Drugs of the Future 1998, 23(5): 539-578

CCC: 0377-8282/98

Information Update

Volume 1-22, Number 5

Estimated developmental phase for this month's updated products:

Preclinical

p-XSC (antineoplastic; American Health Found.)

Phase I

A-007 (antineoplastic, antiestrogen; Dekk-Tek)
Atipamezole (α_2-adrenoceptor antagonist, treatment of male sexual dysfunction; Farmos, Dept. Health Human Services)
Epiroprim (antibacterial, dihydrofolate reductase inhibitor; Roche)
Itameline (cognition enhancer; Hoechst Marion Roussel)
KSG-504 (CCK_A antagonist, treatment of pancreatitis; Kissei)
Panomifene (antineoplastic, antiestrogen; Egis Pharm., Fujimoto)

Phase II

Antineoplaston AS2-1 (antineoplastic; Burzynski Res. Inst.)
ARI-509 (symptomatic antidiabetic, aldose reductase inhibitor; Wyeth-Ayerst)
D-0870 (antifungal; Mochida, Zeneca)
FK-143 (treatment of BPH, 5α-reductase inhibitor; Fujisawa)
Hypericin (anti-HIV, antineoplastic; Yeda, Weizmann Inst., Chemex, VIMRx)
MCI-225 (cognition enhancer, antidepressant; Mitsubishi Chem.)
Napsagatran (thrombin inhibitor; Roche)
Raclopride (antipsychotic, dopamine D_2 antagonist; Astra)
Saterinone (positive inotropic agent, phosphodiesterase III inhibitor; Beiersdorf)
Trimetrexate (antineoplastic; Warner-Lambert, Dainippon, U.S. Bioscience)
Turosteride (antiandrogen, treatment of BPH; Farmitalia Carlo Erba)

Phase III

Abecarnil (anxiolytic, anticonvulsant; Schering AG, Novartis, Novo Nordisk)
AS-101 (immunomodulator, chemoprotectant, radioprotectant; Bar Ilan Univ., Baker Norton)
Emitefur (antineoplastic, antimetabolite; Otsuka)
Falecalcitriol (vitamin D analog, treatment of osteoporosis; Taisho, Sumitomo, Penederm, Discovery Labs.)
Lisofylline (hematopoiesis modulator, immunomodulator, LPAAT inhibitor; Cell Therapeutics, BioChem Pharma, Ortho Biotech, R.W. Johnson)
Org-2766 (neuroprotectant; Organon)
Posatirelin (cognition enhancer; Gedeon Richter, Dainippon, Poli Ind. Chim.)
Ularitide (treatment of acute renal failure; HaemoPep Pharma, Boehringer Mannheim)
Vorozole (antineoplastic, aromatase inhibitor; Janssen)
Xemilofiban (platelet aggregation inhibitor, fibrinogen (gpIIb/IIIa) receptor antagonist; Searle, Sankyo)

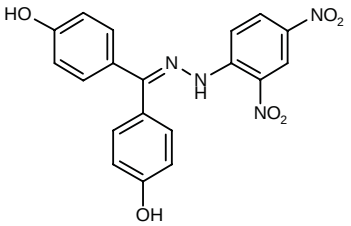
Launched/Year

Abciximab (platelet antiaggregatory, gpIIb/IIIa receptor antagonist; Centocor, Fujisawa, Lilly)/1995
Balsalazide disodium (intestinal antiinflammatory; Biorex, Astra, Menarini, Salix)/1997
Docetaxel (antineoplastic; Rhône-Poulenc Rorer, Chugai)/1995
Irbesartan (antihypertensive, angiotensin AT_1 antagonist; Sanofi, Bristol-Myers Squibb, Shionogi)/1997
Naratriptan (antimigraine, 5-HT_{1D} agonist; Glaxo Wellcome)/1997
Octreotide (antineoplastic, antipsoriatic, antidiarrheal; Novartis)/1988
Pravastatin sodium (hypolipidemic, HMG-CoA reductase inhibitor; Sankyo, Bristol-Myers Squibb)/1989
Quetiapine fumarate (antipsychotic, 5-HT_2 receptor antagonist, dopamine D_2 antagonist; Zeneca)/1997
Topotecan hydrochloride (antineoplastic, topoisomerase inhibitor; SmithKline Beecham)/1996
Toremifene (antineoplastic, antiestrogen; Farmos, Adria, Asta, Nippon Kayaku, Schering-Plough)/1988
Trovafloxacin mesilate (antibacterial, naphthyridine; Pfizer)/1998

A-007

Antineoplastic
Antiestrogen

EN: 164886



$C_{19}H_{14}N_4O_6$ **Dekk-Tek**

In vitro studies of A-007 using human melanoma explants in the colony forming assay show an IC_{50} of 6.01 μg/mg in 30 melanoma specimens, compared to 0.2 μg/ml for doxorubicin and 0.9 μg/ml for paclitaxel. A-007 shows dermal lymphatic accumulation, which may explain its *in vivo* activity (1).

A-007 in combination with delocalized cationic lymphangiophilic dyes showed improved cytotoxic activity in primary histocultures of melanoma and breast cancers and penetrated into rat dermis more effectively than when administered alone (2).

1. Krementz, E.T., Benes, E., Morgan, L.R. *Anticancer activities for 4, 4'-dihydroxybenzophenone-2,4-dinitrophenylhydrazone (A-007) in human melanoma colony forming assays.* Proc Amer Assoc Cancer Res 1997, 38: Abst 1481.

2. Morgan, L.R., Rodgers, A.H., Schwartz, S., Bies, R., Krementz, E.T. *Lymphatic pharmacology of 4,4'-dihydroxybenzophenone-2,4-dinitrophenylhydrazone (A-007) analogs.* Proc Amer Assoc Cancer Res 1998, 39: Abst 4059.

Original monograph - Drugs Fut 1992, 17: 369

Abciximab
ReoPro®

Platelet Antiaggregatory
gpIIb/IIIa Receptor Antagonist

EN: 130762

Immunoglobulin G (human-mouse monoclonal c7E3 clone p7E3V$_H$hC$_{γ4}$ Fab fragment antihuman glycoprotein IIb/IIIa receptor) disulfide with human-mouse monoclonal c7E3 clone p7E3V$_K$hC$_K$ light chain

$C_{2101}H_{3229}N_{551}O_{673}S_{15}$ **Centocor; Fujisawa; Lilly**

Abciximab has been found to protect against microangiopathic hemolytic anemia and microvascular thrombotic renal failure *in vivo* in baboons treated with C4b binding protein and a sublethal infusion of *Escherichia coli* (1).

The hypothesis that abciximab therapy reduces the frequency of repeat revascularization following coronary angioplasty by interrupting ligand binding to $β_3$-integrins on the surface of smooth muscle cells has been evaluated. Immunostaining for $β_3$-integrins was observed in the neointima 1 week following balloon withdrawal-induced injury of brachial arteries in the baboon. Furthermore, $β_3$-integrin expression was localized in cells expressing α-actin. Contralateral uninjured brachial arteries did not stain for $β_3$-integrins. *In vitro* experiments showed that abciximab had affinity for cultured human aortic smooth muscle cells comparable to its affinity for endothelial cells or platelets. Treatment of cultured smooth muscle cells with abciximab partially inhibited thrombospondin- or α-thrombin-induced proliferation and mitogen-associated protein kinase activation, but had no effect on PDGF- or serum-induced proliferation. These results support the hypothesis that the beneficial effect of abciximab therapy is mediated through its binding to $β_3$-integrins on vascular smooth muscle cells, thereby preventing the binding of natural $β_3$-integrin ligands present at sites of vascular injury (2).

The use of abciximab in a high-risk group of patients undergoing PTCA has been evaluated. The drug was effective in 45 of 47 patients (95%); the other 2 patients had reocclusion leading to myocardial infarction. Good safety was also observed, with no cerebral bleeding or deaths (3).

The EPILOG trial conducted in the U.S. and Canada evaluated unplanned coronary stent deployment and the effect of platelet glycoprotein IIb/IIIa blockade using abciximab (ReoPro®) in 326 patients during 6 months of follow-up. Patients treated with abciximab and heparin at low doses required unplanned stents less often than patients treated with placebo and standard-dose heparin. Adverse clinical outcomes such as target vessel revascularization and bleeding events were more frequent in patients with coronary stent deployment than in control patients, but were reduced with abciximab therapy after 30 days and 6 months. Abciximab therapy did not increase bleeding events in stented patients. In short, abciximab therapy reduced the requirement for unplanned stent deployment and produced clinical benefits without increasing bleeding complications. Abciximab therapy should therefore be considered as an option in patients requiring unplanned or provisional stent deployment (4).

1. Taylor, F.B., Coller, B.S., Chang, A.C.K., Peer, G., Jordan, R., Engellener, W., Esmon, C.T. *7E3 F(ab')2, a monoclonal antibody to the platelet GPIIb/IIIa receptor, protects against microangiopathic hemolytic anemia and microvascular thrombotic renal failure in baboons treated with C4b binding protein and a sublethal infusion of Escherichia coli.* Blood 1997, 89(11): 4078.

2. Stouffer, G.A., Hu, Z., Sajid, M., Li, H., Jin, G., Nakada, M.T., Hanson, S.R., Runge, M.S. *β3 Integrins are upregulated after vascular injury and modulate thrombospondin- and thrombin-induced proliferation of cultured smooth muscle cells.* Circulation 1998, 97(9): 907.

3. Grenadier, E., Lashevski, I., Roguin, A., Cohen, S., Beyar, R. *Adjunctive IIb-IIIa receptor blockage in PTCA and stent procedures: Initial clinical and angiographic experience.* Cardiovasc Drugs Ther 1997, 11(Suppl. 2): 401.

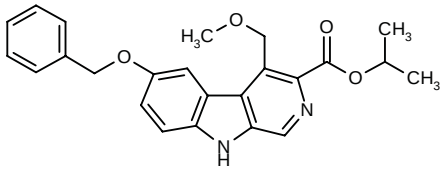
4. Kereiakes, D.J., Lincoff, A.M., Miller, D.P., Tcheng, J.E., Cabot, C.F., Anderson, K.M., Weisman, H.F., Califf, R.M., Topol, E.J. *Abciximab therapy and unplanned coronary stent deployment. Favorable effects on stent use, clinical outcomes, and bleeding complications.* Circulation 1998, 97(9): 857.

Original monograph - Drugs Fut 1995, 20: 457.

Abecarnil

Anxiolytic
Anticonvulsant

EN: 137451



$C_{24}H_{24}N_2O_4$

Schering AG; Novartis; Novo Nordisk

Abecarnil treatment for 7 days prevented the development of a discontinuation syndrome in mice dependent on alprazolam, whereas alprazolam worsened the discontinuation syndrome. Abecarnil replacement therapy following long-term benzodiazepine treatment appears to offer a new approach to rapid tapering (1).

In a study in mice made tolerant to diazepam (25 mg/kg p.o. b.i.d. for 17 days), administration of chronic abecarnil (20 mg/kg p.o. b.i.d.) was shown to reverse the diazepam tolerance, fully restoring its anticonvulsant effect after 8 days of treatment (tested by bicuculline challenge) (2).

In a double-blind, 4-way Latin square design, 24 healthy young males completed a battery of behavioral tests before and several times after abecarnil 2.5 and 5.0 mg, lorazepam 2.0 mg and placebo. Abecarnil showed dose-dependent effects on cognitive and psychomotor tasks. Lorazepam and abecarnil 5.0 mg showed similar impairments, whereas abecarnil 2.5 mg showed substantially less impairment than lorazepam; peak impairments occurred 2-3 h after the oral dose. Drowsiness, lack of concentration and visual disturbances were the most common adverse events for abecarnil 5.0 mg; no difference in the incidence of adverse events was seen between abecarnil 2.5 mg and placebo (3).

1. Pinna, G., Galici, R., Schneider, H.H., Stephens, D.N., Turski, L. *Alprazolam dependence prevented by substituting with the beta-carboline abecarnil.* Proc Natl Acad Sci USA 1997, 94(6): 2719.

2. Natolino, F., Zanotti, A., Pilartiti, M., Contarino, A.,Giusti, P. *Chronic abecarnil administration to diazepam-tolerant mice restores full anticonvulsant activity of diazepam.* Soc Neurosci Abst 1997, 23(Part 1): Abst 377.17.

3. Hege, S.G., Ellinwood, E.H., Wilson, W.H., Helligers, C.A.M., Graham, S.M. *Psychomotor effects of the anxiolytic abecarnil: A comparison with lorazepam.* Psychopharmacology 1997, 131(2): 101.

Original monograph - Drugs Fut 1993, 18: 411.

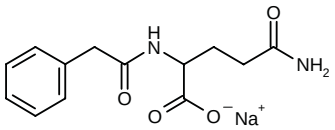
Additional Reference

Ghiani, C.A. et al. *Abecarnil antagonizes the enhanced acetylcholine release in rat brain during the anticipation but not consumption of food.* Soc Neurosci Abst 1996, 22(Part 2): Abst 449.13.

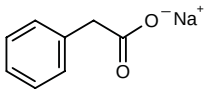
Antineoplaston AS2-1

Antineoplastic

EN: 118983



Component 1



Component 2

Burzynski Res. Inst. (US)

Two patients with liver cancer (hepatocellular carcinoma and colonic carcinoma metastatic to the liver) were treated with transcatheter arterial embolization and microwave coagulation, following which they were maintained on antineoplaston AS2-1. After more than 2 years, both patients remain in good condition and have no limitations in their daily activities (1).

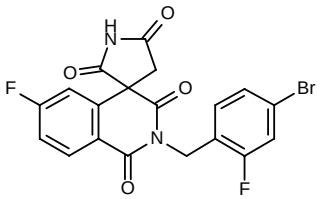
1. Tsuda, H., Sata, M., Saitsu, H., Yamana, K., Hara, H., Yamada, S., Kumabe, T. *Antineoplaston AS2-1 for maintenance therapy in liver cancer.* Oncol Rep 1997, 4(6): 1213.

Original monograph - Drugs Fut 1986, 11: 361.

ARI-509
Minalrestat

Symptomatic Antidiabetic
Aldose Reductase Inhibitor

EN: 164346



$C_{19}H_{11}BrF_2N_2O_4$

Wyeth-Ayerst

A study of the effect of ARI-509 on diabetic-like retinal capillary basement membrane thickening induced in the galactose-fed rat model showed that no significant improvement was seen until 24 months in either the ARI-509-treated group or the galactose withdrawal group. This suggests that human diabetics require intervention before clinical diabetic retinopathy develops (1).

The effects of ARI-509 and aminoguanidine on retinal vasculature and on the expression of vascular endothelial growth factor (VEGF) were studied in the galactose-fed rat model. Rats fed a 50% galactose diet for 2 years were begun on drug therapy either at the onset or after 12 months of galactosemia. All rats developed a vascular retinopathy, with less marked retinopathic changes in those fed ARI-509 from the beginning. Cataract development was also delayed in ARI-509-treated rats. No VEGF immunoreactivity was seen in ARI-509- and aminoguanidine-treated rats (2).

Minalrestat has been proposed as the international nonproprietary name for ARI-509 (3).

1. Robison, W.G. Jr., Jacot, J.L., Glover, J.P., Basso, M.D., Hohman, T.C. *Aldose reductase (AR) inhibitor intervention after significant diabetic-like retinal capillary basement membrane thickening.* Invest Ophthalmol Visual Sci 1997, 38(4, Part 2): Abst 3305.

2. Frank, R.N., Amin, R., Kennedy, A., Hohman, T.C. *An aldose reductase inhibitor and aminoguanidine prevent vascular endothelial growth factor expression in rats with long-term galactosemia.* Arch Ophthalmol 1997, 115(8): 1036.

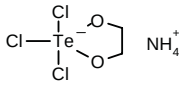
3. *Proposed international nonproprietary names (Prop INN): List 76.* WHO Drug Inform 1996, 10(4): 210.

Original monograph - Drugs Fut 1994, 19: 442.

AS-101
IVX-Q-101
WAX-120337
Ossirene®

Immunomodulator
Chemoprotectant
Radioprotectant

EN: 126952



$C_2H_8Cl_3NO_2Te$ **Bar Ilan Univ. (IL); Baker Norton**

AS-101 injected into SCID mice transplanted with mononuclear cells from systemic lupus erythematosus patients decreased serum human IL-10, all serum human immunoglobulin isotypes, anti-double strand DNA and anti-Sm immunoglobulins. Six-month treatment with AS-101 in NZB/NZW/F1 mice led to a significant decrease in proteinuria (30% in treated group, 100% in untreated) and inhibition of proliferative glomerulonephritis development (1).

1. Kalechman, Y., Gafter, U., Albeck, M., Sredni, B. *Suppression of interleukin 10 by the immunomodulator AS101 inhibits development of autoantibodies and glomerulonephritis in systemic lupus erythematosus (SLE).* J Amer Soc Nephrol 1997, 8: Abst A2503.

Original monograph - Drugs Fut 1989, 14: 410.

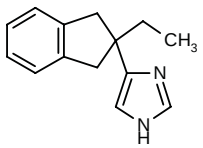
Additional Reference

Shani, A. et al. *Upregulation by AS101 of Fas (APO-1) expression on B16 melanoma cells: Implications for the antitumor effects of AS101.* 8th Int Cong Anti-Cancer Treat (Feb 3-6, Paris) 1998, Abst O 65.

Atipamezole
Antisedan®

α_2-Adrenoceptor Antagonist
Treatment of Male Sexual Dysfunction

EN: 125195



$C_{14}H_{16}N_2$ **Farmos; Dept. Health Human Services (US)**

Atipamezole (30-300 μg/kg), when given to scopolamine-treated rats, was effective in decreasing scopolamine (0.25-0.5 mg/kg)-induced hyperactivity, based on performance in the water maze task, in free swimming and in an open arena task (1).

Atipamezole or norepinephrine injected into mice amygdala led to local expression of *fos*. This effect was blocked by prazosin combined with betaxolol, but not by WAY-100135. The authors suggest that this model is ideal for further study of immediate-early gene expression in central noradrenergic function (2).

1. Niittykoski, M., Hakkarainen, V., Puumala, T., Lappalainen, R., Ruotsalainen, S., Haapalinna, A., Sirviö, J. *Systemic administration of atipamezole, an α_2-antagonist, can reduce scopolamine-induced hyperactivity in rats.* Behav Pharmacol 1997, 8(5): 465.

