Drugs of the Future 1998, 23(11): 1227-1264

CCC: 0377-8282/98

Information Update

Volume 1-22, Number 11

Estimated developmental phase for this month's updated products:

Preclinical

Aspalatone (platelet antiaggregatory; Bukwang)
Epibatidine (analgesic; Dept. Health & Human Services, CytoMed)
GM-237354 (antifungal; Glaxo Wellcome)

Phase I

E-7010 (antineoplastic; Eisai)
Ecteinascidin-743 (antineoplastic; Pharma Mar, Univ. Illinois)
Ibogaine (antiaddictive alkaloid; NDA Int., OmniChem)
Nacolomab tafenatox (antineoplastic, immunomodulator; Pharmacia & Upjohn)
NCX-4016 (antithrombotic, antiinflammatory, analgesic; NicOx, Bayer)

Phase II

AGM-1470 (antiangiogenic, antineoplastic; Takeda)
Allicin (platelet antiaggregatory, hypolipidemic; Tulane Univ., Weizmann Inst.)
Amrubicin hydrochloride (antineoplastic antibiotic; Sumitomo)
CI-994 (antineoplastic; Warner-Lambert)
Domitroban calcium hydrate (treatment of allergic rhinitis, thromboxane A_2 antagonist; Shionogi)
EB-1089 (antineoplastic, vitamin D_3 analog; Leo Denmark)
Foropafant (antiallergic/antiasthmatic, PAF antagonist; Sanofi)
N-0923 (antiparkinsonian, dopamine D_2 agonist; Discovery Therapeutics, Yoshitomi, Schwarz)
Olpadronic acid sodium salt (treatment of osteoporosis; Henkel, Gador)
Peptide T (antiviral, anti-HIV, antiinflammatory; Karolinska Inst., Natl. Inst. Health, Peptech)
Retigabine (anticonvulsant; Arzneimittelwerk Dresden, Asta Medica, Wyeth-Ayerst)
SKI-2053R (antineoplastic, platinum complex; Sunkyong)

Phase III

Ataprost (platelet antiaggregatory; Ono, Dainippon Pharm.)
Atosiban (oxytocin antagonist, treatment of premature labor; Ferring, Ortho-McNeil)
CS-866 (antihypertensive, angiotensin AT_1 antagonist; Sankyo, Recordati)
Cariporide mesilate (cardioprotectant, Na^+/H^+ exchange inhibitor; Hoechst Marion Roussel)
Darifenacin (treatment of irritable bowel syndrome, muscarinic M_3 antagonist; Pfizer)
Israpafant (antiallergic/antiasthmatic, PAF antagonist; Yoshitomi, Japan Tobacco)
Linezolid (oxazolidinone antibacterial; Pharmacia & Upjohn)
Ono-5046 (elastase inhibitor; Ono, Cortech)
Pioglitazone hydrochloride (antidiabetic; Takeda)
Remacemide hydrochloride (anticonvulsant, NMDA antagonist; Astra)
Vapreotide (antineoplastic, somatostatin analog; Tulane Univ., Debiopharm)

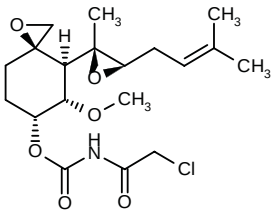
Launched/Year

Amifostine hydrate (chemoprotectant; Southern Res. Inst., US Bioscience, Schering-Plough, Lilly, Alza)/1995
Argatroban monohydrate (anticoagulant, thrombin inhibitor; Texas Biotechnology)/1990
Beraprost sodium (platelet antiaggregatory; Toray, Yamanouchi, Kaken, Bristol-Myers Squibb, Hoechst Marion Roussel)/1992
Bromfenac sodium (antiinflammatory, analgesic; Wyeth-Ayerst, Senju, Block Drug)/1997 (withdrawn)
Lanreotide acetate (antineoplastic, somatostatin analog; Biomeasure; Beaufour-Ipsen)/1995
Lisinopril (ACE inhibitor, treatment of diabetic retinopathy and nephropathy; Zeneca)/1987
Meloxicam (antiinflammatory, COX-2 inhibitor; Boehringer Ingelheim, Almirall Prodesfarma)/1996
Midazolam maleate (sedative; Roche)/1982
Orlistat (antiobesity, pancreatic lipase inhibitor; Roche)/1998
Pamidronate sodium (bisphosphonate, treatment of bone disease; Henkel, Novartis, Almirall Prodesfarma)/1987
Reboxetine mesilate (antidepressant, norepinephrine reuptake inhibitor; Pharmacia & Upjohn)/1997
Tacrine (cognition enhancer, acetylcholinesterase inhibitor; Warner-Lambert, Alza)/1993
Ukrain (antineoplastic alkaloid, immunomodulator; Ukranian Anti-Cancer Inst., Nowicky Pharma)/1996

AGM-1470
TNP-470

Antiangiogenic
Antineoplastic

EN: 161076



$C_{19}H_{28}ClNO_6$

Takeda

In a rat model of induced hepatocarcinogenesis, administration of TNP-470 (30 mg/kg i.p. twice weekly) significantly reduced the number of hepatic nodules, with nodules of all sizes being equally suppressed. The drug was more effective when administered for 8-20 weeks than for 14-26 weeks. Hyperplastic nodules containing normal sinusoidal endothelial cells were not affected by treatment, indicating that TNP-470 suppresses hepatic nodules whose microvessels are capillaries or transitional forms of sinusoids to capillaries (1).

In studies in two cell lines derived from human non-small cell lung cancers, TNP-470 exhibited inhibitory effects on cell proliferation, with an IC_{50} of 50-62.5 μM. Exposure of the cells to Taxol prior to TNP-470 produced a synergistic effect, indicating that the combination regimen may be a promising treatment for non-small cell lung cancers (2).

TNP-470 inhibited the growth of AT6.3 hormone-independent prostatic carcinoma cells *in vitro*, and subcutaneous injections of the compound in mice markedly reduced the number and size of lung metastases originating from inoculated AT6.3 cells (3).

A selective method for the quantitative determination of TNP-470 and two of its metabolites in human plasma, using liquid-liquid extraction and HPLC liquid chromatography separation has been developed. An extraction procedure involving acidification of the blood sample with citric acid has been developed to prevent the degardation of TNP-470. The quantification has been performed using atmospheric pressure chemical ionization coupled with mass spectrometry (4).

In an *in vitro* model system, treatment with both TNP-470 and its metabolite AGM-1883 resulted in concentration-dependent increases in prostate specific antigen (PSA) secretion. TNP-470 also caused an upregulation of PSA and androgen receptor transcription, indicating that clinical use of PSA as a surrogate marker may be problematic (5).

The combined effects of TNP-470 and SN-38 were evaluated in human non-small cell lung cancer cell lines. Inhibition of cell proliferation by TNP-470 was dose-dependent (IC_{50} = 47.3-139.8 μM). Isobologram and combination index values showed synergistic effects in all 4 cell lines tested with sequential exposure to SN-38 followed by TNP-470 (6).

In hamsters bearing fast-growing melanoma, treatment with TNP-470 resulted in a significant decrease in the rate of tumor growth and inhibition of metastasis in 63% of animals. The inhibitory effects of the drug were much weaker in hamsters whose tumors were excised. Since tumor excision appeared to favor angiogenesis, the dose of TNP-470 should be increased to be effective in such circumstances (7).

In mice injected with human pancreatic carcinoma cell line PCI-43, treatment with TNP-470 (30 mg/kg s.c. every other day) for 6 weeks did not suppress maximal size of metastatic colonies, whereas after 10 weeks of treatment there was apparent inhibition. TNP-470 also suppressed proliferation and increased apoptosis in metastatic nodules in the liver. These results indicate that angiogenesis inhibition may be an effective means for suppressing the establishment and growth of hematogenous metastasis of pancreatic adenocarcinoma to the liver (8).

The antimetastatic activity of intravenously injected TNP-470 was evaluated in rats following induction of metastatic liver tumors. Two weeks after administration, the number and size of metastatic tumors decreased in drug-treated rats, as compared to untreated controls. All untreated rats died after 4 weeks, while treated rats were still alive. The percentages of tumors with necrosis and apoptotic cells were significantly higher in untreated rats compared to TNP-470-treated rats (9).

The effects of TNP-470 on bone morphogenetic protein (BMP)-induced ectopic bone formation were investigated in mice. Ectopic new bone formation was dose-dependently inhibited by daily subcutaneous administration of TNP-470 and the number of receptor-positive cells surrounding the implanted BMP pellets was reduced. Results demonstrate that the biological activity of rhBMP-2 was reversibly inhibited by TNP-470 in the early stage of bone induction, and hence, angiogenesis may be crucial in recruiting BMP-receptor-positive cells that respond to rhBMP-2 and differentiate into chondrocytes and/or osteoblasts (10).

