady-state pharmacokinetics of digoxin*. J Clin Pharmacol 1998, 38(2): 178.

9. *Troglitazone approved in the U.K.*. Daily Essentials July 31, 1997.

10. *Romozin now available in U.K.*. Daily Essentials Oct 22, 1997.

11. *Labeling changes for Rezulin; FDA and manufacturer recommend liver function tests*. Daily Essentials Nov 5, 1997.

Original monograph - Drugs Fut 1989, 14: 846

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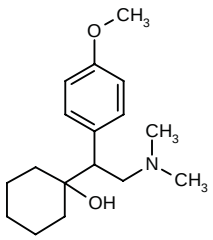

$C_{17}H_{27}NO_2$ **Wyeth-Ayerst; Almirall Prodesfarma; Scios**

Recent studies have shown that venlafaxine decreases monophasic action potential duration and prolongs conduction time in isolated, perfused guinea pig hearts, and that it blocks sodium channels *in vitro* in guinea pig ventricular myocytes, an effect that is completely reversible upon drug withdrawal. This underlying sodium channel-blocking action may explain, at least in part, the unexpected cardiotoxicity observed in some patients treated with the drug (1).

1. Khalifa, M., Daleau, P., Drolet, B., Turgeon, J. *Block of sodium channels underlies unheralded cardiac toxicity observed with the antidepressant agent venlafaxine*. J Mol Cell Cardiol 1998, Abst 534.

Original monograph - Drugs Fut 1988, 13: 839.

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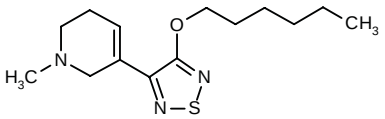

$C_{14}H_{23}N_3OS$ **Lilly; Novo Nordisk**

The therapeutic effects of oral xanomeline (25, 50 and 75 mg t.i.d.) were evaluated in 343 patients with Alzheimer's disease during 7 months. The higher dose was associated with significant improvements on the cognitive subscale of the Alzheimer's Disease Assessment Scale and global status as evaluated by the Clinicians Interview-Based Impression of Change, as compared to placebo. Significant treatment-related reductions were also observed in vocal outbursts, suspiciousness, delusions, agitation and hallucinations as evaluated by the Alzheimer's Disease Symptomatology Scale. End-point analysis of the Nurse's Observational Scale for Geriatric Patients also showed a statistically significant dose-response relationship. The results indicate that xanomeline has favorable effects on disturbing behaviors and may be a novel treatment for noncognitive symptoms of Alzheimer's disease (1).

1. Bodick, N.C., Offen, W.W., Shannon, H.E., Satterwhite, J., Lucas, R., Vanlier, R., Paul, S.M. *The selective muscarinic agonist xanomeline improves both the cognitive deficits and behavioral symptoms of Alzheimer disease*. Alzheimer Dis Assoc Disord 1997, 11(Suppl. 4): S16.

Original monograph - Drugs Fut 1996, 21: 906

Additional References

Bymaster, F. et al. *Xanomeline stimulation of phosphoinositide hydrolysis in vivo: Comparison to other muscarinic agents*. Soc Neurosci Abst 1997, 23(Part 2): Abst 787.14.

Bymaster, F.P. et al. *Xanomeline compared to other muscarinic agents on stimulation of phosphoinositide hydrolysis in vivo and other cholinomimetic effects*. Brain Res 1998, 795(1-2): 179.

El-Assadi, A.A. et al. *CDD-0102 and xanomeline reverse memory deficits produced by IgG-192 saporin*. Soc Neurosci Abst 1997, 23(Part 2): Abst 536.6.

Messer, W.S. Jr. et al. *Xanomeline and CDD-0102, reverse spatial memory deficits following lesions of the basal cholinergic system with IgG-192 saporin*. IBC Conf Alzheimer's Dis. Exploiting Mech Drug Dev Diagn (May 1-2, San Francisco) 1997, 1997.

Perry, K.W. et al. *Effects of xanomeline on monoamine neurotransmitters and metabolites in rat brain areas as measured by microdialysis*. Soc Neurosci Abst 1997, 23(Part 2): Abst 787.15.

Rasmussen, K., Stockton, M.E. *Xanomeline, an M-1 muscarinic agonist, selectively inhibits the activity of A10 dopamine neurons*. Soc Neurosci Abst 1996, 22(Part 2): Abst 500.10.