2. Stone, E.A., Zhang, Y., Hiller, J.M., Simon, E.J., Hillman, D.E. *Activation of fos in mouse amygdala by local infusion of norepinephrine or atipamezole.* Brain Res 1997, 778(1): 1.

Original monograph - Drugs Fut 1990, 15: 448.

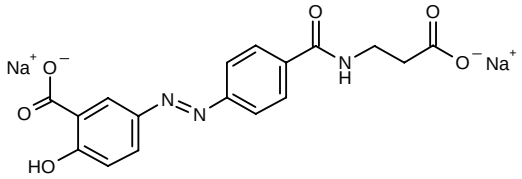
Additional References

Ylinen, A. et al. *A selective antagonist of α_2 adrenoceptors facilitates the excitability of the dentate gyrus and improves the retention of the radial arm maze task.* Soc Neurosci Abst 1996, 22(Part 1): Abst 269.15.

Haapalinna, A. et al. *Evaluation of the effects of a specific α_2-adrenoceptor antagonist, atipamezole, on α_1- and α_2-adrenoceptor subtype binding, brain neurochemistry and behaviour in comparison with yohimbine.* Naunyn-Schmied Arch Pharmacol 1997, 356(5): 570.

Balsalazide Disodium *Intestinal Antiinflammatory*
Colazide®

EN: 090232



$C_{17}H_{13}N_3Na_2O_6$ **Biorex; Astra; Menarini; Salix**

Studies performed to elucidate the mechanism of action of balsalazide in ulcerative colitis showed that the drug inhibited carrageenin edema at pretreatment for 8 h but had no effect on adjuvant arthritis. Furthermore, the drug dose-dependently inhibited PMN chemotaxis activity and compound 40/80-, substance P- and IgE-induced mast cell degranulation (1).

Using 3 different techniques ([^{3}H]-FMLP binding assay, FMLP-induced luminol-dependent chemiluminescent response assay and FMLP-induced chemotaxis assay) it was found that balsalazide produced a concentration-dependent inhibition of FMLP-induced polymorphonuclear leukocyte function (2).

Studies of the effects of balsalazide and its moiety 5-ASA on reactive oxygen species showed that they inhibited O_2^- production, while scavenging OCl^- and OH. They were also found to inhibit thiobarbituric substance production caused by mesenteric ischemic-reperfusion injury (3).

A double-blind multicenter dose-response trial of balsalazide (6.75 and 2.25 g/day) and mesalamine (2.4 g/day) was carried out for 8 weeks in 154 patients with mild to moderately active ulcerative colitis. There was no difference in reported adverse events among the groups. Balsalazide 6.75 g/day resulted in more rapid sigmoidoscopic improvement at 2 weeks than mesalamine. At 8 weeks, the higher dose of balsalazide was significantly superior to the lower dose and was superior to but not statistically significantly different from mesalamine in improving signs, symptoms and quality of life (4).

A randomized, double-blind study comparing balsalazide 6.75 g/day to mesalamine 2.4 g/day for 4, 8 or 12 weeks in 101 patients with acute ulcerative colitis showed that fewer adverse events occurred in the balsalazide group, and balsalazide was superior in relation to number of asymptomatic days, time to first asymptomatic day and symptomatic and complete remission (5).

A randomized, double-blind comparison of balsalazide (2.25 g t.i.d.) and mesalamine (0.8 g t.i.d.) in 99 patients with ulcerative colitis showed that balsalazide was superior in relation to symptomatic remission, complete remission, patient satisfaction, time to first symptom-free day and days with complete symptom relief. Balsalazide-treated patients reported significantly fewer adverse events (6).

The FDA has accepted for review Salix Holdings' NDA for balsalazide disodium (Colazide®) for the treatment of acute ulcerative colitis (7).

Balsalazide disodium (Colazide®) has been launched in the U.K. for the acute teatment of ulcerative colitis and is supplied as capsules, 750 mg. The drug, developed and manufactured by Salix, has been marketed by Astra (8).

1. Kimura, I., Kawasaki, M., Nagahama, S., Kataoka, M., Sato, M. *Anti-inflammatory effects of BX661A, a novel therapeutic drug for ulcerative colitis.* Jpn J Inflamm 1997, 17(5): 499.

2. Furuta, S., Matsuda, A., Kumamoto, T., Kimura, I., Kawasaki, M., Kataoka, M. *Effect of BX661A (therapeutic agent for ulcerative colitis) on polymorphonuclear leukocyte function.* Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-110.

3. Kumamoto, T., Matsuda, A., Furuta, S., Kataoka, M., Kokuba, Y., Fujibayashi, Y. *Effects of BX661A (therapeutic agent for ulcerative colitis) on reactive oxygen species.* Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-636.

4. Levine, D.S., Pruitt, R., Riff, D. et al. *A multi-center, double-blind dose-response trial of Colazide® (balsalazide disodium) and Asacol® (mesalamine) for mild-moderately active ulcerative colitis.* Dig Dis Week (May 10-16, Washington DC) 1997, Abst 4380.

5. Green, J.R.B., Lobo, A.J., Holdsworth, C.D., Leicester, R.J., Gibson, J.A., Kerr, G.D., Hodgson, H.J.F., Parkins, K.J., Taylor, M.D. *Balsalazide is more effective and better tolerated than mesalamine in the treatment of acute ulcerative colitis.* Gastroenterology 1998, 114(1): 15.

6. Green, J.R.B., Holdsworth, C.D., Lobo, A.J. et al. *Balsalazide is more effective and better tolerated than mesalazine in acute ulcerative colitis (UC).* Dig Dis Week (May 10-16, Washington DC) 1997, Abst 4379.

7. *NDA for Colazide accepted for review by FDA.* Prous Science Daily Essentials September 1, 1997.

8. *New products intros.* Drug News Perspect 1997, 10(8): 483.

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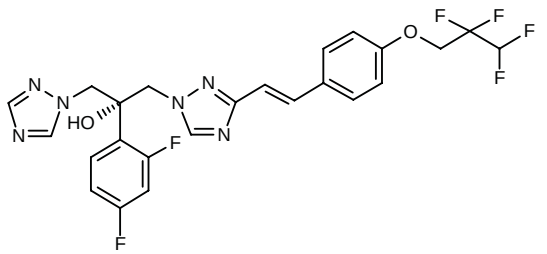
Launch announced for new ulcerative colitis Rx. Prous Science Daily Essentials October 1, 1997.

Kosaki, M. et al. *Pharmacokinetics of BX661A, an agent releasing free 5-aminosalicylic acid (5-ASA) in the large intestine, in a rat model of ulcerative colitis induced by dextran sulfate.* Xenobiotic Metab Dispos 1997, 12(Suppl.): Abst P-238.

D-0870 *Antifungal*
ICI-D0870M-16354
ZD-0870

EN: 182468



$C_{24}H_{20}F_6N_6O_2$ **Mochida; Zeneca**

A controlled study of the anti-Chagas disease activity of D-0870 was conducted in adult Swiss albino mice. Nine different *Trypanosoma cruzi* strains with varying levels of drug resistance were inoculated into the mice and treatment was given for 20 days. D-0870 was seen to be highly active in this model, even against drug-resistant strains (1).

In a murine model of experimental vaginal candidiasis, oral D-0870 (0.5 and 2.5 mg/kg) was more effective than fluconazole in treating *Candida albicans* species, including fluconazole-susceptible and -resistant strains, but it was not effective against *Candida glabrata* (2).

An *in vitro* study compared the activity of D-0870, itraconazole and fluconazole against *Aspergillus fumigatus* and *Candida krusei*. D-0870 and itraconazole showed similar activity against *C. krusei* whole cells, but D-0870 was less effective against *A. fumigatus*. Sterol biosynthesis was similarly affected in both species. D-0870 was superior to fluconazole, apparently due to its stronger inhibition of ergosterol synthesis in *A. fumigatus*, and probably due to reduced drug efflux in *C. krusei* (3).

An open, nonrandomized trial examined 2 multiple-dose regimens of D-0870 in 22 HIV-positive men. Both regimens (50 mg loading dose then 10 mg/day x 4 days and 200 mg loading dose then 25 mg/day x 4 days) were well tolerated, with no drug-related adverse events. PK data were similar to those seen in normal healthy subjects (4).

The efficacy and safety of D-0870 have been evaluated in a multicenter trial in HIV-positive patients with oropharyngeal candidiasis. Of 35 patients treated with either an initial dose of 50 mg followed by 10 mg for 4 days or an initial dose of 100 mg followed by 25 mg for 4 days or 10 mg for 5 days, 27 patients were clinically cured and 6 were improved; 2 patients on the lowest dose who showed very low plasma levels of drug failed therapy. Relapse occurred in 37% of patients within 2 weeks of discontinuing therapy. The treatment was very well tolerated. Clinical outcome was not associated with peak plasma levels, MIC for *Candida albicans*, colony-forming units of culture or baseline CD4 cell counts (5).

D-0870 was initially under development by both Zeneca and Mochida as an antifungal agent. Zeneca discontinued development of the product earlier this year, but Mochida is continuing its development. It is currently in phase II trials in Japan as both oral and injectable formulations for systemic fungal infections (6, 7).

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2. Fidel, P.L. Jr., Cutright, J.L., Sobel, J.D. *Efficacy of D0870 treatment of experimental Candida vaginitis.* Antimicrob Agents Chemother 1997, 41(7): 1455.

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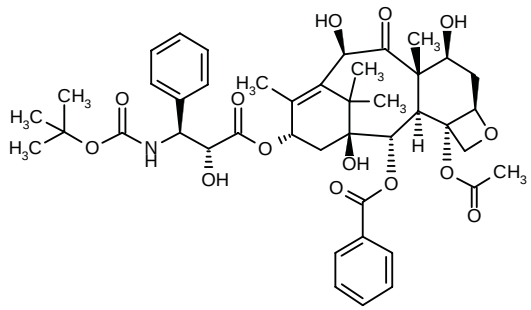
Docetaxel
Taxotere®

Antineoplastic

EN: 140605



$C_{43}H_{53}NO_{14}$

Rhône-Poulenc Rorer; Chugai

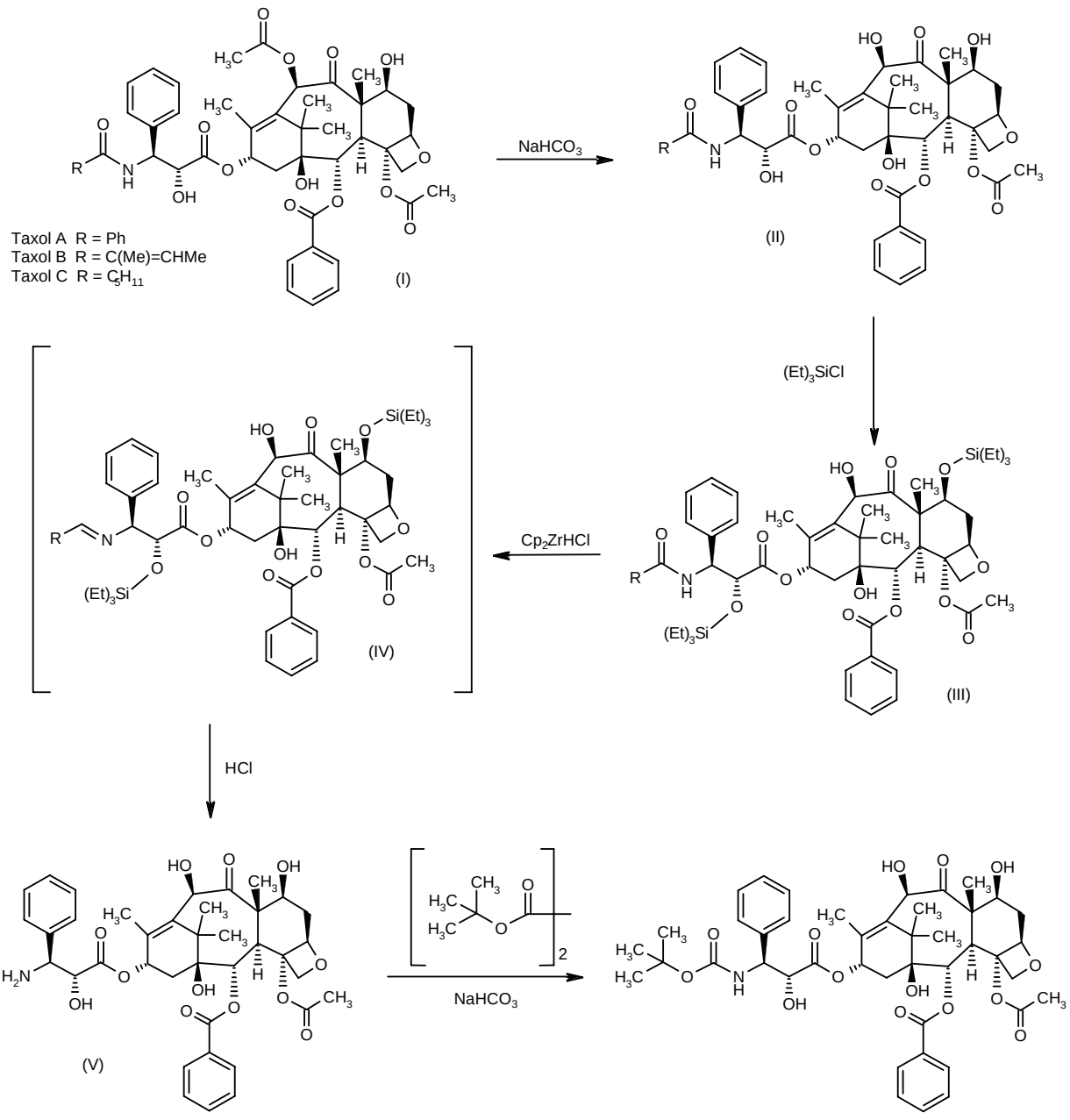
Several partial syntheses of docetaxel have been described: The selective hydrolysis of Taxol A (I, R = Ph), Taxol B (I, R = C(Me)=CHMe) or Taxol C (I, R = C_5H_{11}) with $NaHCO_3$ in THF/water gives the corresponding 10-deacetyl derivatives (II), which by selective silylation with triethylsilyl chloride in pyridine are converted into the 10-deacetyl-2',7-bis(triethylsilyl) compounds (III). The reaction of compounds (III) with zirconocene chloride hydride [bis(cyclopentadienyl)zirconium chloride hydride] in THF afford the corresponding imino derivatives (IV), which,

without isolation are hydrolyzed and desilylated by a treatment with concentrated aqueous HCl in ethanol giving 10-deacetyltaxolamine (V). Finally, this compound is acylated at the amino group by a treatment by di-*tert*-butyl dicarbonate and $NaHCO_3$ in ethyl acetate/water (1). Scheme 1.

A phase II trial of docetaxel (100 mg/m^2 i.v. over 1 h every 3 weeks for up to 6 cycles) was conducted in 68 patients with non-Hodgkin's lymphoma who had previously undergone cytotoxic treatment. No corticosteroid pretreatment was used, and the docetaxel dose was reduced to 75 mg/m^2 if there was grade 3/4 hematologic toxicity (which occurred in almost all patients on first course). Major response rates were 13% for IWF A-C and 16% for IWF D-H, with a time to response of 1.3-2.8 months and a response duration of 1.4-20 months (2).

A pharmacokinetic and pharmacodynamic population study of docetaxel was undertaken in 24 phase II studies

Scheme 1: Synthesis of Docetaxel



involving 936 patients. First-course docetaxel pharmacokinetics were a predictor for hematologic toxicity (TTP, grade 4 neutropenia and febrile neutropenia) and also for fluid retention in patients with non-small cell lung cancer. Elevated hepatic enzymes were associated with decreased clearance and a higher toxicity risk (3).

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2. Budman, D.R., Petroni, G.R., Johnson, J.L., Cooper, M.R., Schlossman, D.M., Barcos, M., Peterson, B.A. *Phase II trial of docetaxel in non-Hodgkin's lymphoma: A study of the cancer and leukemia group B.* J Clin Oncol 1997, 15(10): 3275.

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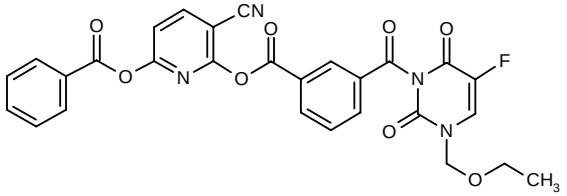
Emitefur

Antineoplastic
Antimetabolite

EN: 140773



$C_{28}H_{19}FN_4O_8$ **Otsuka**

BOF-A2 (20-40 mg/kg/day p.o. for 7 days) was shown to dose-dependently decrease subcutaneously implanted glioma tumors in mice and increase the survival of mice with intracerebrally implanted gliomas and ethylnitrosourea-induced tumors. Moderately high tumor levels of 5-FU were seen after 24 h (1).

In a study comparing the antitumor effects of BOF-A2 and 5-FU in nu/nu mouse-transplanted squamous cell carcinoma cells (from tongue carcinoma), it was found that BOF-A2 resulted in dose-dependent tumor growth suppression (15 mg/kg/day almost totally inhibited cell multiplication). BOF-A2 also increased transglutaminase, involucrin and cytokeratin 19 expression and decreased *in vitro* tumor cell multiplication (2).

Emitefur has been compared to doxifluridine in a randomized phase II trial in patients with gastric cancer. Patients were divided into two groups which received either emitefur (200 mg b.i.d. p.o. for 2 weeks every 4 weeks) or doxifluridine (400 mg t.i.d. p.o. for at least 4 weeks). Of 54 evaluable patients receiving emitefur, 22.2% had a partial (11 patients) or complete response (1 patient), compared to 6.9% (4 partial responses) of 58 patients receiving doxifluridine. The incidence of toxicity was somewhat lower in patients on doxifluridine (grade 1-4: 64.8% on emitefur *vs.* 53.5% on doxifluridine; grade 3-4: 24.1% on emitefur *vs.* 19.0% on doxifluridine), stomatitis and pigmentation being significant on emitefur (3).

Results from a multicenter late phase II trial of emitefur in patients with pancreatic cancer have been reported, showing a median survival time of 202 days using the optimal dose and regimen (200 mg b.i.d. for 2 weeks every 2 weeks). A response rate of 20.6% was previously reported, with major side effects of myelosuppression, gastrointestinal disturbances such as stomatitis, anorexia and diarrhea, and skin symptoms such as pigmentation (4).