In a bone metastasis model in nude mice injected with the human breast cancer cell line MDA-231, TNP-470 (30 mg/kg 3 times weekly) was shown to reduce the number and area of osteolytic bone metastases, inhibit the formation of multinucleated osteoclast-like cells and suppress *in vivo* bone resorption (11).

The inhibitory effects of TNP-470 on angiogenesis were evaluated in a phase II study in 33 patients with metastatic renal carcinoma. Following administration of TNP-470 (60 mg/m^2 i.v. 3 days/week), 1 partial and 1 minor response were reported; 5 patients remained progression-free after 16 weeks of treatment. Major toxicities included CNS toxicity, fatigue and 1 death from massive gastrointestinal hemorrhage in a patient with a prior history of hemoptysis (12).

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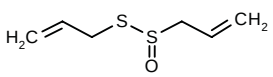
Allicin

Platelet Antiaggregatory
Hypolipidemic

EN: 147782



$C_6H_{10}OS_2$ **Tulane Univ. (US); Weizmann Inst. (IL)**

The benefits of allicin in the setting of lung ischemia and reperfusion were evaluated in a rat lung reperfusion model. Administration of allicin 0.01 or 0.1 mg as a single preoperative dose improved early and late postischemic pulmonary blood flow, but did not reduce postischemic pulmonary leukosequestration. In addition, the administration of allicin at the intermediate dose significantly increased the rate of survival compared with controls (1).

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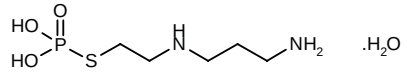
Amifostine Hydrate Ethyol®

Chemoprotectant

EN: 090725



$C_5H_{15}N_2O_3PS.H_2O$ **Southern Res. Inst.; US Bioscience; Schering-Plough; Lilly; Alza**

U.S. Bioscience has achieved a clinical milestone in the development of a new indication for Ethyol®, triggering a milestone payment from development partner Alza. The compound has been successfully evaluated in a phase III randomized trial assessing its radioprotective properties in patients with head and neck cancer (1).

U.S. Bioscience has requested approval from the European regulatory authorities to expand the use of amifostine (Ethyol®) to include protection against acute and late toxicities associated with radiation therapy in patients with multiple tumor types, particularly head and neck cancer (2).

1. *Phase III milestone reached for Ethyol in new indication*. Daily Essentials Feb 13, 1998.

2. *Expanded approval requested for chemoprotective agent*. Daily Essentials Sept 24, 1998.

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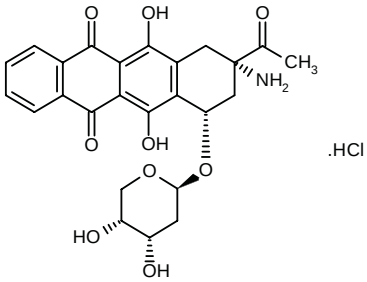
Initial results show Ethyol effective in reducing radiation-induced xerostomia. Daily Essentials Nov 3, 1997.

Amrubicin Hydrochloride

Antineoplastic Antibiotic

EN: 142668

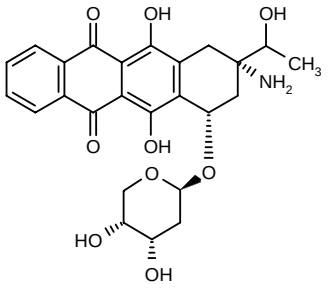


$C_{25}H_{25}NO_9.HCl$ **Sumitomo**

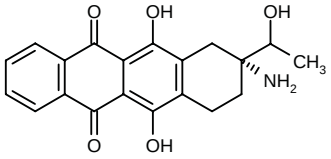
The single-dose pharmacokinetics of radiolabeled amrubicin (0.1, 1.0 and 10 mg/kg i.v.) were evaluated in rats. Multiexponential reductions of radioactivity in plasma and blood cells were observed, with a blood cell concentration of 33-50% as compared to plasma. Plasma concentrations of the major metabolite, amrubicinol, increased rapidly and decreased slowly. High levels of radioactivity were detected in bone marrow, intestinal wall, skin, adrenal gland, spleen, lung, Harderian gland, submaxillary gland, kidney and liver. At 168 h postadministration, 13 and 76% of the initial radioactivity was excreted in urine and feces, respectively; 58% of initial radioactivity was detected in the bile 72 h following injection. Gender-based differences were not observed. Proportions of the prodrug and its main metabolite bound to plasma protein were 92-97 and 78-93%, respectively (1).

Radioactivity in plasma and blood cells following repeated administration of radiolabeled amrubicin (1 mg/kg/day) in rats increased with the number of doses, reaching 6- to 8-fold higher concentrations on day 14 as compared to day 1. AUC values on day 14 were 5-fold higher as compared to day 1. On day 14, high concentrations of amrubicin were detected in submaxillary gland, spleen, lung, thymus and bone marrow, while high concentrations of amrubicinol, the major metabolite, were detected in the thymus, and submaxillary and adrenal glands. Proportions of radioactivity excreted in urine and feces following administration of the final dose were 14 and 80%, respectively (2).

Radiolabeled amrubicin (1.5 mg/kg i.v.) in dogs was distributed to liver, gallbladder, kidney, lung, spleen, pancreas and the prostate gland, and reached maximum concentrations 1-4 h following dosing. Within 168 h after administration, 8 and 74% of the initial dose was excreted in urine and feces, respectively. Major metabolites detected were metB and amrubicinol (3).



[I]



[II]

The metabolism of SM-5887 was studied in rats and dogs after i.v. administration of [^{14}C]-SM-5887. The major radioactive components were amrubicinol (SM-5887-13-OH) [I] and unchanged SM-5887 in rat urine and unknown polar metabolites (M-1, M-2) in rat and dog bile. In dog urine, the major radioactive components were M-2 and Met B [II]. Nonpolar or less polar metabolites (Met B, amrubicinol and unchanged SM-5887) were detected in rat tissues (4).

The maximum-tolerated dose of amrubicin and its efficacy was evaluated in previously untreated patients with non-small cell lung cancer. In a phase I study, 13 patients received the agent (i.v. injection, once a day, for 3 days) starting at 40 mg/m^2 and increased by 5 mg/m^2/day. The maximum-tolerated dose was 50 mg/m^2/day (150 mg/m^2/course). Dose-limiting factors were leukopenia, neutropenia, thrombocytopenia and gastrointestinal complications. In a phase II study, 61 patients received 45 mg/m^2/day for 3 days (135 mg/m^2/course) every 3 weeks. Forty-one assessable patients showed 1 complete response and 13 partial responses. Major toxicity was leukopenia and neutropenia. Amrubicin was determined to effectively treat advanced non-small cell lung cancer (5).

1. Nakai, S. et al. *Studies on the metabolic fate of amrubicin hydrochloride (SM-5887), a novel antitumor agent (I): Blood concentration, distribution, metabolism and excretion after a single intravenous administration to rats*. Xenobiotic Metab Dispos 1998, 13(2): 61.

2. Nakai, S., Akao, K., Ito, M., Kanamaru, H., Nakatsuka, I. *Studies on the metabolic fate of amrubicin hydrochloride (SM-5887), a novel antitumor agent (II): Blood concentration,*

distribution, metabolism and excretion after repeated intravenous administration to rats. Xenobiotic Metab Dispos 1998, 13(2): 78.

3. Nakai, S., Akao, K., Ito, M., Komuro, S., Kanamaru, H., Nakatsuka, I. *Studies on the metabolic fate of amrubicin hydrochloride (SM-5887), a novel antitumor agent (III): Blood concentration, distribution, metabolism and excretion after a single intravenous administration to dogs*. Xenobiotic Metab Dispos 1998, 13(2): 91.

4. Nakai, S., Akao, K., Ito, M., Kanamaru, H., Nakatsuka, I. *Studies on the metabolic fate of amrubicin hydrochloride (SM-5887), a novel antitumor agent (IV): Metabolism of SM-5887 in rats and dogs*. Xenobiotic Metab Dispos 1998, 13(2): 100.

5. Sawa, T., Yoshida, T., Ikoma, T., Toyoda, M., Ariyoshi, Y., Fukuoka, M., Furuse, K. *Phase I and II study of amrubicin (SM5887), a novel 9-amino-anthracycline, for advanced non-small cell lung cancer*. 14th Asia Pac Cancer Conf (Nov 16-19, Hong Kong) 1997, Abst P139.