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2. Yoneda, K., Yamamoto, T., Ueta, E., Osaki, T. *The effect of 3-[3-(6-benzoyloxy-3-cyano-2-pyridyloxycarbonyl)benzoyl]-1-ethoxymethyl-5-fluorouracil (BOF-A2) on nu/nu mouse-transplanted squamous cell carcinoma cells.* Proc Amer Assoc Cancer Res 1998, 39: Abst 2144.

3. Fujii, M., Furue, H., Wakui, A. et al. *A phase II randomized study of BOF-A2 (emitefur) in gastric cancer.* 20th Int Cong Chemother (June 29-July 3, Sydney) 1997, Abst 3117.

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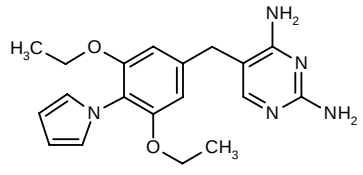
Epiroprim

Antibacterial
Dihydrofolate Reductase Inhibitor

EN: 199018



$C_{19}H_{23}N_5O_2$ **Roche**

Using the agar dilution method, epiroprim was found to be more effective than trimethoprim against *Staphylococcus aureus*, *Enterobacter, Salmonella* and *Shigella*, while against *Klebsiella*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Proteus mirabilis* it was less effective than trimethoprim. In combination with sulfamethoxazole, similar results were seen, except against

Salmonella and *Shigella*, where the trimethoprim/sulfamethoxazole combination was better (1).

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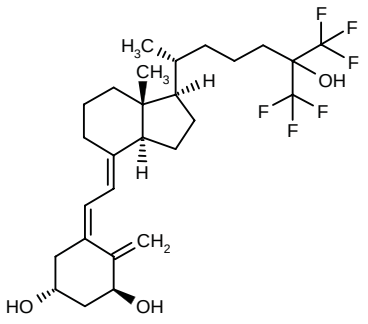
Falecalcitriol
ST-630

Vitamin D Analog
Treatment of Osteoporosis

EN: 141273



$C_{27}H_{38}F_6O_3$

Taisho; Sumitomo; Penederm; Discovery Labs.

Penederm has received a phase I Small Business Innovation Research grant from the National Institute on Aging to support research on falecalcitriol as a potential treatment for acne and premature skin aging. The compound is currently in phase II clinical trials in the U.S. for the treatment of psoriasis (1).

Discovery Laboratories and its majority-owned subsidiary Acute Therapeutics have successfully completed a phase Ia trial of falecalcitriol softgel capsules for the treatment of postmenopausal osteoporosis. The double-blind, placebo-controlled, rising single- and multiple-dose safety, tolerance and pharmacokinetic study involved 30 healthy volunteers. Subjects received either placebo or falecalcitriol on day 1 and days 11-24. The highest dose tested was 0.5 mcg/day. Results of this trial suggest that a clinically active dose of falecalcitriol can be safely administered. There were no incidences of transient or persistent hypercalcemia observed, even in the highest dose group studied. Sumitomo and Taisho are the licensees of the compound in Japan, while Discovery Laboratories holds all other rights to the compound worldwide (2).

A phase Ib, double-blind, placebo-controlled, rising single- and multiple-dose safety, tolerance and pharmacokinetic study of falecalcitriol softgel capsules in 18 postmenopausal female volunteers is under way. Subjects will receive either placebo or falecalcitriol on day 1 and days 11-24. The dose levels tested will be 0.0 (placebo), 0.1875, 0.3125 and 0.4375 mg/day (3).

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2. *ST-630 successfully completes phase Ia trial for osteoporosis.* Prous Science Daily Essentials March 25, 1998.

3. *Discovery Laboratories begins phase Ib trials of ST-630.* Prous Science Daily Essentials April 8, 1998.

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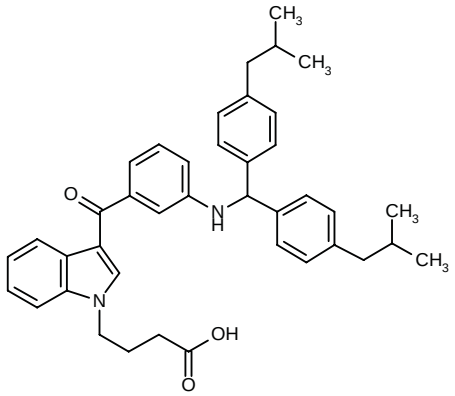
FK-143

Treatment of BPH
5α-Reductase Inhibitor

EN: 178477



$C_{40}H_{44}N_2O_3$

Fujisawa

A study of the tissue distribution kinetics of FK-143 in rats showed that, at doses of 1 and 5 mg/kg i.v., total body clearance was, respectively, 6.96 and 8.76 ml/min/kg, $t_{1/2}$ was 10.31 and 9.83 h, and steady-state distribution volume was 4.11 and 3.33 l/kg. Unidirectional uptake clearance indicated that a membrane-limited process transported the drug to tissues. Further analysis revealed that specific binding of FK-143 in tissues is primarily determined by 5α-reductase (or associated substances) activity (1).

A PK/PD study of FK-143 (0.1-20 mg/kg i.v.) was conducted in rats. Ventral prostate tissue levels were saturated at doses over 5 mg/kg, while blood concentration continued to increase linearly. Analysis suggested that the duration of effect of FK-143 is related to its accumulation in the prostate binding pool (2).

The effects of FK-143 on prostate and other organs in dogs have been compared to those of finasteride and the androgen receptor antagonists allylestrenol and chlormadinone acetate. At oral doses of 10 and 32 mg/kg/day for 12 weeks, FK-143 reduced prostate volume by about 40% and induced dose-dependent glandular epithelial atrophy in the prostate, without affecting organ weight or histology of the adrenal gland, testis, pituitary or liver. Its effect on the prostate was comparable to that of finas-

teride (1.0 mg/kg/day) but less than that of the androgen antagonists. However, allylestrenol (10 mg/kg/day) was associated with an increase in liver weight and chlormadinone (10 mg/kg/day) with an increase in liver weight and a decrease in adrenal weight (3).

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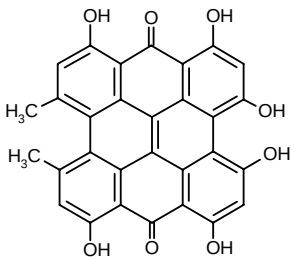
Hypericin
VIMRxyn™

Anti-HIV
Antineoplastic

EN: 140807



$C_{30}H_{16}O_8$ **Yeda; Weizmann Inst. (IL); Chemex; VIMRx**

Hypericin produced a dose-dependent inhibition of cell proliferation in a human glioma cell line and decreased intracellular pH. Mitochondrial hexokinase inhibition occurred 1 h following hypericin, with hexokinase release from mitochondria, a decrease in ATP and glucose-6-P. This effect occurred in the dark but was optimal with photoirradiation. These effects could be used to decrease glioma cell growth (1).

VIMRx has initiated a U.S. phase II trial to evaluate the efficacy and tolerability of VIMRxyn® as a topically applied, light-activated therapy for specific skin diseases including psoriasis, cutaneous T-cell lymphoma and warts (2).

1. Miccoli, L., Sureau, F., Dutrillaux, B., Poupon, M.-F. *Hypericin disrupts the hexokinase mitochondria-binding and affects the pH-dependent metabolism of human gliomas.* Proc Amer Assoc Cancer Res 1997, 38: Abst 4018.

2. *VIMRxyn enters phase II for treatment of skin diseases.* Prous Science Daily Essentials October 27, 1997.

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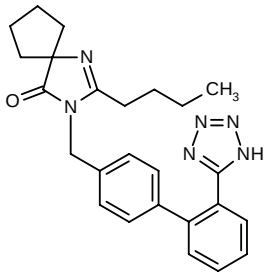
Irbesartan
BMS-186295
SR-47436
Aprovel™
Avapro™
Karvea™

Antihypertensive
Angiotensin AT_1 Antagonist

EN: 176436



$C_{25}H_{28}N_6O$ **Sanofi; Bristol-Myers Squibb; Shionogi**

A recent review has reported that irbesartan has the highest oral bioavailability of the AII receptor blockers, with no effect on absorption by food. It shows linear, dose-related pharmacokinetics with a long elimination half-life and sustained AII receptor blockade 24 h after dosing in doses of 150-300 mg. No dose adjustment is needed for renal or hepatic dysfunction, and no drug interactions have been reported, perhaps due to its low protein binding (1).

A randomized, double-blind, placebo-controlled, parallel-group, crossover study examined irbesartan's inhibitory effect on exogenously administered AII in 18 healthy males. Irbesartan (75, 150 and 300 mg) was given as a single dose, while AII was given 15 min before and then 1, 2, 4, 8, 12 and 24 h later. The AII pressor response was inhibited in a dose-dependent fashion. Irbesartan was well tolerated (2).

A 2-way, crossover study in 16 healthy male subjects showed that oral bioavailability of an irbesartan 300-mg tablet was unaffected by a high-fat meal. C_{max}, t_{max} and AUC were the same when the tablet was taken in the fasting state and 5 min after a high-fat breakfast, indicating that irbesartan can be taken without regard to meals (3).

A study of the effect of age on irbesartan pharmacokinetics was conducted in 12 young healthy males (mean age 29 years) and 12 healthy elderly males (mean age 69 years). Following a single 150-mg dose after fasting overnight, serial plasma and urine samples were assessed. No statistically significant differences were

observed in any pharmacokinetic parameters and in adverse events between the two groups (4).

A randomized, double-blind, placebo-controlled study in 16 healthy male patients studying the effects of irbesartan (300 mg/day) on the PK/PD of warfarin (2.5-10 mg/day) showed that C_{max}, t_{max} and AUC of warfarin were unchanged. No adverse events were reported (5).

A randomized, double-blind, active-controlled, pilot study compared irbesartan (75 mg/day) with amlodipine (2.5 mg/day) for 12 weeks in 47 type II diabetic patients with hypertension. Dosages were doubled at 4 and 8 weeks as needed. Irbesartan had a beneficial effect on kidney function (decreased urinary protein excretion) and fewer adverse events were seen than in the amlodipine-treated group (6).

A double-blind, placebo-controlled, matrix study evaluated the effect of combination irbesartan and hydrochlorothiazide therapy in 683 patients with diastolic hypertension (SeDBP 95-110 mmHg). Safety evaluation showed no difference between the groups. Reductions in blood pressure were greater with the combination than with either drug alone. The antihypertensive effect of irbesartan was dose-dependent. The drug was safe and well-tolerated when administered alone or in combination with hydrochlorothiazide (7).

The results of 6 multicenter, open-label studies of irbesartan for mild to moderate hypertension in 1201 patients were analyzed. Irbesartan was given in doses up to 300 mg/day with adjunctive medications as needed. The majority of patients achieved target normal blood pressure with no unexpected adverse events (8).

A double-blind, placebo-controlled, parallel-group study of irbesartan pharmacodynamics (300 mg/day) in subjects with mild to moderate hypertension showed that blood pressure decreased with AII receptor blockade. Feedback elevations of AII and plasma renin activity occurred, but no effect on renal function or thromboxane A_2 excretion was observed. While peak irbesartan concentration was seen at 1.5 h, the peak antihypertensive effect was seen at 4 h (9).

A randomized, double-blind, parallel-group study compared irbesartan (150-300 mg/day) to enalapril (20-40 mg/day) in severe hypertension. If blood pressure was not controlled by 4 weeks, then other antihypertensives were added. At 12 weeks, the antihypertensive effect of both drugs was equivalent, although irbesartan had better tolerability (10).

A double-blind, placebo-controlled study compared 3 dose regimens of irbesartan (75 mg/day, 150 mg/day and 75 mg b.i.d.) in 215 adults with mild to moderate hypertension. Patients were monitored with 24-h ambulatory blood pressure monitoring. All doses of irbesartan showed antihypertensive efficacy. The 150 mg/day dosage showed sustained blood pressure decreases throughout the 24-h period, equal to 75 mg b.i.d. dosing (11).

A randomized, double-blind study compared irbesartan (75 mg/day) to atenolol (50 mg/day) for 24 weeks in 231 patients with mild to moderate hypertension. Doses were doubled where needed and hydrochlorothiazide was added if required. Both drugs were equally effective in lowering blood pressure, with irbesartan showing a preferable safety profile; more patients stopped treatment due to adverse events with atenolol. Atenolol decreased the heart rate, while irbesartan had no effect (12).

A randomized, double-blind study compared irbesartan (75 mg/day) and enalapril (10 mg/day) in 200 patients with mild to moderate hypertension. Doses were doubled as needed at weeks 4 and 8. At 12 weeks, both drugs showed equal efficacy with similar adverse events, although a trend to more cough was seen with enalapril (13).

A randomized, double-blind, placebo-controlled trial evaluated combination treatment with irbesartan (75 or 150 mg/day) and hydrochlorothiazide (12.5 mg/day) in 178 hypertensive patients with average entry blood pressure of 157/100 mmHg. Both treatment regimens resulted in significant blood pressure reductions beginning at week 2; the higher irbesartan dose resulted in a greater reduction. Adverse events and abnormal laboratory results were equivalent in the treatment and placebo groups (14).

An open-label, multiple-dose, parallel-group study examined irbesartan pharmacokinetics (300 mg/day) in 10 normotensive patients with liver cirrhosis and in 10 healthy controls. Time to steady state, C_{max}, t_{max}, $t_{1/2}$ and AUC were the same in both groups. Therefore, no dose adjustment of irbesartan is needed in patients with hepatic cirrhosis (15).

A randomized, double-blind, placebo-controlled, 12 week, dose-titration study of irbesartan was conducted in 319 patients with mild to moderate hypertension. Patients were started on either placebo, 75 mg irbesartan or 150 mg irbesartan; the dose was doubled at week 6 if needed. Adverse events were the same in all groups. Both treatment groups showed efficacy, but the higher dose combination was more effective in lowering blood pressure (16).

A double-blind, placebo-controlled study evaluated 3 dosage regimens of irbesartan (75 mg/day, 75 mg b.i.d. and 150 mg/day) in 215 mild to moderately hypertensive adult patients for 8 weeks. Adverse events were the same in all groups. Ambulatory blood pressure monitoring revealed the effectiveness of all irbesartan regimens; 75 mg b.i.d. offered no advantage over the 150 mg dosage (17).

An open-label, multiple-dose, parallel-group study compared single-dose and steady-state pharmacokinetics of irbesartan (100 or 300 mg daily x 8 days) in patients with varying degrees of renal dysfunction. C_{max} and AUC_{τ} were not related to creatinine clearance in a linear fashion and no drug accumulation was seen. Hemodialysis did not clear irbesartan. Thus, no adjustment in irbesartan dose is needed with decreased renal function or in hemodialysis patients (18).

A randomized, double-blind, placebo-controlled, parallel-group study examined the pharmacodynamics of irbesartan in 24 mild to moderately hypertensive patients

for 4 weeks. AII receptor blockade and feedback increases in AII and plasma renin activity were seen with irbesartan administration, with no effect on kidney function or thromboxane A_2 excretion. Peak irbesartan concentration occurred at 1.5 h with the peak antihypertensive effect at 4 h (19).

An open-label, multiple-dose, parallel-group study examined the pharmacokinetic parameters of irbesartan (300 mg/day) in 10 healthy subjects and 10 normotensive patients with liver cirrhosis. Time to irbesartan steady state, C_{max}, t_{max}, $t_{1/2}$ and AUC were the same in both groups, with no drug accumulation seen. Treatment of patients with hepatic cirrhosis requires no irbesartan dosage adjustment (20).

A randomized, double-blind, placebo-controlled study examined the effects of irbesartan (12.5, 37.5, 75 and 150 mg) for 12 weeks in 218 patients with symptomatic heart failure and LVEF ≤ 40%. Mean pulmonary artery pressure and PCWP were improved (both acute and long term) by irbesartan in a dose-related manner, with no change in heart rate. Doses of 75 and 150 mg improved LVEF (21).

Thirty-six non-Black, mild to moderate hypertensive patients were treated either with irbesartan 150 mg/day alone or in combination with hydrochlorothiazide 25 mg/day. Pharmacokinetic studies showed that hydrochlorothiazide had no effect on irbesartan pharmacokinetics. Coadministration of the two drugs resulted in greater blood pressure reductions, greater increases in plasma AII levels and plasma renin activity, and raised no clinically significant tolerability issues (22).

An open-label, multiple-dose, parallel-group study of irbesartan was conducted in 40 patients with varying levels of renal functional impairment. Patients received 100 mg/day for 8 days or 300 mg/day for 9 days if on hemodialysis. Creatinine clearance showed no significant linear relationship with C_{max}, AUC or any other pharmacokinetic parameters. Hemodialysis was not shown to clear irbesartan, indicating that no adjustment of starting irbesartan dose is needed with renal functional impairment, including hemodialysis (23).

An overview of 7 placebo-controlled trials has shown that irbesartan is at least as effective as other leading antihypertensives, with an adverse event profile similar to placebo. Once-daily dosing provides 24-h blood pressure control and a high percentage of patients require no additional drugs to control blood pressure (24).

A double-blind, placebo-controlled, pilot study in 109 patients with mild to moderate heart failure (LVEF ≤ 40%) and treated with concurrent diuretics and ACE inhibitors, showed that irbesartan (12.5, 37.5 or 75 mg/day, titrated to 150 mg/day) was well tolerated and produced favorable results on exercise tolerance tests and LVEF (25).

A pilot study in 134 patients with NYHA Class II/III heart failure and LVEF ≤ 40% compared irbesartan (37.5 mg/day, titrated to 150 mg/day) to lisinopril (5 mg/day, titrated to 20 mg/day). Patients had previously been stabilized on diuretics and ACE inhibitors. The ACE inhibitors were stopped when the trial began. There were no statistical differences between the two drugs in relation to clinical outcomes and tolerability over the 12-week study period (26).

A double-blind, 48-week study compared irbesartan (150 mg/day) to atenolol (50 mg/day) in 115 hypertensive patients with elevated left ventricular mass indexes. Doses were doubled at 6 weeks if needed; hydrochlorothiazide or felodipine was added in 6-week intervals as required. Patients on irbesartan showed earlier and greater degrees of LVH regression, and irbesartan was better tolerated and provided improved organ protection (27).

Irbesartan (Aprovel™, Karvea™) has been introduced for the treatment of hypertension in its first markets, the U.K. and Germany. It was first approved in Switzerland in August, 1997 and has also been cleared for marketing in Russia and Mexico; approval is expected shortly in the U.S. Aprovel™/Karvea™ is available as tablets of 150 and 300 mg (28).

The U.S. Food and Drug Administration has approved irbesartan as a first-line treatment for hypertension. Irbesartan, which was discovered by Sanofi, has been codeveloped with Bristol-Myers Squibb since 1993 and will be copromoted and marketed by the two companies in the U.S. under the trade name Avapro™ (29).

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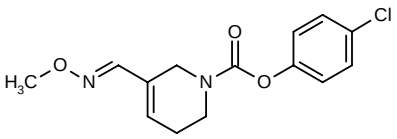
Itameline
RU-47213

Cognition Enhancer

EN: 149652



$C_{14}H_{15}ClN_2O_3$ **Hoechst Marion Roussel**

The effects of RU-47213 on working memory impairment induced by scopolamine have been assessed in rats trained on a radial maze or a T-maze. When given before testing, both RU-47213 (0.2-2 mg/kg) and tacrine (1-5 mg/kg) markedly reduced scopolamine-induced deficits in both tasks, demonstrating the ability of RU-47213 to reduce memory deficits associated with impairment of cholinergic transmission (1).

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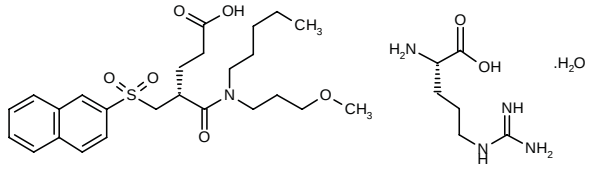
KSG-504

CCK_A Antagonist
Treatment of Pancreatitis

EN: 176915



$C_{25}H_{35}NO_6S.C_6H_{14}N_4O_2.H_2O$ **Kissei**

A study of the activity of FR-127519 and KSG-504 as CCK_A antagonists was conducted in the rat nodose ganglion. The actions of CCK were attenuated by both compounds in a dose-related manner, producing rightward shifts in the CCK dose-response curves, but in a nonparallel manner at low dose for KSG-504. Both compounds were effective CCK_A receptor antagonists (1).

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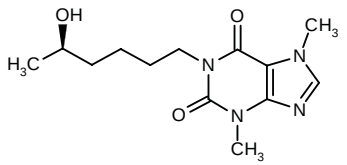
Lisofylline
CT-1501R
ProTec®

Hematopoiesis Modulator
Immunomodulator
LPAAT Inhibitor

EN: 207890



$C_{13}H_{20}N_4O_3$ **Cell Therapeutics; BioChem Pharma; Ortho Biotech; R.W. Johnson**

In a study in 12 healthy volunteers, lisofylline (1, 2 or 3 mg/kg 10-min i.v. infusion q24h for 3 days, followed by 6 mg/kg p.o.) produced a dose-independent fall (64.7 ± 7.4%) in serum free fatty acids 6 h after the first dose, down to a nadir (71.5 ± 5.5%) at 6 h after the last i.v. dose. The effect was still present at 48 h after the last i.v. dose. Serum triglycerides rose in a similar fashion (1).

In a randomized, placebo-controlled trial in 53 patients with metastatic renal carcinoma or malignant melanoma, lisofylline (1.5 mg/kg i.v. bolus q6h during IL-2 treatment) was not shown to alter high-dose i.v. IL-2 toxicity sufficiently to alter the overall IL-2 dose intensity (2).

Cell Therapeutics has reported encouraging preliminary results from a phase II trial of lisofylline (LSF) in patients with newly diagnosed acute myeloid leukemia (AML) conducted at the M.D. Anderson Cancer Center. In this randomized, double-blind, placebo-controlled trial, 70 AML patients were treated with either LSF (3 mg/kg) or placebo along with high-dose chemotherapy. Trial endpoints included the incidence of neutropenia-associated (both serious and nonserious) infections and early mortality (including infectious- and noninfectious-related deaths) in the first 60 days following chemotherapy. In this trial, 6 LSF recipients (17%) developed 7 serious neutropenic infections, compared with 12 placebo recipients (34%) who developed 16 serious neutropenic infections. No patients (0%) in the LSF group developed fun-

gal infections, while 5 placebo patients (14%) developed 6 fungal infections. Although no difference in all-cause mortality was observed between the two groups, fatal infections were reduced more frequently in LSF recipients. Seven (20%) patients receiving placebo developed fatal infections in the first 60 days following chemotherapy, compared with 3 (8.6%) LSF recipients. In addition, a trend in LSF recipients in the reduction of all (serious and nonserious) neutropenia-related infections was also observed. Thirteen LSF recipients had 16 infections while 17 placebo recipients experienced 25 infections. LSF had no observable effect on the acquisition of nonserious infections and no serious adverse effects due to LSF administration were observed (3).

Data presented at the 39th Annual Meeting of the American Society of Hematology indicate that lisofylline may help preserve barrier function in the gastrointestinal tract in patients undergoing high-dose induction chemotherapy for AML by regulating the levels of lipid hydroperoxides, thus reducing infection and mortality. Results from preclinical mucositis research also presented at the meeting demonstrated that the administration of a standard dose of lisofylline prior to and during radiation was dramatically protective in comparison to controls, where marked ulceration and tissue damage were observed. Lisofylline-treated groups never approached frank ulceration and idemonstrated more rapid recovery (4).

The first pivotal phase III trial of lisofylline, a multicenter, double-blind, randomized, placebo-controlled study in patients with advanced hematological malignancies undergoing high-dose radiation and/or chemotherapy accompanied by bone marrow transplantation (BMT) from related donors, has now been completed. Enrollment totaled 132 patients and the last patient has completed treatment and the subsequent 100-day evaluation period. Another pivotal phase III trial is in progress in patients undergoing induction chemotherapy for acute myeloid leukemia, and a third pivotal trial is evaluating lisofylline in patients receiving ablative radiation and/or chemotherapy followed by BMT from unrelated donors (5).

Cell Therapeutics, in collaboration with the NIH's National Heart, Lung & Blood Institute, has announced its plans to evaluate lisofylline in patients requiring mechanical ventilation for acute lung injury. The primary objective of the pivotal phase II/III study will be reduction of mortality at 28 days. It will be conducted at 10 major U.S. medical centers through the NHLBI's Acute Respiratory Distress Syndrome network. An interim analysis of the trial, which is designed to include 800 patients altogether, will be conducted after the first 200 patients are enrolled (6).

The preliminary results from a phase III trial evaluating the safety and efficacy of lisofylline in patients with hematological malignancies undergoing bone marrow transplantation (BMT) from HLA-identical sibling donors have been reported. The preliminary endpoints of reduction in neutropenia-related infections and reduction in BMT treatment-associated mortality were not met in the trial, which may have been the result of using unusually aggressive treatment regimens in older patients who were randomized to the lisofylline arm of the study. In a previous phase II trial, the more intensive regimens were generally used only in younger patients with relapsed disease. Another 4-6 weeks are needed to complete analysis of the trial, and the results of this study could delay the company's previously anticipated filing of a New Drug Application. However, Cell Therapeutics plans to continue developing lisofylline for BMT and for induction chemotherapy in patients with acute myeloid leukemia (AML). Furthermore, trials under way in patients undergoing BMT from unrelated donors are not expected to be affected by these results (7).

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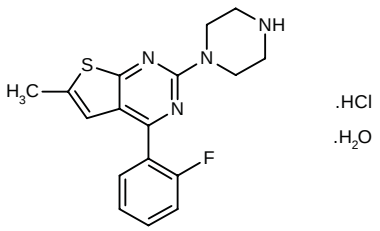
MCI-225

Cognition Enhancer
Antidepressant

EN: 172645



$C_{17}H_{17}FN_4S.HCl.H_2O$ **Mitsubishi Chem.**

The neurochemical profile of MCI-225 has been assessed in an *in vivo* microdialysis study in rats after doses of 10 and 30 mg/kg p.o. The results of this study suggested that the antidepressant effects of MCI-225 are mainly due to a selective increase in extracellular noradrenaline content and functional downregulation of β-receptors (1).

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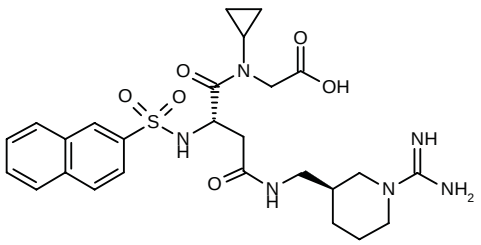
Napsagatran

Thrombin Inhibitor

EN: 213193



$C_{26}H_{34}N_6O_6S$ **Roche**

Using enzyme assay techniques, it was found that napsagatran was the most potent of a group of synthetic thrombin inhibitors, as well as being the most selective. However, it was shown to have a lower potency compared to recombinant hirudin, as a result of a higher dissociation rate constant (1).

In vitro testing using rat plasma showed that S205A-thrombin almost stoichiometrically inhibited napsagatran's anticoagulant effect. *In vivo* in rats, S205A-thrombin normalized the napsagatran-induced aPTT prolongation, an effect which lasted for 5 min (2).

The effects of Ro-46-6240, both alone and in combination with the gpIIb/IIIa antagonist Ro-44-9883, on the response to tissue-type plasminogen activator (t-PA) in a canine model of thrombolysis have been studied. Pretreatment with Ro-46-6240 (5-40 μg/kg/min) dose-dependently prolonged the activated partial thromboplastin and prothrombin times, decreased the time to reperfusion and delayed or prevented reocclusion. It also dose-dependently attenuated the increase in urinary excretion of 2, 3-dinor-TxB_2, the major metabolite of TxA_2. Combination of a subthreshold dose of Ro-46-6240 (5 μg/kg/min) with a dose of Ro-44-9883 (2 μg/kg/min), which abolished platelet aggregation but did not alter the response to t-PA, produced effects similar to higher doses of Ro-46-6240. The results suggest that thrombin is the major mediator of reocclusion during coronary thrombolysis and that such a combination may be useful for enhancing the response to thrombolytic therapy in acute myocardial infarction (3).

A randomized, sequential, dose-finding study was undertaken in 110 patients with acute proximal deep vein thrombosis. Treatment consisted of APTT-adjusted heparin or napsagatran (5 or 9 mg/h). Oral anticoagulation was begun on Day 2 and study drug was discontinued from Day 5. No statistically significant differences were observed in efficacy and adverse events among the three arms (4).

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Naratriptan
Amerge®
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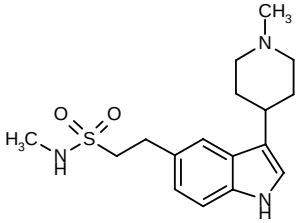
Antimigraine
5-HT_{1D} Agonist

EN: 148862



$C_{17}H_{25}N_3O_2S$ **Glaxo Wellcome**

Using electrophysiological assays (single unit recording from the trigeminal nucleus caudalis or from the spinal dorsal horn) in halothane-anesthetized rats, it was shown that naratriptan inhibited trigeminal responses to noxious stimuli (dural electrical and mechanical facial stimulation) but had no effect on the spinal dorsal horn nociceptive responses to noxious stimuli (mechanical) in intact spinal animals and in spinalized animals (1).

Results from studies in anesthetized cats have demonstrated that intravenously administered naratriptan acts on central trigeminal neurons at clinically relevant doses. Furthermore, as its inhibitory effect on neuronal activity in trigeminal neurons could be reversed by GR-127935, a relatively selective 5-$HT_{1B/1D}$ receptor antagonist, it appears that the antimigraine effects of this class of compound are mediated at least in part by 5-$HT_{1B/1D}$ receptors within the trigeminal nucleus (2).

Absolute oral bioavailability and the effects of gender on the pharmacokinetics of naratriptan were studied in 11 healthy males and 12 healthy females. C_{max} and AUC were lower in men by 34% and 35%, respectively, and the oral bioavailability of naratriptan (5 mg tablet) was higher in men (63% *vs.* 74% in women). These gender differences were not considered clinically significant (3).

The pharmacokinetic/pharmacodynamic effects of concurrent naratriptan (2.5 mg p.o.) and sumatriptan (6 mg s.c.) were studied in 12 healthy female subjects. No additive pressor response was seen when both drugs were given together, nor were there any changes in C_{max} or AUC in either drug. Adverse events were related to sumatriptan alone; naratriptan alone caused no more adverse events than placebo (4).

A randomized, double-blind, placebo-controlled, 4-way, crossover study of the pharmacokinetic/pharmacodynamic effects of naratriptan and dihydroergotamine coadministration was conducted in 12 healthy females. No significant interaction effect on blood pressure was observed with the 2 drugs, either together or administered 24 h apart (naratriptan given first). No safety issues arose. AUC and C_{max} values for naratriptan decreased by 15 and 20%, respectively, when given with dihydroergotamine, but this was of no clinical significance (5).

A randomized, open, 4-period, crossover study in 26 healthy female volunteers examining the pharmacokinetics of oral naratriptan tablets (2.5-10 mg) showed that C_{max}, AUC_{∞} and Ae_{24} varied linearly with dose, while $t_{1/2}$ and t_{max} did not vary over the dose range (6).

A randomized, double-blind, placebo-controlled, 4-way crossover trial in 10 healthy female volunteers was conducted to assess the interaction of naratriptan (2.5 mg p.o.) and ergotamine (1 mg p.o. with 100 mg caffeine). Ergotamine coadministration did not affect diastolic blood pressure and had no clinically significant effect on systolic blood pressure. Naratriptan pharmacokinetics were unaffected by ergotamine. No safety issues arose in the trial (7).

A double-blind, placebo-controlled, 4-way, crossover study in 12 healthy males who were given 2 identical tablets of naratriptan (1+1, 2.5+2.5 and 5+5 mg) and 2 identical placebo tablets separated by a 2-h interval showed that naratriptan had no clinically significant effect on blood pressure. Pharmacokinetics were linear, with a $t_{1/2}$ of more than 7 h being observed (8).

A review of several studies of naratriptan pharmacokinetics has been presented. Following intravenous administration, a 2-compartment model describes plasma profiles; systemic clearance is 24-30 l/h and 200 l is the approximate volume of distribution. Following oral naratriptan (5 mg), C_{max} is lower and oral clearance is greater in men than women (this has no clinical significance), $t_{1/2}$ is 6 h and t_{max} is 3 h. Urinary excretion accounts for 80% of naratriptan elimination (50% unchanged); renal clearance is 220 ml/min. Dose-proportional pharmacokinetics have been observed for doses of 2.5-10 mg (9).

A double-blind, placebo-controlled, crossover trial compared the acute effects of codeine (30, 60 and 90 mg p.o.) to naratriptan (1.0, 2.5 and 5.0 mg p.o.) in healthy volunteers who showed positive responses to hydromorphone 8 mg p.o. Using measures of subjective and objective effects, naratriptan produced positive effects of lesser magnitude than codeine, and greater negative effects than codeine (10).

Oral naratriptan pharmacokinetics was studied in an open, single-dose, parallel-group study of 8 subjects with moderate compensated liver disease and 8 matched controls. While C_{max} was the same in both groups, mean AUC and $t_{1/2}$ increased, and mean total clearance decreased in patients with liver disease. Four adverse events occurred; all were mild to moderate and resolved fully (11).

A randomized, open, crossover study in 11 men and 12 women examined the pharmacokinetics of naratriptan 1.5 mg as an i.v. infusion over 15 min, followed at least 4 days later by a 5 mg oral tablet. Naratriptan had a systemic clearance of 400-500 ml/min, a volume of distribution of 200 l and an elimination half-life of 6 h, with primarily renal clearance (proportion of systemic clearance was greater in women). In men, the AUC and C_{max} values were 34% and 35% lower, respectively (12).

An open, single-dose study of oral naratriptan was conducted in 15 male and female patients with renal impairment and in matched healthy volunteers. Healthy volunteers received 5 mg naratriptan, while patients with renal impairment received either 2.5 mg or 5 mg, depending on the degree of impairment. Analysis of clearance data showed that naratriptan clearance decreased with decreases in creatinine clearance and regression analysis revealed that formulae could be used to describe total and renal clearance. No serious adverse events occurred (13).

A randomized, double-blind, placebo-controlled, 4-period crossover study of naratriptan tablets (0.25, 1.0 and 2.5 mg) in 682 migraine patients (treating up to 4 attacks) showed that the optimal dose was 2.5 mg, with 68% of patients having headache relief at 4 h postdose. The adverse event profile was similar to that of placebo (14).

A randomized, double-blind, placebo-controlled study in 694 migraine patients treating a single migraine attack with oral naratriptan (0.1, 0.25, 1.0 and 2.5 mg) showed that 2.5 mg was the optimal dose based on headache relief, clinical disability and relief of nausea, phonophobia and photophobia. The adverse event profiles for naratriptan-treated groups were the same as for placebo treatment (15).

Treatment with naratriptan (2.5 mg tablets) for migraine attacks was studied in migraine patients over a 6-month period. Overall, headache relief was experienced within 4 h postdose in 68% of attacks, with a median percentage of attacks/patients treated for migraine recurrence of 7%. Naratriptan was well tolerated (16).

A randomized, placebo-controlled, crossover study examined the effect of naratriptan (1.5 mg s.c.) on myocardial perfusion in 34 migraine patients with no history or evidence of cardiac ischemia. PET was used to assess resting and dipyridamole-induced hyperemic myocardial blood flow following naratriptan administration. Although a statistically significant decrease in coronary vasodilator reserve was seen with naratriptan, this was not clinically significant (17).

A randomized, double-blind, placebo-controlled, 4-way, crossover study of 19 migraine patients examined the effects of naratriptan (1, 5 and 10 mg s.c.) on forearm blood flow. No significant effect was observed with any of the doses and the drug was well tolerated (18).

A randomized, double-blind, 2-attack, crossover study compared naratriptan (2.5 mg tablets) with sumatriptan (100 mg tablets) in the treatment of migraines in 264 patients. Both treatments were equally efficacious, but headache recurrence and adverse events were significantly less common with naratriptan (19).