Original monograph - Drugs Fut 1988, 13: 962.

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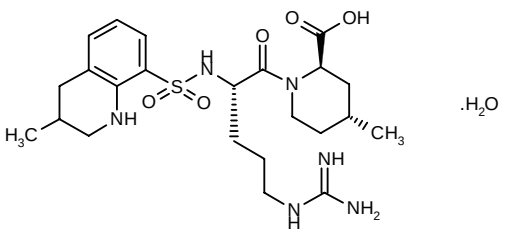
Yana, T. et al. *Phase II study of amrubicin (SM-5887), a 9-amino-anthracycline, in previously untreated patients with extensive stage small-cell lung cancer (ES-SCLC): A West Japan Lung Cancer Group trial*. Proc Amer Soc Clin Oncol 1998, Abst 1734.

Argatroban Monohydrate
Novastan®
Slonnon®

Anticoagulant
Thrombin Inhibitor

EN: 090744



$C_{23}H_{36}N_6O_5S.H_2O$ **Texas Biotechnology**

Texas Biotechnology has received a nonapprovable letter from the FDA for argatroban (Novastan®) (1).

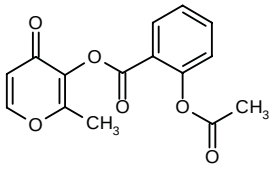
1. *FDA issues nonapprovable letter for Novastan*. Daily Essentials May 14, 1998.

Original monograph - Drugs Fut 1982, 7: 810.

Aspalatone

Platelet Antiaggregatory

EN: 217628



$C_{15}H_{12}O_6$ **Bukwang**

The effect of aspalatone on kainic acid-induced neurotoxicity was evaluated in the rat. The neurotoxicity induced by kainic acid is, at least partially, mediated via free radical formation. Pretreatment with aspalatone or maltol significantly attenuated neuron seizure induced by kainic acid. Pretreatment with aspirin, aspirin with maltol or vitamin E did not protect against kainic acid toxicity which suggested that the mechanism of action for aspalatone on kainic acid-induced neurotoxicity differed from that of aspirin. Thus, an aspalatone-related antioxidant mechanism, linked to the maltol moiety, may be involved in the neuroprotective effect against kainic acid (1).

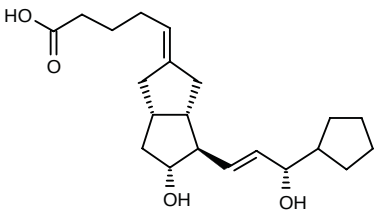
1. Kim, H.C. et al. *Aspalatone, a new antiplatelet agent, attenuates the neurotoxicity induced by kainic acid in the rat*. Soc Neurosci Abst 1998, 24(Part 2): Abst 769.3.

Original monograph - Drugs Fut 1995, 20: 1109.

Ataprost

Platelet Antiaggregatory

EN: 090731



$C_{21}H_{32}O_4$ **Ono; Dainippon Pharm.**

Beagle dogs administered OP-41483 for 30 min before ischemia (2 μg/kg/min) and for 3 h after reperfusion (0.5 μg/kg/min) showed improvements in hepatic tissue blood flow and liver function and experienced only transient hypotension. The 2-week survival rate was 100% (1).

1. Totsuka, E., Todo, S., Zhu, Y., Ishizaki, N., Kawashima, Y., Jin, M.B., Urakami, A., Shimamura, T., Starzl, T.E. *Attenuation of ischemic liver injury by prostaglandin E-1 analogue, misoprostol, and prostaglandin I-2 analogue, OP-41483*. J Am Coll Surg 1998, 187(3): 276.

Original monograph - Drugs Fut 1984, 9: 833.

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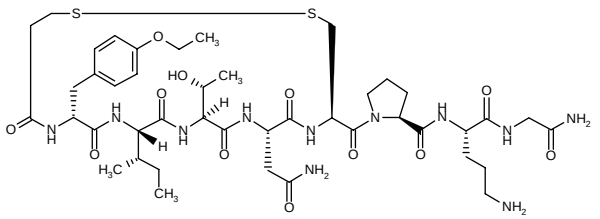
Abe, A. et al. *The inhibitory effects of OP-41483, a prostacyclin analogue, on the contractions of vascular smooth muscle*. Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-321.

Atosiban
Antocin®

Oxytocin Antagonist
Treatment of Premature Labor

EN: 140299



$C_{43}H_{67}N_{11}O_{12}S_2$ **Ferring; Ortho-McNeil**

The Reproductive Health Drugs Advisory Committee of the U.S. FDA has voted against recommending approval of atosiban injection (Antocin®), since treatment with the compound did not significantly prolong labor or delay progression. Furthermore, there were concerns about the safety of the product in fetuses, although it was confirmed to be safe in pregnant mothers (1).

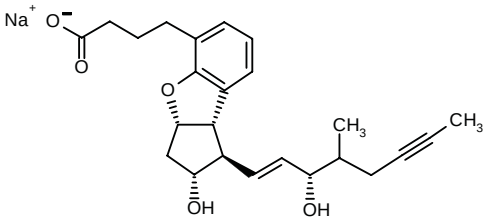
1. *FDA advisory committee votes against approval of tocolytic*. Daily Essentials May 4, 1998.

Original monograph - Drugs Fut 1994, 19: 985.

Beraprost Sodium
Procylin®
Dorner®

Platelet Antiaggregatory

EN: 116067



$C_{24}H_{29}NaO_5$ **Toray; Yamanouchi; Kaken; Bristol-Myers Squibb; Hoechst Marion Roussel**

The cardioprotective effects of beraprost sodium were compared with those of propranolol and diltiazem in guinea pig coronary perfused right ventricular preparations. Preparations were subjected to 30 min of no-flow ischemia with or without drugs followed by 60-min drug-free reperfusion and contractile force was monitored. All three drugs resulted in significant recovery of contractile force after reperfusion. A marked decrease in contractile force was observed under normoxic conditions in preparations treated with propranolol (30 μM) and diltiazem (10 μM), whereas beraprost (0.1 μM) produced no inotropic effect under normoxic conditions or during ischemia. These results indicate that, in contrast to propranolol and diltiazem, beraprost does not have cardiodepressive effects (1).

1. Tanaka, H., Matsui, S., Shigenobu, K. *Cardioprotective effects of beraprost sodium against experimental ischemia and reperfusion as compared with propranolol and diltiazem*. Res Commun Mol Pathol Pharmacol 1998, 99(3): 321.

Original monograph - Drugs Fut 1986, 11: 956.

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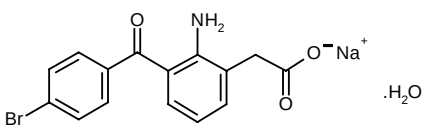
Suh, B.Y. et al. *Open-label, uncontrolled, 6-week clinical trial of beraprost in patients with chronic occlusive arterial disease*. Curr Ther Res 1998, 59(9): 645.

Takita, Y. et al. *Study of the efficacy of PGI_2 derivative (beraprost) in hypertension in patients with chronic pulmonary disease*. Jpn Circ J 1997, 61(Suppl. 1): Abst P112.

Bromfenac Sodium
Duract®

Antiinflammatory
Analgesic

EN: 144797



$C_{15}H_{11}BrNNaO_3.3/2H_2O$ **Wyeth-Ayerst; Senju; Block Drug**

The Wyeth-Ayerst division of American Home Products has voluntarily withdrawn Duract® from the U.S. market. This action is based on postmarketing reports of

severe hepatic failure resulting in death in 4 patients and liver transplant in 8 patients, all but 1 case involving patients who used Duract® for over 10 days; the exception was a patient with preexisting significant liver disease (1).

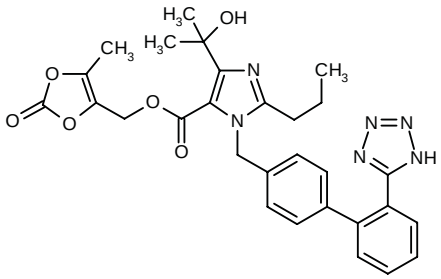
1. *Duract withdrawn from the U.S. market due to reports of hepatotoxicity*. Daily Essentials Jun 24, 1998.

Original monograph - Drugs Fut 1988, 13: 943.