Ten patients undergoing coronary angiography were administered naratriptan 1.5 mg subcutaneously. No significant changes in heart rate, ECG morphology or cardiac index were seen. Mean arterial and mean pulmonary artery pressures increased, but no change in coronary artery diameter occurred (20).

A randomized, placebo-controlled study examined the effect of naratriptan tablets (0.1, 0.25, 1.0 and 2.5 mg) on treating a single attack of migraine in 694 migraine patients. The greatest effect was observed for the 1.0 and 2.5 mg doses. With the 2.5 mg dose at 4 h postdose, headache relief, clinical disability scores of 0-1 and absence of nausea, phonophobia and photophobia were reported in 60-70% of patients. There was no significant difference in adverse events between drug-treated and placebo-treated groups, and no changes in laboratory tests were reported (21).

A randomized, placebo-controlled, 4-period, crossover study examined the effect of naratriptan tablets (0.25, 1.0 and 2.5 mg) in treating up to four migraine attacks in 740 migraine patients. Naratriptan 2.5 mg was significantly better than placebo at various times for relief of symptoms and clinical disability, and naratriptan 1.0 mg and 2.5 mg were effective for headache relief at 8, 12 and 24 h postdose. Adverse events were similar in placebo- and drug-treated groups, and no changes in laboratory findings were observed (22).

Naratriptan tablets (1.0, 2.5, 5.0, 7.5 and 10 mg) and sumatriptan tablets (100 mg) were compared in a randomized, placebo-controlled study for the control of one migraine attack in 643 migraine patients. Overall 24-h treatment success was greater for naratriptan (2.5, 7.5 and 10 mg) than sumatriptan, and fewer naratriptan patients (all doses) experienced headache recurrence. The incidence of adverse events was similar to placebo among patients treated with the 1.0 mg or 2.5 mg doses (23).

Oral absorption of naratriptan (2.5 mg) in 15 female migraine patients was compared during a migraine and during a migraine-free period. Pharmacokinetic analysis showed that C_{max}, AUC and $t_{1/2}$ were the same with and without a migraine, but t_{max} decreased during the migraine attack, likely due to delayed gastric emptying. No serious adverse events occurred, and no clinically significant changes were found in laboratory values, physical examination, vital signs or ECG (24).

A randomized, double-blind, placebo-controlled, parallel-design study was performed in 127 migraine patients who were given a single oral dose of naratriptan (0.25, 1.0 or 2.5 mg) or placebo for an acute migraine episode. Oral clearance decreased with age and hormone contraceptive use, and increased with tobacco use and in some blacks. Volume of distribution increased with body weight and in blacks, and was lower with hormone contraceptive use. None of these effects required dosage adjustment and all doses of the drug were well tolerated (25).

In a study to assess the tolerability and efficacy of oral naratriptan (2.5 mg taken at migraine onset, repeated 4-24 h later if needed for recurrence) treatment over a 12-month period, it was found that 14,953 migraine attacks occurred. Of these, 417 patients had at least 1 attack, 253 patients treated attacks over 12 months, and 185 patients had more than 36 attacks. In 70% of all attacks, relief was obtained within 4 h, with a recurrence rate of 8%. The drug was well tolerated, with a good or excellent rating being given in 64% of all attacks treated (26).

A double-blind, placebo-controlled, 4-period, crossover study in 682 migraine patients examined the effect of various doses of naratriptan (0.25, 1.0 and 2.5 mg) and placebo in treating up to 4 migraine attacks. The largest percentage of patients getting headache relief within 4 h was 68%, occurring with naratriptan 2.5 mg (statistically significant compared to placebo and other doses). Both naratriptan 2.5 mg and 1.0 mg showed a significant improvement over placebo for relief at 8, 12 and 24 h. There was no difference in adverse events between drug- and placebo-treated groups (27).

A randomized, double-blind, placebo-controlled, 44-center, parallel-group study of oral naratriptan (0.25, 1.0 and 2.5 mg) in 300 adolescent migraine patients showed that active drug was not significantly different from placebo in the acute treatment of a single migraine attack. Adverse events were more common in drug-treated groups than in the placebo group, with nausea/vomiting being the most frequently reported event (28).

Two open, single-dose studies examined oral naratriptan pharmacokinetics in patients with renal impairment, hepatic impairment and matched healthy controls. Healthy subjects in the renal study received 5 mg, while renally impaired patients received either 2.5 or 5 mg, depending on renal status. All patients in the hepatic study received 2.5 mg. C_{max} remained the same in all subjects, while AUC and $t_{1/2}$ increased in both renally and hepatically impaired subjects. Clearance decreased in renal impairment proportionally with the creatinine clearance; no relationship for the clearance decrease in hepatic impairment could be found. All adverse events were mild or moderate and resolved completely (29).

A randomized, double-blind, placebo-controlled, parallel-group study in 613 migraine patients who treated one attack with naratriptan tablets (0.1, 0.25, 1 or 2.5 mg) or placebo showed that the most effective dose in relation to headache relief, clinical disability and absence of nausea, phonophobia and photophobia at 4 h was 2.5 mg ($p < 0.05$). Adverse events were the same in all groups and there were no clinically significant changes in any of the safety measures (30).

An open-label study, using naratriptan 2.5 mg tablets for all migraine attacks in 414 patients over a 6-month period, showed that 68% of 6770 moderate to severe migraine attacks were relieved within 4 h, with a median number of 1 tablets used. Naratriptan was rated good/excellent in 61% of treated attacks. Nausea was the most frequent adverse event; only 5 patients decreased the dose to 1 mg as a result of adverse events (31).

A 2-part, placebo-controlled, population PK/PD study with 142 patients showed that oral naratriptan tablets showed decreased absorption during migraines. Using a logit model for headache relief, half the maximum time effect occurred at 4 h, CE_{50} was 30 ng/ml and the equilibration half-life was 0.5 h. Clearance and distribution volume were moderately affected by age, body weight, smoking and oral contraceptive use (32).

A multicenter, double-blind, randomized, parallel-group trial in 694 patients diagnosed with migraine has compared treatment with naratriptan (0.1, 0.25, 1.0 or 2.5 mg as tablets) and placebo for a single migraine attack. At 4 h postdose, headache relief (reduction in migraine pain severity) was obtained in 60, 50, 35, 32 and 34% of patients on naratriptan 2.5, 1.0, 0.25 and 0.1 mg and placebo, respectively, and 70, 63, 47, 48 and 48% of patients, respectively, reported mild or no clinical disability at this time. Efficacy rates as regards absence of nausea, photophobia and phonophobia at 4 h were similar to those for headache relief. Side effects were similar in all groups. The results indicate that a dose of 2.5 mg naratriptan is associated with the highest antimigraine efficacy and is well tolerated (33).

Naratriptan (Naramig™) has been launched by Glaxo Wellcome in the U.K. for the acute treatment of the headache phase of migraine attacks with or without aura. It is supplied as tablets, 2.5 mg (34).

Glaxo Wellcome has launched naratriptan hydrochloride (Amerge®) in the U.S. The product offers a new choice for patients with migraines of long duration, those who experience migraine recurrence and those who have tolerability problems with other migraine therapies (35).

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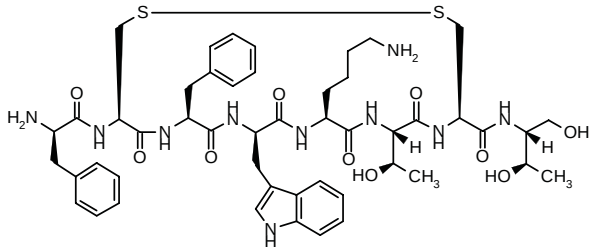
Octreotide
Sandostatin®

Antineoplastic
Antipsoriatic
Antidiarrheal

EN: 120090



$C_{49}H_{66}N_{10}O_{10}S_2$ **Novartis**

In a study analyzing 217 patients treated either with placebo or octreotide beginning 1 h before angioplasty and continuing for 3 weeks, it was shown that octreotide had no effect on minimal luminal diameters, restenosis rates and the incidence of clinical events. Gastrointestinal side effects were 3 times as common in the octreotide-treated group as compared to placebo (1).

The Montefiore Medical Center has announced that a new clinical study is now under way for the evaluation of octreotide acetate in comparison to loperamide as a potential treatment for severe, chemotherapy-induced diarrhea. Patients with cancer of the colon or rectum who are currently undergoing chemotherapy with 5-fluorouracil and who suffer from severe and debilitating diarrhea, will be treated with low-dose (150 µg x 3/day) or high-dose (1500 µg x 3/day) octreotide or with loperamide, the existing standard treatment for chemotherapy-induced diarrhea (2).

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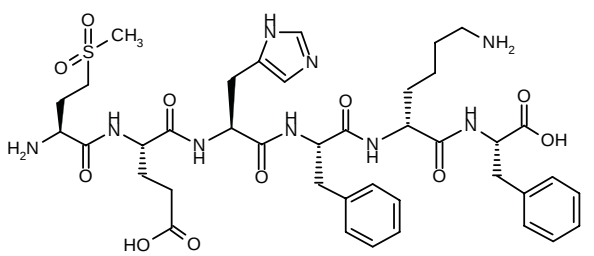
Org-2766

Neuroprotectant

EN: 090199



$C_{40}H_{55}N_9O_{11}S$ **Organon**

A randomized, multicenter, double-blind, placebo-controlled study examined the efficacy of Org-2766 in the prevention of cisplatin-induced neuropathy in 196 women with advanced ovarian carcinoma being treated with cisplatin (75-100 mg/m^2) and cyclophosphamide (600-1000 mg/m^2). On the basis of serial measurements of vibration perception threshold, Org-2766 was not found to be protective, and, in fact, the rate of change and degree of neuropathies appeared to increase by its administration (1).

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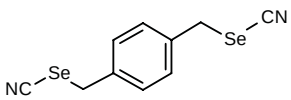
p-XSC

Antineoplastic

EN: 235940



$C_{10}H_8N_2Se_2$ **American Health Found. (US)**

When given as a dietary supplement, *p*-XSC (10 and 30 ppm) decreased the rate of 4-NQO-induced tongue squamous cell carcinoma development in rats both during (77% and 91% decreases at 10 and 30 ppm, respectively) and following 4-NQO administration (91% and 100% at 10 and 30 ppm, respectively). Cell proliferation biomarkers were also suppressed (1).

Using groups of 5-week old male F344 rats injected with azoxymethane (15 mg/kg, 2 injections 1 week apart) or saline, and fed either high- or low-fat diets, with or without *p*-methoxy-BSC or *p*-XSC for 38 weeks, it was shown that both agents were effective as chemoprotection for colon cancer. The effects of *p*-XSC were greatest with a low-fat diet (2).

Using a DEN-PB-induced hepatocarcinogenesis model in rats, *p*-XSC was shown to significantly decrease the development of liver tumors, with significantly smaller glutathione *S*-transferase placental form positive foci and smaller liver tumors observed over the 24-week experimental period (3).

Using a lung tumor model in female A/J mice, it was found that *p*-XSC inhibited NNK-induced lung tumor multiplicity and DNA-oxidative damage. These results indicate that *p*-XSC acts as a suppressing agent for lung neoplasia induced by tobacco-specific carcinogens (4).

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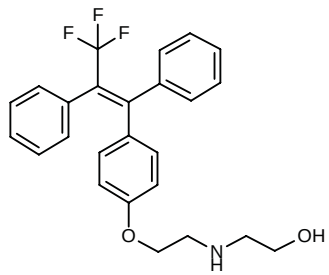
Panomifene

Antineoplastic
Antiestrogen

EN: 090524



$C_{25}H_{24}F_3NO_2$ **Egis Pharm.; Fujimoto**

The *in vitro* metabolism of panomifene was compared using liver microsomes from dogs, rats, mice and humans. Side chain modifications and hydroxylations were the metabolic transformations seen, but there were some clear species differences; 3 metabolites were produced exclusively by dog microsomes, and human microsomes were the only ones to produce an oxidized form with a double side chain bond (1).

The clinical pharmacokinetics, tolerability and endocrine effects of panomifene have been profiled in a phase Ia trial. Thirteen postmenopausal female volunteers received single oral doses of the compound (24, 48, 96 or 120 mg). At the selected dose of 24 mg p.o., peak plasma concentration was 67.7 ± 17.4 ng/ml and time to peak was 3.6 ± 1.8 h. Mean terminal half-life was 70.0 ± 23.1 h. Nine of 10 volunteers tolerated the drug well at all doses tested, with only 1 subject complaining of abdominal pain at the highest dose level (2).

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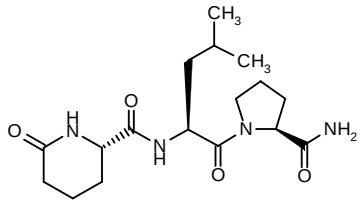
Original monograph - Drugs Fut 1985, 10: 395.

Posatirelin
Pyladox®

Cognition Enhancer

EN: 113576



$C_{17}H_{28}N_4O_4$ **Gedeon Richter; Dainippon; Poli Ind. Chim.**

Posatirelin (10 mg/kg/day) was given for 4 and 8 weeks to rats subjected to monolateral and bilateral nucleus basalis magnocellularis lesions. Drug treatment had no effect on the quantity of nerve cell profiles or of glial fibrillary acidic protein-immunoreactive astrocytes following surgery. Posatirelin did increase silver-gold impregnated fibers in the hippocampus and partially restored choline acetyltransferase immunoreactivity and frontal cortex acetylcholinesterase reactivity following 8 weeks of treatment after surgery (1).

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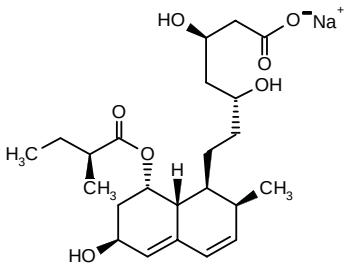
Pravastatin Sodium
Pravachol®

Hypolipidemic
HMG-CoA Reductase Inhibitor

EN: 103471



$C_{23}H_{35}NaO_7$ **Sankyo; Bristol-Myers Squibb**

A retrospective, blinded chart review of all cerebrovascular events occurring in patients in the Cholesterol and Recurrent Events (CARE) study was done. It showed that pravastatin significantly reduced stroke incidence by 32% ($p = 0.03$) and stroke or transient ischemic attack incidence by 27% ($p = 0.02$) following myocardial infarction in patients who had average cholesterol levels (1).

Pravastatin sodium (Pravachol®) has been approved by Health Canada for the new use of preventing a first heart attack in at-risk adults with high cholesterol levels but with no history of heart disease (2).

The U.S. FDA has cleared a significant new indication for Bristol-Myers' pravastatin sodium (Pravachol®) for use in reducing the risk of stroke or transient ischemic attack (TIA) in patients who have had a heart attack and have normal cholesterol levels, and to reduce the risk of a recurrent heart attack and death from heart disease in this patient population. This marks the first time that the FDA has cleared an HMG-CoA reductase inhibitor for use in reducing the risk of stroke; it is also the first time that a statin has been approved in the U.S. for reducing the risk of heart attack and death from heart disease in patients with normal cholesterol levels (3).

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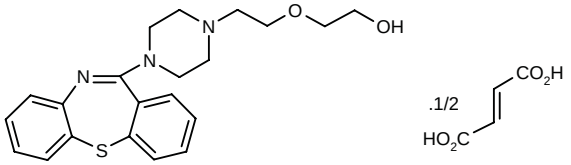
3. *FDA clears pravastatin for stroke prevention.* Prous Science Daily Essentials March 31, 1998.

Original monograph - Drugs Fut 1987, 12: 437.

Quetiapine Fumarate
Seroquel®

Antipsychotic
5-HT$_2$ Receptor Antagonist
Dopamine D$_2$ Antagonist

EN: 186731



$C_{21}H_{25}N_3O_2S.1/2C_4H_4O_4$ **Zeneca**

In a multicenter, open-label trial in 151 elderly psychotic patients, quetiapine (25-800 mg/day) was shown to be safe and tolerable across the dosage range. The most frequent side effects were somnolence, dizziness and postural hypotension; 5 patients dropped out due to adverse events. Hematology, clinical chemistry, ECGs and vital signs were not significantly affected (1).

A multicenter, double-blind, placebo-controlled trial of 286 hospitalized schizophrenic patients (chronic/subchronic) compared the efficacy of quetiapine (≤ 250 mg/day and ≤ 750 mg/day) treatment for 6 weeks. Of the 280 evaluable patients, 159 dropped out because of treatment failure. High-dose quetiapine showed a significant improvement in reducing positive symptoms, but its effect on negative symptoms was not as consistent. Quetiapine was well tolerated, did not induce extrapyramidal symptoms and had no clinically significant effects on serum prolactin and hematology values (2).

A double-blind, placebo-controlled trial in 361 chronic schizophrenic patients suffering acute exacerbations compared treatment with quetiapine (75, 150, 300, 600 or 750 mg/day) and haloperidol (12 mg/day). High doses of quetiapine (150-750 mg/day) were significantly better than placebo in relation to positive symptoms, and 300 mg/day was seen to be better regarding negative symptoms; no differences were seen compared to haloperidol. No safety concerns were observed; extrapyramidal symptoms and changes in serum prolactin in quetiapine-treated patients were no more frequent than in placebo-treated patients (3).

The efficacy and tolerability data on quetiapine from five phase II/III trials have been reviewed. In these 6-week, multicenter, double-blind, randomized trials, quetiapine was compared to placebo, haloperidol or chlorpromazine in patients with acute exacerbations of chronic schizophrenia. Quetiapine was associated with significantly greater improvement in both positive and negative symptoms compared to placebo as evaluated on the BPRS and PANSS rating scales, and assessment using the CGI scale confirmed its clinical efficacy. It was shown to be at least as effective as haloperidol and chlorpromazine. The drug was effective over the dose range of 150-750 mg/day and could be given twice daily (4).

The FDA has granted approvable status for Zeneca's Seroquel™ for the treatment of schizophrenia (5).

Zeneca launched Seroquel™ (quetiapine fumarate) on September 22, 1997 in the U.K. It is supplied as tablets of 25, 100 and 200 mg (6).