CS-866

Antihypertensive
Angiotensin AT_1 Antagonist

EN: 217950



$C_{29}H_{30}N_6O_6$ **Sankyo; Recordati**

The effects of CS-866 on blood pressure and endocrine parameters was studied in 16 patients with mild to moderate hypertension on a sodium-restricted diet. Doses of 2.5, 10, and 40 mg or 5, 20 and 80 mg were well tolerated, and produced significant reductions in blood pressure when administered at doses of more than 5 mg. Increases in plasma renin activity and plasma angiotensin II concentrations were also observed, and reached C_{max} 3 h after administration. Single oral doses of 10-20 mg produced optimum effects (1).

In an 8-week, double-blind, placebo-controlled study in 334 hypertensive patients, once-daily doses of CS-866 (5, 20, 80 mg) were as effective as twice-daily doses (2.5, 10, 40 mg) in lowering ambulatory blood pressure. The drug was very well tolerated with both regimens, and the number of adverse events between treatment groups was not statistically different (2).

1. Puchler, K., Nussberger, J., Laeis, P., Witte, P.U., Brunner, H.R. *Blood pressure and endocrine effects of single doses of CS-866, a novel angiotensin II antagonist, in salt-restricted hypertensive patients*. J Hypertens 1997, 15(12): 1809.

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Original monograph - Drugs Fut 1997, 22: 1205.

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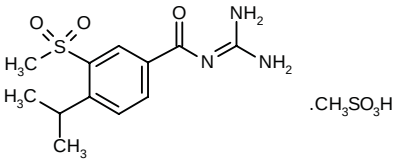
Focus on Sankyo's R&D activities at home and abroad. Daily Essentials Oct 9, 1998.

Cariporide Mesilate
Hoe-642

Cardioprotectant
Na^+/H^+-Exchange Inhibitor

EN: 215949



$C_{12}H_{17}N_3O_3S.CH_4O_3S$ **Hoechst Marion Roussel**

Two new related ways for the synthesis of cariporide mesilate have been reported: Scheme 1.

1) The reaction of 4-isopropylbenzoic acid (I) with chlorosulfonic acid gives 3-(chlorosulfonyl)-4-isopropylbenzoic acid (II), which is reduced wth sodium sulfite/NaOH to the sorresponding sulfinic acid (III). The methylation of (III) with methyl iodide/NaOH in dimethylacetamide affords 4-isopropyl-3-(methanesulfonyl)benzoic acid methyl ester (IV), which is finally condensed with gunidine (V).

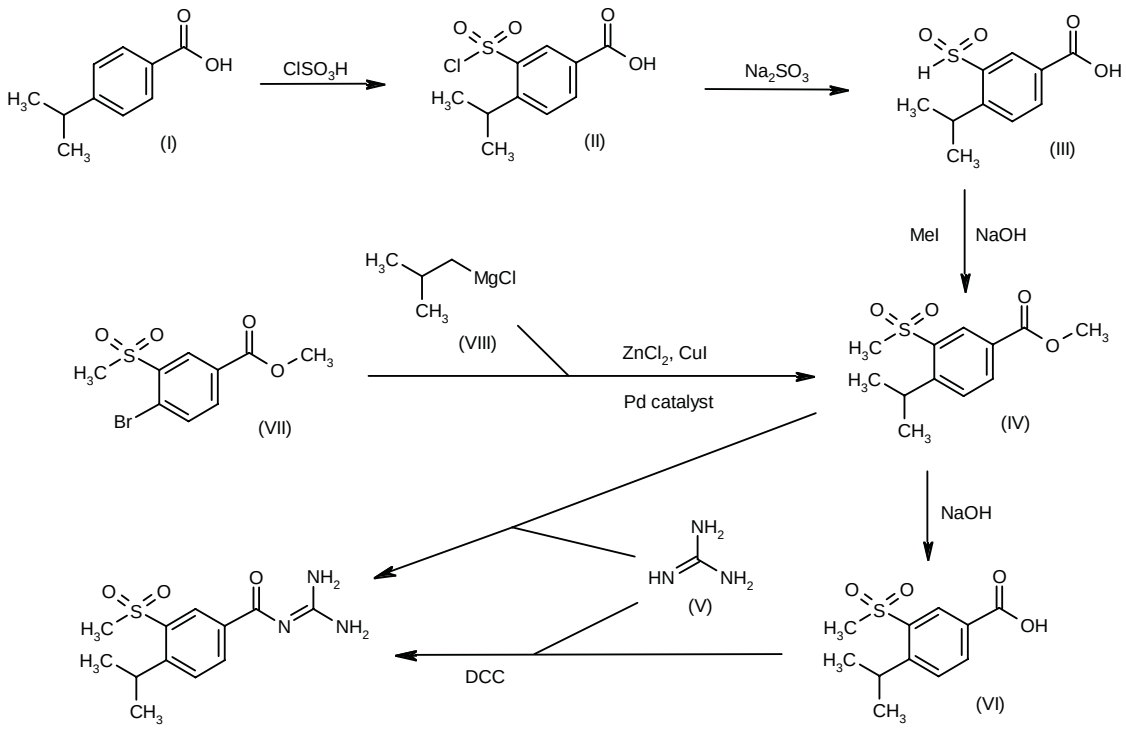
2) The hydrolysis of benzoate (IV) with NaOH in methanol/water gives the corresponding free acid (VI), which is then condensed with guanidine (V) by means of dicyclohexylcarbodiimide (DCC) in THF.`

3) Benzoic ester (IV) can also be obtained by alkylation of 4-bromo-3-(methanesulfonyl)benzoic acid methyl ester with isopropylmagnesium chloride by means of CuI, $ZnCl_2$ and a $PdCl_2$ catalyst in THF (1).

In vitro inhibition of Na^+/H^+ exchange by Hoe-642 during simulated ischemia in isolated rat cardiomyocytes provided cells with protection against irreversible hypercontracture. Effects on intracellular Ca^{2+} concentration and pH were not observed (2).

The cardioprotective effects of cariporide were evaluated in electrically paced isolated rat hearts subjected to total ischemia and reperfusion with cariporide alone (5 μM) or in combination with isoflurane, sevoflurane or sufentanil. All drugs enhanced left ventricular developed pressure to >90% of preischemic values, as compared to a 40% recovery observed in control hearts. Ventricular

Scheme 1: Synthesis of Cariporide



pressure recovery in the presence of cariporide was more rapid and was accompanied by reduced left ventricular end-diastolic pressure. Cariporide administered with volatile anesthetics enhanced recovery of left ventricular developed pressure to >100%, but without further reductions in left ventricular end-diastolic pressure (3).

In an *in vitro* study, an 80% reversible inhibition of the sarcolemmal Na^+/H^+ exchanger was observed when isolated rat ventricular myocytes or hearts were exposed to Hoe-642 (1 μM). Isolated hearts infused with Hoe-642 (5 min) prior to prolonged (40 min) ischemia or brief periods (3 plus 5 min) of ischemic preconditioning (PC) displayed a 45 ± 7% and 68 ± 2% improvement, respectively, in postischemic recovery of left ventricular developed pressure (LVDP). Exposure of Hoe-642-pretreated hearts to 60 min of ischemia and PC, produced additive improvements of LVDP (66 ± 2% *vs.* 37 ± 4% Hoe-642 without PC). Results showed that although the Na^+/H^+ exchanger is not involved in the cardioprotective effects associated with PC, inhibition of the exchanger may enhance the protection afforded by PC (4).

An *in vitro* study demonstrated that preinfusion with Hoe-642 (1 μM) of isolated rat hearts exposed to 25 min of ischemia at 37 °C resulted in improvement of aortic flow of 18 ± 4%, a rate inferior to that observed with cardioplegia (53 ± 7%). Recovery of aortic flow in hearts subjected to 35 min ischemia at 37 °C was improved further with cardioplegia and pretreatment with Hoe-642 or early reperfusion with Hoe-642. Similar additive improvements were observed with cardioplegia and Hoe-642 in hearts exposed to 120 min of ischemia during moderate hypothermic conditions and 300 min of ischemia during severe hypothermia. A reduction in creatine kinase leakage during reperfusion was also noted with improvement in aortic flow (5).

The inhibitory effects of cariporide on type-1 Na^+/H^+-exchange were evaluated in isolated rabbit hearts perfused to regional ischemia and reperfused with 1 μM of the drug. Cariporide reduced the level of ST deviation from the isoelectrical line and counteracted the increase in dispersion. Left ventricular end-diastolic pressure increased to a lesser degree in the presence of the drug, and the recovery of the action potential was delayed. Cariporide thus appeared to protect the heart from ischemic damage without affecting the size of the electrically silent area (6).

A high dose of cariporide was necessary to reduce reperfusion-injury in pigs. Ischemia, induced in anesthetized pigs by 60 min LAD occlusion, was followed by 180 min of reperfusion; cariporide (3 or 10 mg/kg) or the vehicle was administered to the left ventricle 1 min prior to reperfusion. Left ventricle end-diastolic pressure moderately increased in all groups following 60 min ischemia. While the 180 min reperfusion caused a significant

decrease in mean arterial pressure and dP/dt_{max} in vehicle-treated animals, no such effects were observed in pigs treated with the high dose of cariporide. In addition, cariporide at 10 mg/kg significantly decreased infarct size by 31% while the low 3 mg/kg dose of the agent and the vehicle were ineffective (7).

Rabbits pretreated with cariporide (0.01, 0.03, 0.1 and 0.3 mg/kg i.v.) 10 min before occlusion exhibited a dose-dependent reduction in infarct mass as compared to control animals, whereas the area at risk was similar in both groups. The compound was less effective when administered only on reperfusion (8).

Administration of Hoe-642 (2 mg/kg i.v.) in dogs prevented atrial shortening and loss of rate adaptivity of refractoriness induced by ischemia. The results indicate that atrial ischemia may play a role in electrical remodeling induced by atrial fibrillation (9).

In a pig model of ischemic infarction, administration of Hoe-642 (10 mg/kg)1 min prior to reperfusion significantly reduced the infarct size, indicating that a high concentration of the drug is necessary at the Na^+/H^+ exchanger site in order to achieve a protective effect (10).

The potential beneficial effects of pretreatment with dietary cariporide mesilate have been investigated in a rat model of myocardial infarction. Animals were subjected to either sustained coronary ligation (3 h and 45 min) or 45-min ligation followed by 3-h reperfusion. Ventricular fibrillation induced by ischemia (incidence of 42% in controls) was completely abolished in the cariporide-fed groups and ischemia-induced tachycardia was significantly reduced (from 82% in controls to 19% in those given cariporide). Although the effect was not significant, a clear trend for reduction in the incidence of apoptosis in these hearts was observed in rats fed cariporide. This study appears to confirm a role for Na^+/H^+ exchange in myocardial damage postinfarction, and also demonstrates beneficial effects for dietary cariporide (11).

The effects of cariporide 50 mg/kg s.c. on left ventricular function and remodeling were studied in rats with experimental myocardial infarction. Hemodynamic evaluation 3 weeks postinfarction revealed no significant differences between cariporide-treated animals and controls in left ventricular end-diastolic pressure or left ventricular volume, although there was a trend for greater survival rates in the cariporide group (12).

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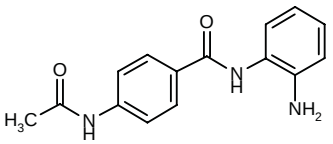
CI-994
Acetyldinaline
PD-123654
Goe-5549

Antineoplastic

EN: 137584



$C_{15}H_{15}N_3O_2$ **Warner-Lambert**

The antitumor effects of CI-994 in combination with adriamycin were evaluated in the M16C tumor model. Treatment began 3 days after tumor implantation, and CI-994 and adriamycin were given i.p. daily x 5 for 3 weeks and q7d x 3, respectively. The maximum tolerated dose of CI-994 at 20 mg/kg and adriamycin at 2.3 mg/kg produced a tumor growth delay of 16.2 days, while CI-994 20 mg/kg and adriamycin 2.3 mg/kg produced a tumor growth delay of 12.6 days. The growth inhibitory effects of both combination regimens were superior to the effects observed witheither drug (1).

The pharmacodynamics and pharmacokinetics of CI-994 were evaluated in mice following oral administration of 50 mg/kg during 14 days. Plasma distribution and elimination half-life were 51 min and 9.4 h, respectively, on day 1, decreasing to 31 min and 3.4 h, respectively, on day 14. AUCs on day 1 and 14 were 2879 and 2407 mcg/ml/min, respectively. Urinary excretion of CI-994 increased on day 14 as compared to day 1, while the proportion of drug excreted in the feces remained the same. Colon tumor growth in drug-treated mice decreased by 22% on day 19 as compared to controls, and the blood cell count for all cells was reduced, with white blood cells being most affected. Pretreatment levels of blood cells were reached quickly following drug withdrawal (2).

The preclinical toxicity of orally administered CI-994 was assessed in Wistar rats (9, 30 and 90 mg/m^2) and in beagle dogs (10, 40 and 100 mg/m^2). Results showed that CI-994 primarily affects tissues with rapidly dividing cell populations, and that bone marrow suppression was the dose-limiting toxicity. The release and/or maturation of cells in the bone marrow also appeared to be disrupted by CI-994. Severe clinical signs and mortality occurred in both species with the highest doses (3).

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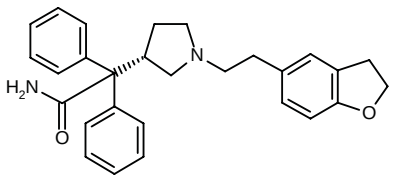
Darifenacin

Treatment of Irritable Bowel Syndrome
Muscarinic M_3 Antagonist

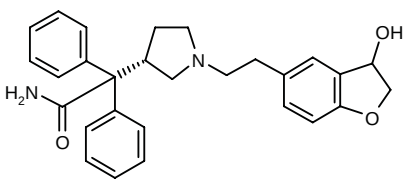
EN: 168032



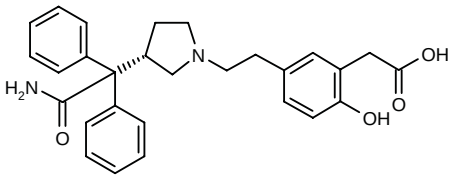
$C_{28}H_{30}N_2O_2$ **Pfizer**

Plasma half-life following intravenous administration of darifenacin 2.5 mg/kg was more than 2 h in animals, while oral administration of more than 4 mg/kg produced signs of clearance saturation. Oral clearance in man was high with respect to blood flow. Radioactivity in feces originating from unmetabolized darifenacin was low in all study models, indicating that the drug was absorbed well from the gut. Darifenacin was metabolized by three main pathways; monohydroxylation of either the dihydrobenzfuran ring or diphenylacetamide moiety, with hydroxylation of dihydrobenzfuran ring producing [I] representing 10, 5, 5 and 12% in mouse, rat, dog and man, respectively; oxidative dihydrobenzfuran ring opening mediated by an aldehyde, which when oxidized to an acid [II] represents the major metabolite, representing 35, 34, 37, and 21% of the original dose in mouse, rat, dog and man, respectively; and *N*-dealkylation at the pyrrolidine nitrogen [III] representing 17, 2, 9, and 24% of the original dose in mouse, rat, dog and man, respectively (1).

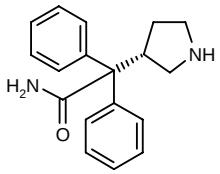
In male Heidenhain pouch beagle dogs, darifenacin administered at doses up to 1 mg/kg had no effect on pentagastrin-stimulated gastric acid secretion. When the dose was increased to 3 mg/kg, gastric acid secretion



[I]



[II]



[III]

was inhibited by 31%. These results suggest that darifenacin has minimal M_1 antagonist activity at doses which inhibit small bowel digestive motility (2).

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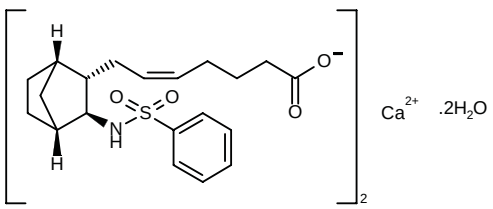
Domitroban Calcium Hydrate

S-1452 *Treatment of Allergic Rhinitis*

Anboxan® *Thromboxane A_2 Antagonist*

EN: 171665



$C_{40}H_{52}CaN_2O_8S_2.2H_2O$ **Shionogi**

Administration of S-1452 (50 mg p.o.) to 8 healthy adult males in the fasted and fed states produced C_{max} values of 78.1 and 34.6 ng/ml, respectively, and t_{max} values of 0.5 and 1.9 h, respectively. Calculated AUC values were 84.1 and 80.8 ng·h/ml before and after food intake, respectively, but were not significantly different. Food intake did not affect the rate of urinary excretion of S-1452 (1).

The pharmacokinetics of S-1452 (10 mg p.o.) and its inhibitory effect on platelet aggregation were compared in 8 young and 8 elderly male subjects in a single-blind, placebo-controlled, crossover study. Mean maximum plasma concentrations were higher in the elderly than in the young (28.7 *vs.* 16.4 ng/ml), and mean ratio of metabolites to unchanged compound was significantly lower in the elderly than in the young (1.1 *vs.* 1.7). The inhibitory effect of the drug on platelet aggregation *ex vivo* lasted up to 6 and 9 h after dosing in young and elderly subjects, respectively (2).