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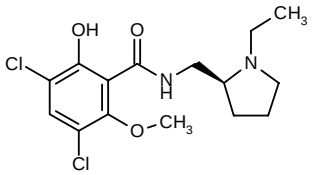
Raclopride

Antipsychotic
Dopamine D_2 Antagonist

EN: 100338



$C_{15}H_{20}Cl_2N_2O_3$ **Astra**

PET scans using [^{11}C]-raclopride were taken before and after administration of ketamine (0.5 mg/kg i.v. infusion over 20 min) to 7 male controls. Cortisol levels increased and dopamine receptor availability was decreased in the striatum, but remained unchanged in the cerebellum. Subtraction of cerebellar binding from striatal binding decreased significantly following ketamine infusion. Thus, ketamine increases striatal dopamine concentrations, demonstrating the role of the NDMA receptor in dopamine function modulation (1).

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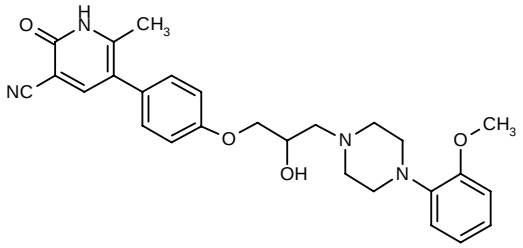
Saterinone

Positive Inotropic Agent
Phosphodiesterase III Inhibitor

EN: 117231



$C_{27}H_{30}N_4O_4$ **Beiersdorf**

A double-blind, placebo-controlled study of saterinone was conducted in 36 patients with moderate to severe heart failure. Saterinone significantly lowered systemic vascular resistance, systemic blood pressure and pulmonary capillary wedge pressure. Heart rate increased and cardiac index was unchanged. Norepinephrine, epinephrine and renin activity were not affected and heart rate variability analysis showed no effect on autonomic tone (1).

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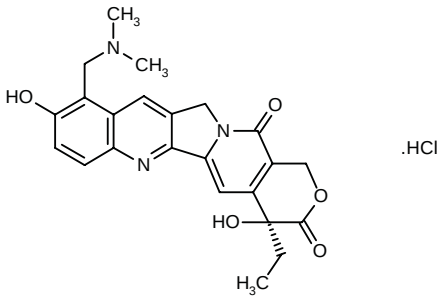
Topotecan Hydrochloride
Evotropin®
Hycamtin®

Antineoplastic
Topoisomerase Inhibitor

EN: 149556



.HCl

$C_{23}H_{23}N_3O_5$.HCl **SmithKline Beecham**

A panel of 6 pediatric neuroblastoma xenografts was used to determine topotecan activity and minimum effec-

tive dose levels to induce complete responses (CR) and partial responses (PR). Doses of 2.0, 1.0, 0.61 and 0.36 mg/kg/day were given using a [(dx5)2]3 schedule. With 0.61 mg/kg (AUC 88 ng.h/ml), there were 4 CR and 1 PR, while with 0.36 mg/kg (AUC 52 ng.h/ml) 3 CR and 1 PR were seen (1).

The pharmacodynamics of cisplatin (35, 50, 75 or 100 mg/m^2 on day 1) and continuous topotecan infusion (0.4 or 0.5 mg/m^2/day x 14 days) were studied in a phase I trial in 26 patients with advanced cancer. The nadir neutrophil count (ANCn) could be related to the median steady-state topotecan concentration (T_{ss}) as follows: log(ANCn) = 10.0 - 1.43 x T_{ss} - 0.03 x cisplatin dose. The results indicate that monitoring T_{ss} appears to be of no clinical relevance (2).

A phase I trial evaluated the combination of cyclophosphamide (40 mg/kg over 1 h on day 1) and continuous topotecan infusion (1.5 or 1.8 mg/m^2 i.v. over days 2-6) in 14 patients with refractory or relapsed leukemia (11 AML, 2 CML-B, 1 ALL). Complete recovery of normal hematopoiesis was seen in 3 AML patients, and 3 AML patients showed complete marrow tumor clearance but failed to achieve full recovery. Dose-limiting toxicity occurred in 2 cases (liver failure, grade 4 mucositis). Further study with dose escalation continues (3).

A phase I pharmacokinetics study performed to develop treatment schedules for oral topotecan which provide prolonged exposure examined schedules administering topotecan once daily for 5 days, once daily for 10 days, twice daily for 10 days and twice daily for 21 days. Toxicity appeared to be related to the schedule used rather than AUC per course. Pharmacokinetic and safety analyses could not identify any schedule as preferable, although the once daily for 5 days schedule was preferred for patient convenience (4).

An open-label, multicenter, phase II study in 20 women with advanced breast cancer failing first-line therapy showed a 10% response rate to topotecan 1.5 mg/m^2/day given as a 30-min infusion for 5 days every 3 weeks. Stable disease was seen in 8 patients. Hematologic toxicity was reversible, and no sequelae resulted from nonhematologic adverse events, which were usually mild. The authors recommended a longer treatment period before response evaluation (5).

Two open-label, noncomparative, phase II studies in 34 women with advanced breast cancer failing first-line therapy were conducted. No complete or partial responses were seen with either topotecan 22.5 mg/m^2 as a 30-min infusion every 3 weeks (median number of courses per patient was 2.5) or topotecan 1.5 mg/m^2 as a 24-h infusion every week (median number of courses per patient was 2.0). Thus, no efficacy was shown with these regimens (6).

To decrease systemic exposure variability to topotecan in children with normal kidney and liver function, 8 children with solid tumors were given 30-min infusions of topotecan daily for 5 consecutive days for 2 weeks every 4 weeks, starting at 1.4 and 2.0 mg/m^2/day. The dose was then adjusted to achieve a target lactone single day AUC of 150 ± 30 ng.h/ml using a 2-compartment model for pharmacokinetic analysis. AUC variability was reduced using this method (7).

A phase II study of topotecan as a continuous low-dose infusion at a dosage range of 0.4-0.6 mg/m^2/day for 21 days was conducted in 11 patients with small cell lung cancer as a second-line therapy. Substantial interpatient and intrapatient variability in systemic exposure to topotecan was observed. The most important toxicity was myelosuppression. Three partial responses were seen with durations of 10, 16 and 18 weeks (8).

A case report of a 6-year old epileptic boy with newly diagnosed high-risk medulloblastoma treated with topotecan (using target lactone AUC to adjust the dose) showed that topotecan clearance was increased by 30% with concurrent phenytoin administration ($p < 0.05$) This finding suggests that topotecan may be metabolized by hepatic oxidation (9).

In a phase II study, topotecan (0.5 mg/m^2/day continuous infusion escalated until at least grade 2 toxicity was seen) was given to 26 patients with metastatic colorectal cancer. The overall response rate was 8% of entered patients. Toxicities were hematological, infection, nausea, phlebitis, diarrhea and gastrointestinal (10).

A phase II trial of topotecan (1.5 mg/m^2/day x 5 days every 3 weeks) was conducted in 46 patients with advanced urothelial cancer failing one previous chemotherapy regimen. The anticipated toxicity was seen with no treatment-related deaths. The response rate was 10% (all partial responses), with a median response duration of 16 weeks. Overall, topotecan had little activity in previously treated urothelial carcinoma (11).

A randomized phase II trial is underway comparing standard topotecan (1.5 mg/m^2 i.v. over 30 min daily x 5 days every 3 weeks) to topotecan 1.75 mg/m^2 over 24 h weekly every 6 weeks in patients with previously treated epithelial ovarian cancer. At the time of reporting 68 patients had been entered; 33 were evaluable for response and 38 for toxicity. Thus far, usual toxicities have occurred, and the overall response rate was 12%. When the number of evaluable patients reaches 60, the response rate for each treatment arm will be calculated (12).

Independent radiological review was conducted for claimed responders in 422 patients with advanced ovarian cancer who had failed earlier chemotherapy (platinum and paclitaxel) and were treated with topotecan (1.5 mg/m^2/day as a 30-min infusion x 5 days every 3 weeks). On review of the radiographs and scans, response was confirmed in 66/95 claimed responses, reducing the overall response rate from 23% to 16% (13).

A study of topotecan (1.25 mg/m^2/day, 30-min infusion x 5 days every 3 weeks) in 11 heavily treated ovarian cancer patients was conducted, without hematopoietic growth factors support or dosage adjustment. Dose escalation to 1.5 mg was possible in 5 patients, with only 10% of cycles delayed due to hematotoxicity. Of 8 evaluable patients, 2 had partial response and 4 stable disease (14).

Topotecan (starting at 0.4 mg/m^2/day c.i.v. every 28 days) is being studied in a phase II trial in 29 patients with recurrent progressive high grade gliomas. So far, objective responses were seen in 11.5%, stable disease in 4% and progressive disease in 61%. Severe toxicities included granulocytopenia (11.5%), infection (7.7%), anemia

(7.7%), nausea/vomiting (7.7%), leukopenia (3.8%), fever (3.8%) and diarrhea (3.8%). The results suggest that combination therapy of topotecan with radiotherapy or other agents warrants study (15).

In a phase II trial, topotecan (1.5 mg/m^2/day, 30-min infusion every 3 weeks) was studied in 35 patients with stage IIIB or IV squamous cell lung cancer with no previous chemotherapy. Partial remission was seen in 24.1%, minor response in 6.9%, stable disease in 13.8% and progressive disease in 55.2%, with an overall median survival of 40 weeks. Grade 3-4 toxicities included granulocytopenia (74% of treatment cycles) and thrombocytopenia (12% of treatment cycles). No deaths occurred from toxicity (16).

A multicenter, phase II study examined topotecan (starting at 0.5 or 0.6 mg/m^2/day c.i.v. x 21 days every 28 days) in 26 patients with non-small cell lung cancer. One partial response for 7 months was seen, as well as 6 stable disease and 19 progression of disease. A 1-year survival of 39% and a median survival of 9 months were calculated. A decrease in cancer-related symptoms was observed; 40% of 58 baseline symptoms resolved by the end of best response. Grade 3-4 hematotoxicities included grade 4 neutropenia (1% of courses), grade 4 thrombocytopenia (2% of courses) and grade 3-4 anemia (8% of courses) (17).

A randomized, two-stage, phase II study compared topotecan (1.25 mg/m^2 x 5 days) combined with cisplatin (75 mg/m2 on day 1) to topotecan (1.0 mg/m^2 x 5 days) combined with taxol (190 mg/m^2 on day 1) in 83 patients with advanced non-small cell lung cancer. Treatment cycles were 28 days long, and filgrastim was used in both arms to ameliorate leukopenia. Excessive toxicity and inadequate activity led to early closure of the cisplatin arm. Estimated 1-year survivals were 18% with taxol and 26% with cisplatin. Severe thrombocytopenia was seen in 76% of cisplatin/topotecan-treated patients, as compared to only 1.6% in the taxol/topotecan group. Since efficacy was no better than current regimens, neither regimen warrants further study (18).

Intravenous topotecan (starting at 2.0 mg/m^2/day to 2.4 mg/m^2/day x 5 days every 3 weeks) was given to 40 patients (under 21 years of age) with newly diagnosed nonparameningeal metastatic rhabdomyosarcoma. Granulocyte-colony stimulating factor was given for neutrophil support when needed to raise the absolute neutrophil counts to more than 5000/µl. Complete response was seen in 2 patients and partial response in 16 patients, for an overall response rate of 45% (19).

A phase II study of topotecan (2.0 mg/mg^2 i.v. daily x 5 given over 30 min every 3 weeks) was performed in 150 pediatric patients with relapsed/resistant solid tumors. Granulocyte-colony stimulating factor was given only if neutropenia with fever developed after the first course or if cycles were postponed. No response was seen in 90 patients, partial response in 8, stable disease in 21 and mixed response in 1; neuroblastoma was particularly responsive. Myelosuppression was the main side effect (20).

Topotecan (i.v. over 30 min 5 days a week for 2 consecutive weeks) was given to 8 pediatric patients with relapsed solid tumors, with dose adjustment to reach a target topotecan lactone systemic exposure of 150 ± 30 ng.h/ml; the target was reduced to 100 ng.h/ml due to dose-limiting hematologic toxicity. Of the 4 patients with objective responses, 3 had a greater than 50% reduction in tumor volume and 1 had a greater than 75% reduction (21).

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Toremifene
Estrimex®
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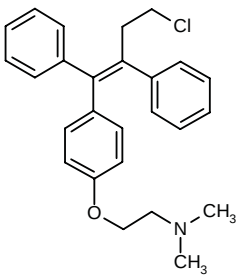
Antineoplastic
Antiestrogen

EN: 109868



$C_{26}H_{28}ClNO$

Farmos; Adria; Asta; Nippon Kayaku; Schering-Plough

Schering-Plough has received FDA clearance to market toremifene citrate (Fareston®) as first-line treatment of metastatic breast cancer in postmenopausal women with estrogen receptor-positive or receptor-unknown tumors (1).

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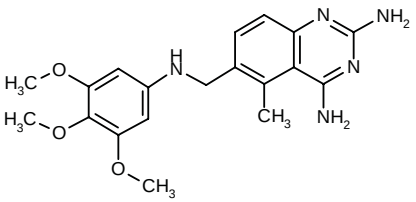
Trimetrexate

Antineoplastic

EN: 090194



$C_{19}H_{23}N_5O_3$

Warner-Lambert; Dainippon; U.S. Bioscience

A pharmacokinetic study of the oral bioavailability of oral trimetrexate (10 mg/m^2/day given b.i.d. x 5 days, repeated every 2 weeks) was conducted in 33 patients. Liquid and tablet mean AUCs were 1.95 ± 1.14 and 2.47 ± 0.76 μm.h/l, respectively, with a tablet/liquid AUC ratio of 1.17 in 11 matched samples. Stable disease (10-56+ weeks) was seen in 8 patients. Good oral bioavailability of the tablet preparation was demonstrated, but efficacy at the dose used remains to be established (1).

Final results of a trial in previously treated colorectal cancer patients of sequential trimetrexate (escalated in 30 mg/m^2, 30-min infusion), followed 24 h later by fluorouracil (500 mg/m^2) and high-dose leucovorin (500 mg/m^2), then an oral leucovorin dose of 10 mg/m^2 for trimetrexate rescue 6 h later showed excellent survival results: partial response rate of 20%, median survival of 14 months, 57% 1-year survival, median time to progression 6.3 months and median survival in 8 partial responders of 14.5 months (2).

The combination of weekly trimetrexate (110 mg/m^2), 5-FU (500 mg/m^2), leucovorin (200 mg/m^2), with oral leucovorin later as needed for 4-6 weeks followed by 2 weeks of rest was given to 17 patients with pretreated advanced colorectal carcinoma by community physicians. Overall partial response rate was 35%, with the regimen being well tolerated. No treatment-limiting gastrointestinal or hematological toxicities were observed. Symptoms similar to histamine release were experienced by 4 patients, but antihistamine pretreatment controlled the symptoms in 3 of the patients (3).

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Antibacterial
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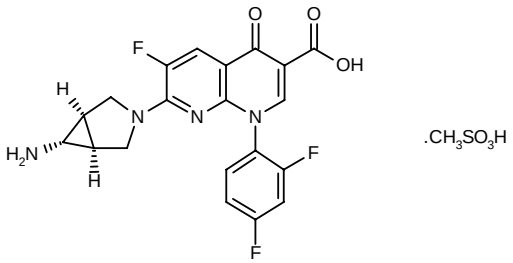

$C_{20}H_{15}F_3N_4O_3.CH_4O_3S$

Pfizer

In an *in vitro* study, using a meningitis model in rabbits, trovafloxacin was bactericidal to a penicillin-resistant (4 and 4 μg/ml, MIC and minimum bactericidal concentration, respectively) strain of *Streptococcus pneumoniae*. Results when used in combination with ampicillin or rifampin were indifferent (1).

A study of the *in vitro* activity of trovafloxacin against *Bacteroides fragilis* showed that it was bactericidal; had a lower MIC_{90} than ciprofloxacin, ofloxacin and sparfloxacin; was more active than cefoxitin, chloramphenicol, clindamycin, metronidazole, imipenem and ornidazole; and showed a postantibiotic effect against 2 strains (2).

Using NCCLS recommended broth microdilution, trovafloxacin activity against 590 clinical isolates of anaerobic bacteria was tested. Overall, trovafloxacin was comparable to metronidazole, with concentration-dependent bactericidal activity. Different pHs, inoculum sizes and increased protein concentration had little effect on trovafloxacin activity (3).

A study of the efficacy of 3-day oral trovafloxacin against 2 strains of ciprofloxacin-susceptible, methicillin-resistant *Staphylococcus aureus* experimental endocarditis in rats showed that the drug was bactericidal against both strains. Once-daily oral trovafloxacin was at least as effective as intravenous vancomycin, with no *in vivo* or *in vitro* selection of resistant strains (4).

In a time-kill study, trovafloxacin was found to have the lowest bacteriostatic concentrations against 6 anaerobic bacteria, compared to ciprofloxacin, sparfloxacin, metronidazole, cefoxitin, piperacillin and piperacillin/tazobactam (5).

Using an agar dilution method, trovafloxacin activity against 1132 isolates from 952 hospitalized patients suffering from nosocomial infections was evaluated. Trovafloxacin showed greater activity than ciprofloxacin, norfloxacin, penicillins, cephalosporins and aminoglycosides against both Gram-negative and Gram-positive organisms (6).

Trovafloxacin MICs determined by the standard microdilution broth method were found to be 1-2 dilutions lower than those found using the Etest for Gram-positive

and Gram-negative bacteria. Compared to ciprofloxacin and ofloxacin, trovafloxacin was the most active against Gram-positive bacteria and *Citrobacter freundii*, *Proteus mirabilis*, *Proteus vulgaris*, *Morganella morganii* and *Serratia marcescens*. Against other Gram-negative bacteria, trovafloxacin was at least as effective. Trovafloxacin also showed synergy with other antibiotics (gentamicin, ampicillin/sulbactam) against *Enterococcus faecium* and *Enterococcus faecalis* (7).

An *in vitro* study of trovafloxacin activity against a range of recent clinical isolates showed that it has a broad spectrum of activity, and is more active than ofloxacin and ciprofloxacin against clinically important Gram-positive bacteria (8).

Looking at a number of studies it can be seen that trovafloxacin has excellent *in vitro* activity against both penicillin-sensitive and penicillin-resistant *Streptococcus pneumoniae*. Trovafloxacin also shows a high level of activity in the mouse pneumonia and rabbit meningitis models (9).

In a comparison of activity against Gram-positive bacteria using an agar dilution technique, trovafloxacin was found to be the strongest antibiotic against staphylococci and showed 4-8 times greater activity than ciprofloxacin against streptococci. Good activity was seen against vancomycin-susceptible *Enterococcus faecalis* and *Enterococcus faecium*, with less activity against vancomycin-resistant strains. In time-kill studies, trovafloxacin was at least as good as amoxycillin against *Streptococcus milleri* and viridans group streptococci (10).

In a study of trovafloxacin's *in vitro* activity against *Chlamydia trachomatis*, it was found that all 19 strains tested were sensitive; IR_{90} was 0.05 ± 0.07 mg/l, compared to 0.17 ± 0.07 mg/l for erythromycin, 0.10 ± 0.03 mg/l for doxycycline and 0.35 ± 0.15 mg/l for ofloxacin (11).

In 4 of 6 strains of *Pseudomonas aeruginosa* tested, trovafloxacin, at concentrations of 0.5, 1, 2 and 4X MIC, was found to have a postantibiotic effect lasting for 0.3-2.3 h. The duration of the effect was longer with increased trovafloxacin concentration and increased exposure time (12).

Using agar dilution techniques, trovafloxacin, ofloxacin and ciprofloxacin MICs for 296 clinical isolates (many of which were ciprofloxacin-resistant) were determined. Overall, trovafloxacin showed the greatest activity against the isolates, particularly against Gram-positive bacteria and various nonfermenters. Trovafloxacin, at an MIC of at least 8 ig/ml, was effective against 56-70% of staphylococci that were highly resistant to ciprofloxacin (13).

Using standard microdilution techniques, MICs for trovafloxacin, ciprofloxacin, imipenem and ceftazidime were determined against 496 bacterial isolates from pediatric patients. Against Gram-positive pathogens, trovafloxacin was the most active, while against Gram-negative pathogens it showed greater activity than ceftazidime and similar activity to the other two antibiotics evaluated (14).

Using agar dilution techniques, the activity of trovafloxacin and 32 other antibiotics was tested against more than 9000 clinical isolates. Against all 25 *Streptococcus pneumoniae* tested, trovafloxacin had the highest activity (MIC_{90} = 0.5 ig/ml); it similarly had the lowest MIC_{90} against methicillin-resistant *Staphylococcus aureus* (15).

The *in vitro* activity of trovafloxacin against 382 enteropathogens (including *Salmonella* spp., *Shigella* spp. and *Viridans cholerae*) was evaluated using agar dilution. Trovafloxacin showed high activity against all of the enteropathogens tested (16).

The *in vitro* activity of trovafloxacin against 4 virulent strains of *Listeria monocytogenes* was evaluated. Using the human colon carcinoma, enterocyte-like cell line Caco-2 (ATCC HTB 37) to evaluate intracellular bactericidal effect, trovafloxacin was shown to begin reducing intracellular bacteria at 2 h (by 1-2 logs) and completely eradicate them within 24 h (3 strains) or reduce them by 3 logs (1 strain) (17).

In vitro activity of trovafloxacin and levofloxacin against *Legionella pneumophila* was evaluated using vero cells infected with 1,000,000 CFU of *Legionella*. Significant intracellular killing was seen and both antibiotics were highly effective (18).

Trovafloxacin's *in vitro* activity, alone and in combination with cefepime or cefoperazone, was assessed against 6 isolates of *Pseudomonas aeruginosa* from the respiratory tract. An NCCLS described saline microdilution technique was used and time-kill studies were performed. Synergy was seen with the combinations of trovafloxacin and cefepime (4 strains) and trovafloxacin and cefoperazone (5 strains). An additive effect was seen with the remaining strains (19).

A study of the *in vitro* susceptibilities of 12 strains of *Chlamydia pneumoniae* to trovafloxacin, ofloxacin, doxycycline, erythromycin and azithromycin revealed that the activity of trovafloxacin was equivalent to that of ofloxacin (MIC_{90} = 1.0 μg/ml). However, doxycycline, erythromycin and azithromycin were all more active than trovafloxacin (20).

The *in vitro* activity of trovafloxacin was compared to that of other agents against bacterial isolates from patients with severe intraabdominal sepsis. Of the 438 strains tested, 435 were inhibited by trovafloxacin at concentrations ≤ 2 μg/ml. Trovafloxacin showed similar activity against *Enterobacteriaceae* and *Pseudomonas* as the other quinolones tested, but was superior against streptococci, enterococci and anaerobes (21).

Time-kill assays were used to assess the activities of trovafloxacin (3 mg/l), ampicillin-sulbactam (100/50 mg/l) and the two in combination, against 21 strains of vancomycin-resistant *Enterococcus faecium* and 2 strains of *Enterococcus faecalis*. An *in vitro* 2-compartment model was also used to study the drugs' activity against 6 strains of *E. faecium* at high doses (simulating human doses of trovafloxacin 300 mg q12h and ampicillin-sulbactam 2/1 q6h). Trovafloxacin showed reductions of 2-4 logs in

trovafloxacin-susceptible strains (MICs ≤ 2 mg/l). No synergism with ampicillin-sulbactam was observed (22).

In a study of *in vitro* activity against enterococci strains (38 non-β-lactamase-producing ampicillin-resistant, 34 ampicillin-susceptible, 3 vancomycin-resistant), trovafloxacin was found to be more active than ciprofloxacin. Using a checkerboard method, trovafloxacin was additive with gentamicin, ampicillin-sulbactam and novobiocin. Reduced killing was seen with rifampin, vancomycin and teicoplanin (23).

Using an agar dilution method, trovafloxacin was found to be active against all 250 aerobic (MIC = ≤ 0.5 mg/l) and most of 137 anaerobic (MIC = ≤ 2 mg/l) clinical isolates obtained from animal and human bite wounds. The exceptions were fusobacteria (MIC_{90} = ≤ 4 mg/l) (24).

An *in vitro* study of the potential synergistic activity of trovafloxacin with ceftriaxone or vancomycin against 47 clinical isolates of *Streptococcus pneumoniae* with varying degrees of penicillin susceptibility showed that synergy occurred with ceftriaxone in 55% of isolates and with vancomycin in 15% of isolates. Importantly, synergy was seen with the trovafloxacin-ceftriaxone combination in 13/17 of isolates that were intermediate or ceftriaxone-resistant (25).

An *in vivo* study in mice infected i.p. with tachyzoites of *Toxoplasma gondii* demonstrated that combinations of trovafloxacin with clarithromycin, pyrimethamine or sulfadiazine resulted in enhanced activity against toxoplasmosis (26).

A study of the efficacy of trovafloxacin in experimental endocarditis revealed that both a penicillin-susceptible and a penicillin-resistant streptococcus were susceptible to trovafloxacin. A 3-day oral treatment in rats with experimental endocarditis showed superior efficacy compared to ceftriaxone ($p < 0.05$). Significant reductions were seen in vegetation bacterial densities, with no selection of resistant bacteria (27).

Using a standardized *in vivo* system to assess phototoxicity, trovafloxacin was shown to be one of the least phototoxic fluoroquinolones. Only at higher doses (90 and 250 mg/kg) did BALB/c mice, that were exposed to UVA light for 4 h, develop a mildly positive response, as compared to a strong and persistent response developing from lomefloxacin at 71 mg/kg under similar conditions (28).

Using an intraperitoneal, immunocompetent mouse sepsis model, trovafloxacin was shown to be more active than ciprofloxacin against both a penicillin-intermediate and a penicillin-resistant strain of *Streptococcus pneumoniae*. PD_{50} values were significantly lower for trovafloxacin (29).

The *in vivo* effects of trovafloxacin on T-cell subsets and memory T-cell response in senescent mice infected with *Bacteroides fragilis* were evaluated. Mice were treated for 10 days, either with a trovafloxacin prodrug or saline control. Splenocyte cell proliferation and cytokine production were the same in both groups, as were the CD4/CD8 ratios. Trovafloxacin eliminated *B. fragilis* infection and did not interfere with the immune response (30).

Rat and mice models (aged 6 and 24 months) of intraabdominal abscess were used for determining trovafloxacin levels. High therapeutic trovafloxacin levels were achieved in the infected site and tissues, with even greater levels achieved in the older mice. Overall, trovafloxacin concentrations at the infected site were 5 times the serum concentrations (31).

The activity of trovafloxacin was compared to that of clindamycin for the treatment of *Bacteroides fragilis* intraabdominal abscesses in young and senescent mice. While serum trovafloxacin pharmacokinetics was similar in young and old mice, tissue levels were higher in old mice. Intraabdominal abscesses were sterilized in 94% of young mice and 73% of old mice (difference not statistically significant). Trovafloxacin and clindamycin showed similar therapeutic activity (32).

The *in vivo* interaction of trovafloxacin and rifampin was observed in rats with experimental pyelonephritis due to *Enterococcus faecalis*. The rats were treated with either drug alone or both drugs. No evidence of antagonism was observed, based on the mean $\log_{10}$ CFU of *E. faecalis* from the kidney (33).

Using a mouse pneumonia model, the efficacy of trovafloxacin (12.5-300 mg/kg q8h or q12h for 3 days) against *Streptococcus pneumoniae* (penicillin-susceptible and multiresistant strains) showed that trovafloxacin (25 mg/kg) was the most effective agent as compared to amoxicillin, ciprofloxacin, temafloxacin and sparfloxacin. Survival rates were 2-16 times higher with trovafloxacin (34).

Streptococcus pneumoniae type 3 (SP3), exposed to either ceftriaxone or trovafloxacin, was given intracisternally to 12 antibiotic-pretreated rabbits (q3h over 9 h). CSF WBC counts were lower in the trovafloxacin-exposed group. When meningitis was induced by intracisternal SP3 in 20 rabbits, trovafloxacin-treated rabbits had a delayed inflammatory response (based on CSF TNF, IL-1β and WBC levels), which may have resulted from delayed release of proinflammatory bacterial products (35).

Using the rabbit meningitis model with intracisternal *Streptococcus pneumoniae* inoculation, it was found that trovafloxacin delayed TNF and IL-1β release, likely through retarding bacterial cell wall component release into the subarachnoid space. Experiments also showed that CSF leukocytosis was less prominent with trovafloxacin-pretreated *S. pneumoniae* than with ceftriaxone-pretreated *S. pneumoniae* (36).

An experimental pneumococcal meningitis model in rabbits was used to assess the effect of trovafloxacin on the antibiotic-induced inflammatory response. Significantly less leukocytosis was seen with intracisternal injection of trovafloxacin-pretreated *Streptococcus pneumoniae* than with ceftriaxone pretreatment. Furthermore, trovafloxacin was shown to delay antibiotic therapy-induced inflammatory host reaction, based on CSF TNF and IL-1β levels (37).

The pharmacokinetics of trovafloxacin and ciprofloxacin were evaluated in rabbit vitreous humor, both with and without coagulase-negative staphylococcal

endophthalmitis. The presence of inflammation increased the penetration ($AUC_{vitreous}/AUC_{serum}$) of ciprofloxacin more than trovafloxacin, but trovafloxacin showed excellent penetration both with and without inflammation, exhibiting 10-fold greater activity against *Staphylococcus epidermidis* (38).

A randomized, controlled trial evaluated the effect of oral trovafloxacin (250 mg/kg b.i.d. x 6 days) in the rabbit model of experimental *Staphylococcus epidermidis* endophthalmitis. Sterilization of infected eyes was seen within 5 days with trovafloxacin treatment, and they showed less inflammation and tissue damage on clinical and histological examination than untreated eyes (39).

Using the rabbit model of left-sided staphylococcal endocarditis, the efficacy of trovafloxacin (13.3 mg/kg q12h) was compared to that of vancomycin (25 mg/kg q8h). Infection was produced with either a nafcillin-susceptible or nafcillin-resistant strain, and treatment was given for 4 days. The two treatments showed equal efficacy in clearing bacteremia and reducing bacterial counts in vegetations and tissues. No trovafloxacin-resistant strains emerged (40).

Single intravenous infusions of alatrofloxacin (equivalent to 30, 100, 200 and 300 mg of trovafloxacin) were given to 15 healthy males. Rapid *in vivo* conversion to trovafloxacin occurred. Mean trovafloxacin AUC increased with dose; $t_{1/2}$ ranged from 10.4 to 12.3 h and was dose-independent. No adverse events were seen (41).

Twelve healthy males received theophylline for 7 days to achieve a steady-state plasma concentration of 8-15 mg/l. From day 8-15, either trovafloxacin 200 mg daily or placebo was added. Steady-state concentrations of theophylline were unaffected by steady-state concentrations of trovafloxacin, and no adverse events were observed (42).

Oral bioavailability of trovafloxacin was examined in two studies: a randomized, 2-way crossover study with 12 fasting healthy males and a randomized, open, 3-way crossover study in 12 healthy males (comparing oral tablets and oral suspension in the fed or fasting state). Good oral bioavailability was seen, and no clinically significant effect of food consumption was observed (43).

A randomized, open, placebo-controlled, 4-way crossover study in 12 healthy males examined the effect of concurrent omeprazole and Maalox on trovafloxacin bioavailability. Maalox significantly decreased initial trovafloxacin absorption, leading to decreases in AUC and $t_{1/2}$. Omeprazole had no clinically significant effect, although it did reduce mean relative bioavailability to 82% (44).

The pharmacokinetics of single and multiple doses of trovafloxacin and alatrofloxacin were evaluated in 103 healthy subjects. For trovafloxacin (100 mg) C_{max} was 1.0 ig/ml on day 1 and 1.1 ig/ml on day 17, while with 300 mg the corresponding values were 2.4 and 3.3 ig/ml. C_{max} and AUC increased with dose for alatrofloxacin; Cmax increased by 1 ig/ml for each mg/kg administered. Clearance and volume of distribution were dose-independent (45).

Using an open, placebo-controlled, 2-way crossover study, the effect of cimetidine (400 mg b.i.d. x 5 days) on trovafloxacin (200 mg/day x 3 days) pharmacokinetics was evaluated in 12 healthy males. Trovafloxacin C_{max}, t_{max} and AUC were unaffected by cimetidine administration (46).

Tissue pharmacokinetics of [^{18}F]-trovafloxacin were studied by PET in 16 healthy volunteers, who were given oral trovafloxacin 200 mg/day for 5-8 days. Approximately 3 h after the last dose, they were given an infusion of 10-20 mCi [^{18}F]-trovafloxacin over 1-2 min and then scanned. The radiolabelled drug accumulated rapidly in all organs, reaching tissue concentrations that would be well above the MIC_{90} for common pathogens, including some forms of meningitis (47).

A double-blind, placebo-controlled trial in healthy males was conducted to examine the effect on bowel microflora of trovafloxacin (200 mg/day x 10 days). Trovafloxacin and placebo treatments were equivalent in relation to prevalence, appearance and disappearance of aerobic Gram-positive cocci, anaerobic bacteria and yeasts. *Enterobacteriaceae* were all susceptible to trovafloxacin. The results suggest that trovafloxacin can decontaminate the bowel without producing adverse effects on the microflora (48).

A 2-arm parallel study in 203 age- and gender-matched subjects showed that the pharmacokinetic profile of trovafloxacin (200 mg/day x 10 days) was independent of age, gender and creatinine clearance, while that of ofloxacin (400 mg b.i.d. x 10 days) was altered by age, gender and creatine clearance. Both drugs were well tolerated with no laboratory abnormalities (49).

The pharmacokinetic/pharmacodynamic effects on a single dose of theophylline (300 mg) at steady-state concentrations of trovafloxacin (300 mg/day for 7 days) were examined in 12 healthy nonsmoking men. An increase of 8.4% in theophylline AUC was seen when given in the presence of trovafloxacin, but this was not clinically significant, assuming that this was based on oral clearance. Furthermore, no pharmacodynamic changes were seen (50).

Achieved CSF concentrations of trovafloxacin were determined in 12 healthy subjects given an intravenous infusion of alatrofloxacin (300 mg trovafloxacin equivalent). Within 1 h, CSF trovafloxacin concentration was 5.8 μg/ml, with a mean CSF/serum ratio of 0.25 from 5-24 h postinfusion. Mild or moderate adverse events included dizziness, nausea and rash. Rapid CSF penetration suggests that intravenously administered alatrofloxacin may be clinically useful for treating bacterial meningitis (51).

In a study of the effect of oral trovafloxacin (200 mg/day) on digoxin steady-state pharmacokinetics in 16 healthy males, subjects were given digoxin for 20 days, and on day 11, trovafloxacin was added. Digoxin AUC_{τ} and clearance were unchanged by trovafloxacin, and trovafloxacin had no effect on steady-state digoxin serum concentrations (52).

An open-label, noncomparative, multicenter trial in patients with acute sinusitis showed that trovafloxacin, 200 mg/day, resulted in clinical treatment success in 91% of patients, with pathogen eradication occurring in 96-100% of cases (depending on the pathogen). Adverse events included dizziness/lightheadedness, headache, diarrhea, nausea and vomiting (53).

In a comparison study of trovafloxacin, ciprofloxacin, levofloxacin, ofloxacin, sparfloxacin and norfloxacin activity against bacterial isolates from cancer patients, it was found that trovafloxacin had similar activity as the other compounds against Gram-negative isolates and was the most active against *Stenotrophomonas maltophilia*. In relation to Gram-positive organisms, trovafloxacin was the most active of the antibiotics tested (54).

Twenty-seven patients undergoing bronchoscopy were given single or multiple doses of trovafloxacin, following which trovafloxacin concentrations were measured in serum, bronchial mucosa, alveolar macrophages and epithelial lining fluid. All concentrations were higher than the MIC_{90}s for common respiratory pathogens such as *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae* (55).

Two related studies of the effect of age and gender on the single- and multiple-dose pharmacokinetics of trovafloxacin (200 and 300 mg/day for 8-10 days) were conducted on 24 elderly patients (12 females and 12 males) and 24 young patients (12 females and 12 males). HPLC/UV was used to evaluate trovafloxacin concentrations. In the doses studied, no effect of age or gender on trovafloxacin pharmacokinetics was seen (56).

A randomized, 2-treatment, 2-period crossover study in 12 AIDS patients (average age 38.3 years) given oral trovafloxacin (2 x 100 mg/day for 7 days) or the equivalent of alatrofloxacin showed that the pharmacokinetics were unaltered in AIDS patients when compared to historical controls (57).