Shionogi has withdrawn its NDA in Japan for domitroban in the indication of asthma. However, the company will continue development of the compound for the treatment of allergic rhinitis (3).

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3. *Shionogi redirects development of TxA_2 antagonist.* Daily Essentials Jul 1, 1998.

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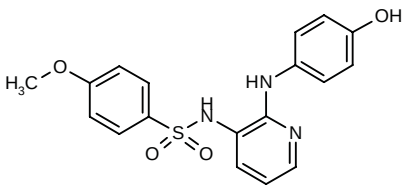
E-7010 *Antineoplastic*

EN: 185537



$C_{18}H_{17}N_3O_4S$ **Eisai**

In a phase I study, 16 cancer patients were administered E-7010 as a single dose (80-480 mg/m^2 p.o.) and 41 patients received repeated doses of E-7010 for 5 days (30-240 mg/m^2/day p.o.). Dose-dependent moderate gastrointestinal toxicity was observed, as well as hematolog-

ical toxicity. Plasma E-7010 increased rapidly after single-dose administration (half-life = 4.4-16.6 h) with no drug accumulation observed. E-7010 showed good absorption and elimination, with 77.5 ± 11.4% of total drug recovered from urine at 72 h. A 74% reduction in spinal cord metastasis was observed in the single-dose study in a uterine sarcoma patient in addition to 1 minor response. In the repeated-dose study, 1 patient with stomach cancer and another with uterine cervical carcinoma exhibited reductions in the tumor markers carcinoembryonic antigen and squamous cell carcinoma antigen, respectively. Phase II doses of 320 mg/m^2 and 200 mg/m^2/day x 5 were recommended for single- and repeated-dose studies, respectively (1).

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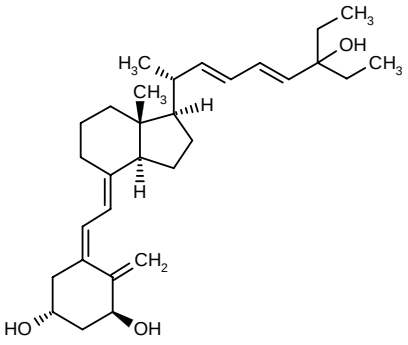
EB-1089
Seocalcitol

Antineoplastic
Vitamin D_3 Analog

EN: 174617



$C_{30}H_{46}O_3$

Leo Denmark

The synthetic vitamin D analog, EB-1089, was tested *in vivo* for its effects on apoptosis in cultured human breast cancer cells and in nitrosomethylurea-induced rat mammary tumors. Results indicated that EB-1089 may promote tumor regression by inducing active cell death (1).

The metabolites of 1α,25-dihydroxyvitamin D_3 (hydrolyzed at positions C26 and C26a) made a minor contribution to the biological profile of EB-1089. The potency and selectivity of the EB-1089 metabolites in mediating gene regulatory effects were drastically reduced as compared to the parent compound. Nonetheless, the compounds proved to be tools to understand the selective biological profile of EB-1089 (2).

In mice injected with syngeneic WEHI-3BD+ cells, treatment with EB-1089 (0.01, 0.05, 0.25, 0.5, 0.75, 1.0 and 1.25 μg/kg) significantly inhibited clonal growth of cells, without producing hypercalcemic effects, except for the highest dose tested. At day 100, leukemic mice treated with EB-1089 1.0 μg/kg i.p. every other day had survived longer than mice receiving vehicle only (30% *vs.* 5%) (3).

Nude mice with MCF-7 xenografts were treated with EB-1089. After 5 weeks of treatment, tumor volume was 4 times less in treated mice as compared to vehicle-treated mice. A 6-fold increase in DNA fragmentation occurred, and apoptotic cell morphology with a decreased proportion of epithelial cells to stroma was seen with EB-1089 treatment (4).

EB-1089 was evaluated in a phase II study in 22 patients with hepatocellular carcinoma. Therapy was initiated at a dose of 10 μg/day and escalated every 2 weeks according to serum calcium levels. Complete response was observed in one patient after 6 months. A new lesion appeared after 10 months, which disappeared after 5 months of continuing therapy. Another subject demonstrated a partial response after 3 months, with only 5% of the original tumor mass remaining after 6 months, and a third patient with a large tumor mass remained stable for more than 66 weeks. Reported adverse effects were mostly related to hypercalcemia (5).

The toxicity of EB-1089 was assessed in 10 previously treated patients with blastic MDS or acute myelogenous leukemia in remission. Patients were administered 10 μg/day of EB-1089 orally for 3 months, with biweekly increases of 5-10 μg/day until hypercalcemia developed. Serious treatment-associated side effects were not observed, and the highest tolerated doses for the 3-month study were 20 μg in 1 patient, 10 μg in 6 patients and 7 μg in 1 patient. Rising platelet counts were observed in 2 subjects, while responses on neutrophils or transfusion dependency were not reported (6).

Seocalcitol is the new proposed international nonproprietary name for EB-1089 (7).

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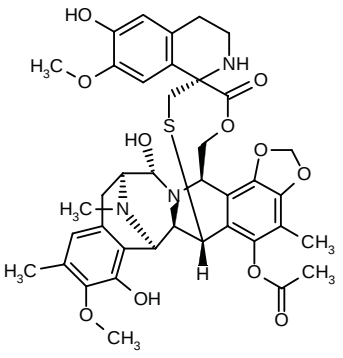
Ecteinascidin-743

Antineoplastic

EN: 139221



$C_{39}H_{43}N_3O_{11}S$ **Pharma Mar; Univ. of Illinois (US)**

Ecteinascidin-743 has been shown to have very potent cytotoxic effects due to minor groove alkylation resulting in protein concealed DNA single strand breakages. The IC_{50} values in the low nM range were obtained when human colon carcinoma cells were exposed to the agent; cell cycle arrest was also observed occurring in the G_2 phase. Temperature-sensitive DNA protein cross-links were also detected after μM exposures. An unidentified single protein species appeared to be cross-linked with evidence suggesting that it was not topoisomerase I or II. (1).

A phase I study examining the cytotoxic effects *in vitro* of ecteinascidin-743 on human hemopoietic progenitors and tumor cell lines demonstrated that prolonged exposure may be an appropriate regimen for clinical studies. Ecteinascidin-743 exposures of 24-h (3.1 ng/ml) and 1-h/day x 5 (3.2 ng/ml) resulted in higher toxicity than 1-h exposure (9.2 ng/ml). Differentiated cells were more responsive to the agent than immature progenitors and inhibitory activity decreased with culture time; together these results suggest that ecteinascidin-743-induced myelotoxicity was AUC-dependent. Prolonged exposure of tumor cells resulted in increased toxic activity especially in ovarian cancer cell lines (2).

The mechanism of action of ecteinascidin-743 was investigated with results showing that the agent does not inhibit DNA topoismerase I and II nor cause DNA breakage or interstrand cross-links In addition to apoptosis detected in several cell lines, cell cycle perturbances including accumulation of cells in the S phase and suppression of the G_2M phase were observed in colon cancer cell lines exposed to equitoxic ecteinascidin-743 concentrations. The compound was more effective in overexpressing P-gp cell lines and ecteinascidin-743-induced resistance to ecteinas-cidin-743 was observed with prolonged exposure of ovarian and colon cell lines (3).

The cytotoxic effects and multiple cellular targets of ecteinascidin-743 (14 day continuous or 1-h exposure with 0.1 nM to 1 μM) was demonstrated *in vitro* with human primary tumors (breast, non-small cell lung, ovary and melanoma) from 89 patients. Continuous exposure resulted in dose-dependent inhibition of tumor colony formation in all tumor types although percent survival varied between concentrations for each exposure. Incomplete cross-resistance was observed with continuous exposure of 10 nM of ecteinascidin-743 and paclitaxel, doxorubicin and cisplatin. However, 0.01 μM ecteinascidin-743 was effective in 16/39, 11/22 12/28 and 5/13 tumors resistant to 0.2 μg/ml cisplatin and 0.25, 2.5 and 10 μg/ml paclitaxel, respectively (4).

An *in vitro* study has described gender differences in the pharmacokinetics of ecteinascidin-743 in rats with significantly greater NADPH-dependent elimination noted from male microsomal preparations. Metabolism of ecteinascidin-743 was induced by phenobarbital and dexamethasone while inhibition was observed with chemical inhibitors of cytochrome P450 enzymes 3A, 2C and 1A and cytochrome P450 3A2 serum indicating a role for these enzymes in the sex-dependent differences in metabolism of the agent; no gender differences were noted in plasma drug profiles. Distribution half-lives of the compound were shorter in females than males (3.0 and 6.4 min, respectively) whereas clearance, V_{ss} and biliary excretion were similar. Biliary excretion of a cytotoxic ecteinascidin-743 metabolite, ecteinascidin-729, was greater in females suggesting that this metabolite is responsible for gender differences observed in heptotoxi-

city. Sex-dependent metabolism is unlikely in humans since no differences have been observed in expression of subclasses of cytochrome P450 enzymes (5).

In a phase I trial enrolling 20 patients with advanced solid malignancies, ET-743 (6, 12, 24, 48, 96, 144 and 216 μg/m^2) was administered by 1-h infusion, daily x 5 every 21 days. Grade III elevations in hepatic transaminases (LFT) represented the most severe toxicity, and affected a single patient during the first and second course of treatment at the highest dose level. One patient at the same dose level had grade I LFT elevations during the first and second course. In both cases LFTs peaked on day 8 and returned to baseline by day 21. Grade I-II nausea and emesis, neutropenia, phlebitis and transient elevations in creatinine levels were also reported. Pharmacokinetics appeared to be linear, and no drug accumulation was observed on day 5 of treatment. No major responses were obtained in this study. However, as the toxicities observed in this trial at the AUC associated with the LD_{10} in mice were tolerable, further dose escalation appears to be warranted (6).

Parallel structural and modeling studies with ececteinascidin-743 and ececteinascidin-736 were performed through examination of DNA adduct NMR properties. Results identified a unique parallel hydrogen bonding linkage of the A- and B-subunits to a three base-pair region (5-AGC and 5-CGG) in both agents responsible for the sequence recognition and reactivity of the compounds (7).

The pharmacokinetics of ecteinascidin-743 were found to follow a three exponential decay with a terminal half life of 20-h when examined in three phase I studies. Patients received either a 1-h infusion (50 μg/m^2) every 3 weeks, 24-h infusion (50 μg/m^2) every 3 weeks or a 1-h infusion (6 μg/m^2/d)/day x 5 every 3 weeks. A large interpatient variability was observed and regimen-independent clearances were similar in all three trials. Plasma metabolites have not been found in patients as of yet (8).

In an ongoing pharmacokinetic phase I trial, 26 patients with colo-rectum, ovary, sarcoma, renal, breast, bladder, larynx, gastric, and ACUP solid tumors were administered a 24-h continuous i.v. infusion of ecteinascidin-743 (50-1500 μg/m^2) every 21 days over 8 doses. Grade 2 nausea/vomiting and reversible increases in transaminases were noted starting with the 600 μg/m^2 dose. Toxicity was self-limiting and was not observed in the second treatment cycle. The maximum tolerated dose was not achieved in this study (9).

In an ongoing phase I clinical trial, 33 patients with refractory solid tumors were administered a 1-h i.v. infusion of ecteinascidin-743 (50-1100 μg/m^2) every 21 days for 8 dose levels. No dose-limiting heptotoxicity was observed with doses less than 800 μg/m^2. However, 12 patients displayed reversible grade 1/2 transaminase elevation and another patient had grade 3 phlebitis. At the maximum acceptable dose determined to be 1100 μg/m^2, significant toxicity was observed including grade 4 thrombocytopenia, grade 3 fatigue, grade 1 alkaline phosphatase elevation, transient grade 4 neutropenia and transient grade 3/4 elevation of transaminases. Although no objective responses have been observed, one uterine sarcoma patient had clinical improvement for 19 weeks and a melanoma patient experienced stable disease for 30 weeks. Accrual is ongoing using a dose of 1000 μg/m^2 to determine an appropriate phase II dose (10).

The pharmacokinetics of ET-743 were evaluated in 24 patients with advanced solid malignancies receiving doses of 6, 12, 24, 48, 96, 144, 216 and 287 μg/m^2/day. No major responses were observed following administration, with the most common toxicity observed being transient and isolated elevations of hepatic transaminase levels. Nausea, emesis, neutropenia, phlebitis and transient creatinine phosphate levels were also observed. In conclusion, the toxicities observed following administration of ET-743 at doses producing AUCs corresponding to LD10 in mice were tolerable, and further dose-escalating studies are in progress (11).

Human plasma ecteinascidin-743 was analyzed and results from conventional liquid chromatography with ultraviolet detection and miniaturized liquid chromatography coupled to an electrospray outlet and two quadruple mass analyzers were compared. Plasma samples were extracted prior to analysis using solid phase methods. Lower limits of quantification of 1 ng/ml and 10 pg/ml were achieved with the conventional and miniaturized chromatography, respectively. The miniaturized chromatography method, currently being used for analysis in phase I pharmacokinetic studies on ececteinascidin-743, was determined to be precise, accurate and provided a broad linear concentration range (12).

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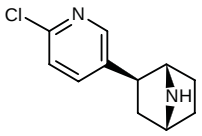
Epibatidine

Analgesic

EN: 202254



$C_{11}H_{13}ClN_2$ **Dept. of Health & Human Services (US); CytoMed**

Pretreatment of the prefrontal cortex, medial striatum, nucleus accumbens, amygdala and superior colliculus of rat brain with Sch-23390, MK-801 and mecamylamine inhibited the induction of Fos protein by epibatidine (5, 10, 50 μg/kg), indicating that dopamine D_1, NMDA and nicotinic ACh receptors may be involved in epibatidine-induced Fos protein expression in rat brain (1).

In order to identify potential central nervous system action sites for the effects of epibatidine on the flexor reflex, responses after nucleus raphe magnus and spinal (T13-L1) injections of epibatidine were evaluated. Findings suggested that an overall antinociceptive effect of systemic administration of epibatidine was partially mediated by the nucleus raphe magnus. Epibatidine appeared to have additional potentiating effects at other sensory neuroaxis sites such as the lumbo-thoracic spinal cord (2).

The heterologous expression of epibatidine- and α-bungarotoxin-binding human α_7-nicotinic receptor in a native receptor-null human epithelial cell line was evaluated. Results indicate that stable expression of the human α_7 subunit could give rise to cell surface receptors that bound [^{3}H]-epibatidine and [^{125}I]-labeled α-bungarotoxin with high affinity and showed homologous regulation and pharmacological properties consistent with native neuronal α_7-nicotinic acetylcholine receptors (3).

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PAF Antagonist

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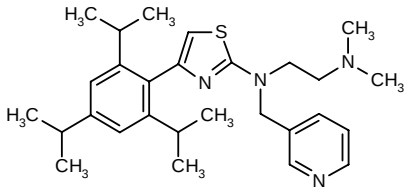

$C_{28}H_{40}N_4S$ **Sanofi**

In a double-blind, placebo-controlled, crossover study in 12 nonsmoking patients with mild asthma, SR-27417A (20 mg) was shown to moderately reduce PAF-induced neutropenia and rebound neutrophilia, and to increase respiratory systemic resistance and alveolar-arterial pressure difference for oxygen. Decreased arterial oxygen tension was also observed. Thus, SR-27417A appeared to be effective in inhibiting systemic, cellular and pulmonary effects following PAF challenge in patients with mild bronchial asthma (1).

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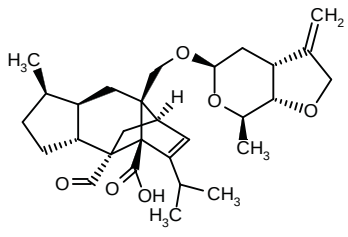
GM-237354

Antifungal

EN: 250638



$C_{29}H_{40}O_6$ **Glaxo Wellcome**

A pharmocokinetic/pharmacodynamic (PK/PD) study of sordarin derivatives was conducted in a lethal *C. albicans* infection in mice. Pharmacokinetic parameters

(AUC, C_{max}) were obtained after a single subcutaneous dose of GM-237354 (50 mg/kg) in healthy animals. Following subcutaneous doses (2.5, 5, 10, 20 and 40 mg/kg) every 4, 8 or 12 h (total daily dose range: 5-240 mg/kg), findings showed that treatments significantly prolonged survival as compared to untreated controls. Significant correlation between pharmacokinetic parameters *in vitro* and *in vivo* activity of sordarin derivatives was demonstrated. Thus, a PK/PD approach is useful to evaluate relationships between pharmacokinetic parameters and efficacy in antifungals research (1).