The effect of hepatic impairment on trovafloxacin safety, tolerability and pharmacokinetics was evaluated in 6 patients with Child-Pugh Class A impairment (given single and multiple 100 mg doses), 6 patients with Child-Pugh Class B impairment (given single and multiple 200 mg doses) and 12 matched controls. Trovafloxacin was well tolerated, and no clinically significant changes in pharmacokinetics were seen that would require dosage alteration in cases of hepatic impairment (58).

The effect of renal impairment on trovafloxacin safety, tolerability and pharmacokinetics was evaluated in patients with varying degrees of renal failure (mild to moderate, severe and severe on dialysis) and controls. Although mean renal clearance was decreased in the severely impaired, based on the C_{max} and AUC values measured, it appears that no dosage adjustment is needed in patients with renal impairment (59).

The penetration of trovafloxacin (2 x 100 mg/day for a minimum of 3 days, with a dose prior to operation) into prostatic tissue was evaluated in 32 subjects undergoing transurethral resection of the prostate. The mean tissue/serum ratio was 0.96 at 2-6 and 6-12 h, and reached 0.98 at 12-30 h. The concentrations achieved were many times the MIC_{90} for common pathogens causing prostatitis, and they lasted for up to 28 h (60).

Trovafloxacin pharmacokinetics was evaluated in 14 children and 6 infants after a single dose (4.0 mg/kg i.v.) of alatrofloxacin. No significant differences were seen for the two groups tested, and the overall pharmacokinetic profile was similar to that seen in adults (61).

Alatrofloxacin (180 mg/m^2 i.v.) was given to 37 children and infants (3 months to 12 years) to assess CSF penetration and pharmacokinetics. CSF penetration was 22-30%. A 5 mg/kg i.v. infusion over 1 h given to 11 infants reached a maximum trovafloxacin concentration of 1.51 μg/ml 2.6 h after administration. The pharmacokinetics in children from 1-12 years of age appear to be similar to those seen in adults (62).

Based on a review of 6 multicenter, double-blind, comparative clinical trials of trovafloxacin in radiologically confirmed community acquired pneumonia in 1998 patients, it was found that trovafloxacin was highly effective against both penicillin-susceptible and penicillin-resistant *Streptococcus pneumonia*. Clinical efficacy rates were comparable to or better than other drugs, especially in penicillin-resistant cases (96% for trovafloxacin *vs.* 73% for others) (63).

A double-blind, randomized, multicenter study compared the effect of trovafloxacin to that of ceftriaxone combined with erythromycin (C+E) in 443 patients hospitalized with community acquired pneumonia. Clinical success rates were 90% with trovafloxacin and 87% for C+E at end of treatment. All cause mortality was lower for trovafloxacin treatment (3.6% *vs.* 7.0% for C+E), but no differences were statistically significant. Tolerance was high in both groups, with a similar rate of adverse events and withdrawals (64).

A randomized, double-blind, multicenter study compared trovafloxacin (200 mg/day) with clarithromycin (500 mg b.i.d) in the treatment of ambulatory community acquired pneumonia. A total of 359 patients were treated for 7-10 days. The two treatments were statistically equivalent and had similar rates of adverse events and withdrawals (65).

A randomized, double-blind, multicenter study compared trovafloxacin (i.v. alatrofloxacin 300 mg/day followed by oral trovafloxacin 200 mg/day) with ciprofloxacin (twice daily i.v. followed by oral administration) with or without clindamycin or metronidazole (for suspected anaerobes) in the treatment of 267 patients with nosocomial pneumonia. The two treatment arms were statistically equivalent, with all cause mortality rates of 24% for trovafloxacin and 25% for ciprofloxacin (66).

An open-label, noncomparative study evaluated the efficacy of trovafloxacin (200 mg/day x 10 or 14 days) in the treatment of 225 diabetic outpatients with foot infections. A total of 44% of patients were cured, 49% had improved and 7% were treatment failures at end of treatment; the rates 30 days after start of treatment were 71, 16 and 8%, respectively. No serious adverse events were reported (67).

A multicenter, double-blind trial compared oral trovafloxacin (100 mg tablet) with oral ofloxacin (2 x 200 mg capsules) given under supervision to 625 patients with uncomplicated gonococcal urethritis or cervicitis. Both treatments were statistically equivalent, with a 99% eradication rate for trovafloxacin and 98% for ofloxacin. The two drugs were well tolerated and the most frequent side effect for both drugs was vaginitis (68).

The FDA has cleared Pfizer's Trovan™ (trovafloxacin) for the treatment of a number of bacterial infections in adults, including acute bacterial exacerbations of chronic bronchitis, acute sinusitis, community- and hospital-acquired pneumonia, complicated intraabdominal infections, uncomplicated urinary tract infections, pelvic inflammatory disease, chlamydial cervicitis, gonorrhea, skin and skin structure infections and oral prophylactic use in surgery. The product is available in both oral (trovafloxacin mesilate) and injectable (alatrofloxacin) formulations and can be administered once daily (69).

Pfizer's Trovan™ has been available to distributors in the U.S. since January 19, 1998 and is expected to be on pharmacy shelves by mid-February. Trovan™ tablets contain 100 and 200 mg of trovafloxacin (as trovafloxacin mesilate), and the vial formulation (40 and 60 ml) contains 5 mg trovafloxacin/ml as alatrofloxacin mesilate (70).

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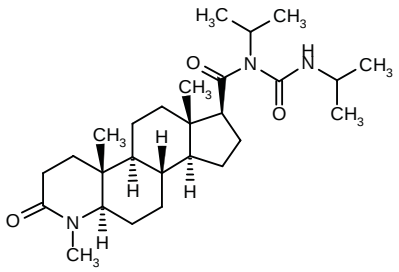
Turosteride

Antiandrogen
Treatment of BPH

EN: 174825



$C_{27}H_{45}N_3O_3$ **Farmitalia Carlo Erba**

The synthesis of [^{14}C]-turosteride has been reported: The reaction of 20-[^{14}C]-3-hydroxy-5-pregnen-20-one (I) with iodine and pyridine gives the pyridinium derivative (II), which is treated with sodium methoxide and methanol yielding 3-hydroxy-5-androstene-17β-carboxylic acid methyl ester (III). The oxidation of (III) with cyclohexanone and aluminum isopropoxide affords 3-oxo-5-androstene-17β-carboxylic acid methyl ester (IV), which is oxidized with potassium permanganate and sodium periodate to the propionic acid derivative (V). The cyclization of (V) with methylamine in diglyme at 180 °C affords 4-methyl-3-oxo-4-aza-5-androstene-17β-carboxylic acid methyl ester (VI),which is hydrogenated with H_2 over PtO_2 in acetic acid to the corresponding saturated compound (VII). The saponification of (VII) with KOH in refluxing methanol/water gives the 4-methyl-3-oxo-4-aza-5α-androstane-17β-carboxylic acid (VIII), which is finally condensed with diisopropylcarbodiimide (IX) in refluxing dichloromethane (1). Scheme 2.

1. Fontana, E., Angiuli, P., Pignatti, A., Panzeri, A., Dostert, P. *Synthesis of carbon-14 labelled 1-[4-methyl-3-oxo-4-aza-5α-androstane-17β-carbonyl]-1,3-diisopropylurea (turosteride), a new 5α-reductase inhibitor.* J Label Compound Radiopharm 1996, 38(7): 667.

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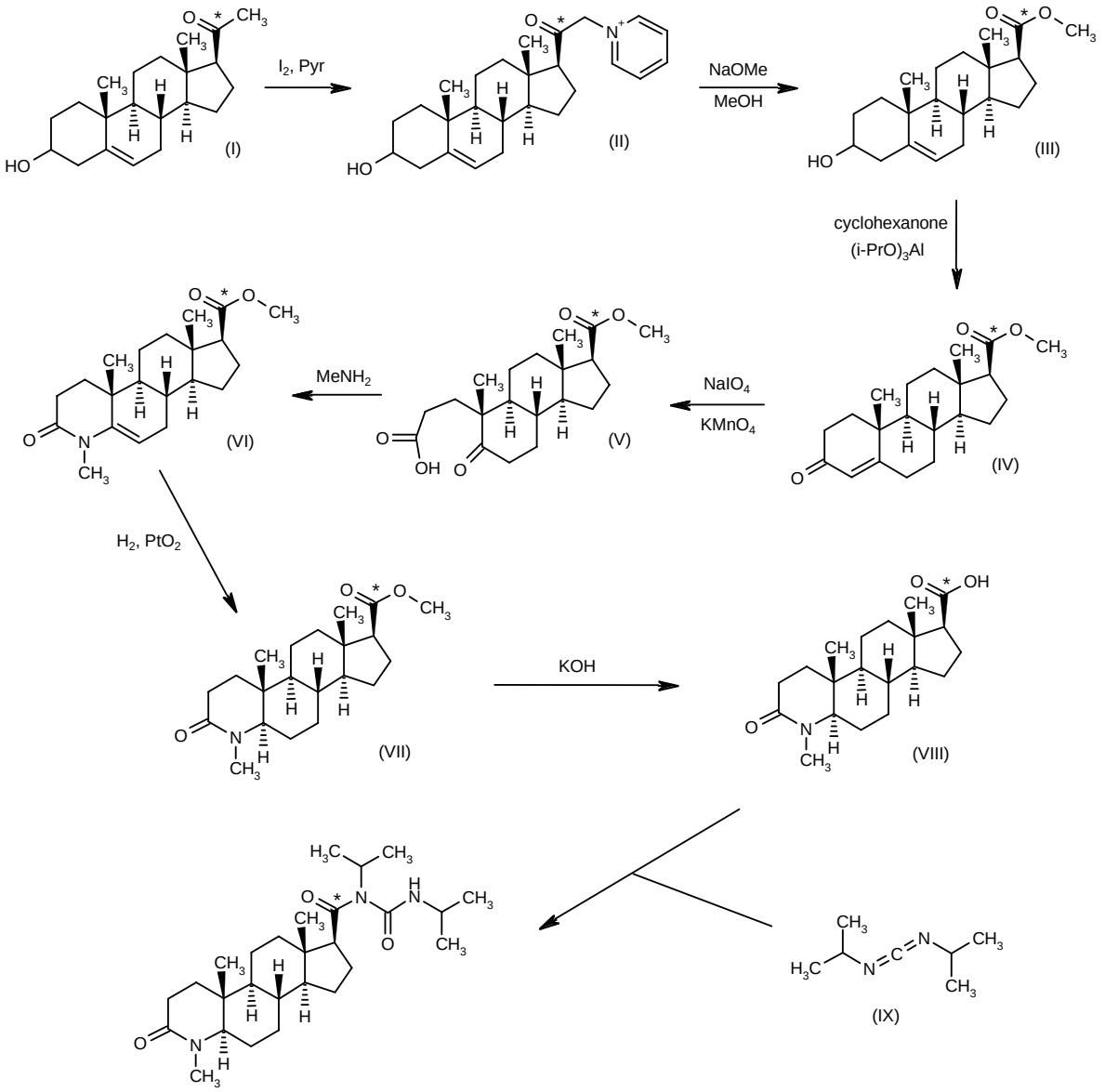
Scheme 2: Synthesis of [^{14}C]-Turosteride



Ularitide

Treatment of Acute Renal Failure

EN: 145124

Threonyl-alanyl-prolyl-arginyl-seryl-leucyl-arginyl-arginyl-seryl-seryl-cysteinyl-phenylalanyl-glycyl-glycyl-arginyl-methionyl-aspartyl-arginyl-isoleucyl-glycyl-alanyl-glutaminyl-seryl-glycyl-leucyl-glycyl-cysteinyl-asparaginyl-seryl-phenylalanyl-arginyl-tyrosine cyclic (11-27)-disulfide

$C_{145}H_{234}N_{52}O_{44}S3$

HaemoPep Pharma; Boehringer Mannheim

Using human umbilical vein endothelial cells, it was found that ularitide acetate given alone decreased thrombin-induced increases in permeability and increased cyclic nucleotides, and in a more than additive fashion when the cells were pretreated with aminophylline (1).

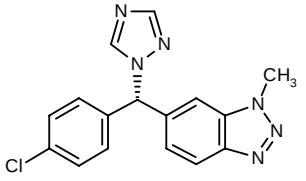
1. Korn, C., Neidlein, R., Strein, K., Wilhelms, O.-H. *Comparison of the effects of ularitide acetate and other bronchorelaxing substances on the thrombin-induced permeability raise of human endothelial cell monolayers.* Arzneim-Forsch-Drug Res 1998, 48(3): 251.

Original monograph - Drugs Fut 1995, 20: 490.

Vorozole
Rivizor®

Antineoplastic
Aromatase Inhibitor

EN: 172112



$C_{16}H_{13}ClN_6$

Janssen

A single-dose, open-label, pharmacokinetic study of vorozole was conducted in 12 healthy young males, 12 postmenopausal females (< 65 years of age) and 12 elderly females (> 70 years of age). Hot flushes and headache were the most frequent adverse events and were more common in females. C_{max} and $t_{1/2\beta}$ were higher in postmenopausal females than in young males but AUC was smaller. Therefore, dosage adjustment may be needed in older patients if tolerability is a problem (1).

A randomized, open-label, 3-way, crossover trial of vorozole (1, 2.5 and 5 mg) in 12 healthy postmenopausal females examined single- and multiple-dose pharmacokinetics. Steady state was reached after 3 days with 1 mg and 4 days with 2.5 and 5 mg. C_{max} and AUC increased in a greater than dose proportional manner with mean accumulation ratios at steady state of 1.4, 1.7 and 2.0 for 1, 2.5 and 5 mg doses (2).

A randomized, stratified, open-label study comparing oral vorozole (2.5 mg/day) and Megace® (40 mg q.i.d.) in 452 postmenopausal breast cancer patients who had relapsed following tamoxifen showed a better median duration of response for the vorozole-treated group (18.2 months in 20 responders *vs.* 12.5 months in 14 responders). Drug-related adverse events included hot flushes for vorozole and excess weight gain for Megace®. Both treatments were well-tolerated (3).

The results have been published of an EORTC phase II clinical trial evaluating vorozole in 27 postmenopausal women with advanced breast cancer who had been previously treated with tamoxifen. Based on prior endocrine studies, which indicated that maximum estrogen suppression is obtained at the dose of 2.5 mg/day, patients received this dose in a tablet formulation until disease progression or excessive toxicity was observed. The objective response rate to vorozole in this patient group was 30%, with 2 complete responses and 6 partial responses. Sites of response included skin, lymph nodes, lung and chest wall plus lymph nodes in 3, 2, 2 and 1 patients, respectively. Nine further patients had disease stabilization for a mean of 7.9 months (range 3.7-40.1 months). The overall time to progression in the entire patient group was 6 months, although in 10 patients disease progression was documented within 3 months of starting vorozole therapy. Response to vorozole was most favorable in those patients with small tumor burden and predominant soft tissue localizations, and was less favorable in women with predominant bone metastases or with multiple visceral involvement. Furthermore, patients who had previously responded to treatment with tamoxifen were most likely to respond under vorozole. Neither disease-free interval nor performance status appeared to have any effect on response to the study drug. Tolerability was good in all subjects, with mild or moderate drug-related toxicities reported in 15/27 patients. The investigators recommended further comparison of vorozole with progestins (*e.g.*, medroxyprogesterone acetate or megestrol acetate) and with aminoglutethimide, in order to define the exact place for this agent in the sequential treatment of patients with advanced metastatic disease (4).

A randomized, open, phase III study compared vorozole (2.5 mg/day) to aminoglutethimide (250 mg b.i.d.) plus hydrocortisone (30 mg/day) in treating locally advanced or metastatic breast cancer in postmenopausal patients failing with tamoxifen. Vorozole showed improved quality of life, greater clinical benefit and a better safety profile as compared to aminoglutethimide (5).

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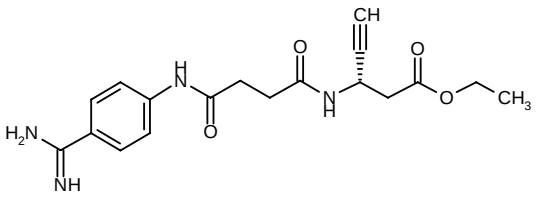
Xemilofiban
CS-551
SC-54684

Platelet Aggregation Inhibitor
Fibrinogen (gpIIb/IIIa) Receptor Antagonist

EN: 199965



$C_{18}H_{22}N_4O_4$

Searle; Sankyo

PK/PD parameters of single oral doses of xemilofiban (5 and 10 mg) in hemodialysis patients showed that mean AUC decreased by 66% with hemodialysis, with a further 34% decrease with charcoal hemoperfusion. Levels rebounded mildly after dialysis, but were below effective concentrations. Platelet aggregation increased with the hemodialysis procedures as well (1).

A randomized, placebo-controlled study in 30 patients with unstable angina undergoing percutaneous coronary interventions showed that xemilofiban (35 mg p.o. before and 20-25 mg t.i.d. for 30 days after angioplasty) rapidly produced a marked and prolonged inhibition of platelet aggregation. One patient died post-CABG surgery complicated by a severe bleeding diathesis, 3 patients suffered major bleeding episodes, and mild mucocutaneous bleeding was also reported (2).

A randomized, single-blind, dose-ranging, placebo-controlled trial of xemilofiban (5, 10, 15 and 20 mg p.o. b.i.d) in patients after intracoronary stent placement (also receiving aspirin 325 mg/day) showed that xemilofiban produced dose-dependent inhibition of platelet aggregation for the entire 2 weeks of therapy. A dose of at least 10 mg was needed to produce at least 50% inhibition lasting 8-10 h. No significant hemorrhages were seen (3).

A randomized, placebo-controlled trial of xemilofiban (15 or 20 mg t.i.d. for 2 weeks then b.i.d. for 2 weeks) following coronary revascularization (CR) included 549 patients, all of whom also received aspirin 325 mg/day and 29% of whom received abciximab during CR (with reduced xemilofiban doses). *Ex vivo* dose-dependent inhibition of platelet aggregation was observed for xemilofiban (4).

Safety and efficacy data from a randomized, placebo-controlled trial of xemilofiban (15 or 20 mg t.i.d. x 2 weeks then b.i.d. x 2 weeks) in 549 patients following percutaneous coronary intervention showed that the drug was well tolerated during chronic therapy. A trend towards reduction of cardiac events at 3 months was seen in the xemilofiban treated group (5).

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