The toxicological potential of GM-191519, GM-193663 and GM-237354 was evaluated through studies of nonclinical toxicity including genotoxicity screens, safety pharmacology, acute single-dose and subchronic multiple-dose in rats and dogs. Treatment related changes for these three sordarin derivatives included slight increases in liver weight and/or vacuolation and slight decreases in erythropoesis. No changes precluded further development (2).

The *in vitro* activity of GM-193663, GM-222712 and GM-237354 alone and in combination with other antifungal agents such as amphotericin B, fluconazole, itraconazole and voriconazole was evaluated against clinical isolates of *Candida albicans*, *Aspergillus* spp. and *Scedosporium apiospermum*. These sordarins produced synergy or additivity when combined with other systemic antifungal agents. No increased toxicity was seen when the same combinations were tested on mammalian cell lines (3).

The *in vitro* pharmacodynamic parameters of GM-191519, GM-237354 and GM-193663 were evaluated using a new quantitative approach and compared with commercially available drugs: atovaquone, pentamidine and trimethoprim/sulfamethoxazole. These sordarin derivatives were at least 5000-fold more active than trimethoprim/sulfamethoxazole. Further studies to determine *in vitro* and *in vivo* correlations employing this approach are necessary (4).

The pharmacokinetic properties of GM-222712, GM-193663 and GM-237354 were evaluated in several animal species following intravenous administration of 20 mg/kg. The pharmacokinetic properties of these systemic antifungal agents are scalable by conventional allometry (5).

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Ibogaine Endabuse®

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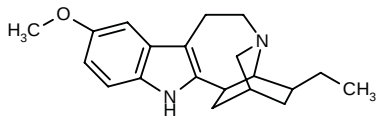

$C_{20}H_{26}N_2O$ **NDA Int.; OmniChem**

Ibogaine pretreatment was shown to completely prevent the acute effects of cocaine on striatal and nigral neurotensin systems. Ibogaine-induced increases in neurotensin-like immunoreactivity in striatum, nucleus accumbens and substantia nigra were blocked by a D_1 receptor antagonist. These findings indicate that neurotensin may contribute to an interaction between ibogaine and the dopamine antagonist system and that neurotensin may be involved in the antiaddictive mechanisms of ibogaine (1).

To clarify the effects of ibogaine on dopamine activity, male Long Evans rats were administered ibogaine (40 mg/kg i.p.) prior to testing for preference for natural rewards like sweet solutions. No attenuation of preference occurred for glucose-saccharin or for a neutral flavor previously combined with a sweet taste. In separate experiments, locomotion was significantly lower in ibogaine-treated rats that had been previously exposed to amphetamine (4 doses of 1.5 mg/kg) than in those rats that had not been exposed (2).

Results of a study in rats evaluating the potential of lysergic acid dimethylamide and (–)-2,5-dimethoxy-4-methyl-amphetamine to substitute for the ibogaine-

induced discriminative stimulus indicate that ibogaine may exert its actions via a 5-HT_{2A} receptor-mediated mechanism. However, this mechanism does not seem to be essential to the ibogaine-induced discriminative stimulus (3).

Direct infusion of ibogaine, its metabolite noribogaine or harmaline into the striatum of rats produced an increase in dopamine, which may mediate the antiaddictive effects of these alkaloids (4).

The effects of ibogaine on the expression of locomotor sensitization in chronic cocaine-treated rats were investigated. Animals were randomized to receive 40 mg/kg ibogaine or vehicle 19 h before sensitization testing with cocaine (7.5 mg/kg). The procedures were replicated after 3-4 days. Results indicate that ibogaine augments sensitivity to psychomotor stimulant effects of cocaine, and this increase depends on previous drug history and possibly on the number of ibogaine treatments. The antiaddictive properties of ibogaine may be due to an ability to increase the aversiveness of cocaine in chronic cocaine users (5).

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Y-24180
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Antiallergic/Antiasthmatic
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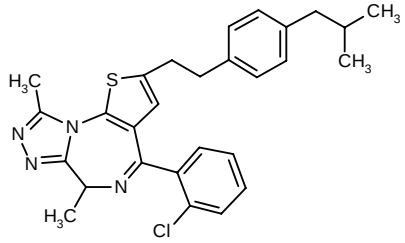

$C_{28}H_{29}ClN_4S$ **Yoshitomi; Japan Tobacco**

In mice sensitized with ovalbumin and then challenged intratracheally with ovalbumin 3 times every 4 days, Y-24180 (3 mg/kg) dose-dependently suppressed eosinophil infiltration and suppressed IL-5 release. WEB-2086 had no effect with a once-daily dose, but did suppress eosinophil infiltration when given twice daily (30-200 mg/kg/day) (1).

The pharmacological profile and antiasthmatic effects of Y-24180 were evaluated in actively sensitized guinea pigs. Y-24180 displaced the specific binding of [^{3}H]-WEB 2086 in the lung with an IC_{50} of 8.2 nM, and showed a more potent suppression of PAF-induced reactions. The suppression of PAF-induced bronchoconstriction lasted longer with Y-24180 than with WEB-2086. Oral administration of Y-24180 also suppressed antigen-induced airway hyperresponsiveness, as well as immediate and late asthmatic response. Antigen-induced accumulation of eosinophils in the bronchoalveolar lavage fluid and airway vascular hyperpermeability were also suppressed by Y-24180 (2).

Preincubation of human peripheral blood polymorphonuclear leukocytes with Y-24180 inhibited leukotriene B4-induced activation of leukocytes by arresting the increase in intracellular calcium ion $[Ca^{2+}]_i$ level. This effect was mediated by antagonistic action against intracellular PAF-induced upregulation of $[Ca^{2+}]_i$ level (3).

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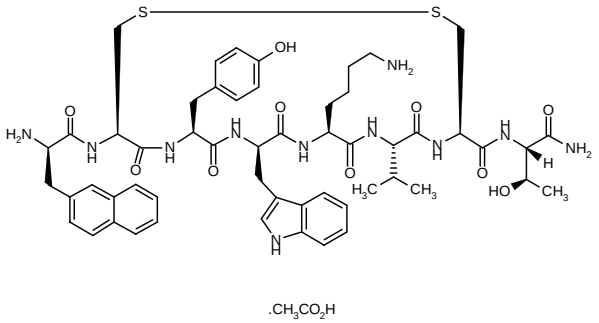

$.CH_3CO_2H$

$C_{54}H_{69}N_{11}O_{10}S_2.C_2H_4O_2$ **Biomeasure; Beaufour-Ipsen**

Lanreotide acetate (Somatuline) has been launched in the U.K. by Ipsen Ltd. for the treatment of acromegaly when levels of growth hormone remain abnormal after surgery or radiotherapy, and for the relief of symptoms of neuroendocrine tumors. The compound is formulated as microparticles for intramuscular injection and incorporates a copolymer that extends the product's duration of action considerably, enabling dosing at up to 14-day intervals (1).

1. *Somatostatin analogue launched in U.K.* Daily Essentials May 19, 1998.

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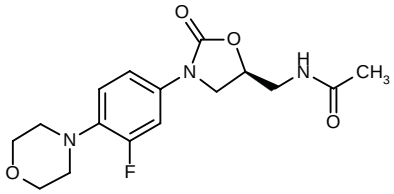
Linezolid

Oxazolidinone Antibacterial

EN: 224298



$C_{16}H_{20}FN_3O_4$ **Pharmacia & Upjohn**

Potent activity with linezolid was observed *in vitro* against vancomycin-resistant enterococci, methicillin-resistant *S. aureus* and penicillin-resistant pneumococci; all isolates tested were inhibited by the agent at concentrations of 8 μg/ml or lower (1).

In vitro in agar dilution, the antibacterial activity of linezolid was evaluated against 183 pneumococci, 126 strains of *Staphylococcus aureus*, 103 coagulase-nega-

tive staphylococci and 106 enterococci. At concentrations of 2 mg/l or lower, linezolid inhibited all strains tested with the exception of one *Enterococcus faecalis*, without signs of cross-resistance with other relevant antibiotics (2).

Linezolid showed promising activity *in vitro* against *Mycobacterium avium* complex (MAC), a frequent source of infection in AIDS patients that generally develops macrolide resistance after some 4 months of treatment. Based on the potent anti-MAC activity observed in this preliminary study, especially when used in combination with ethambutol, linezolid appears to warrant further investigation for the treatment of MAC infection (3).

The potential utility of linezolid in treating animal bite wound infections was evaluated *in vitro* in comparison to other macrolides. The compound showed good activity against 148 clinical isolates of *Pasteurella* species, showing MIC_{90}s in the range of 2-32 μg/ml; all isolates were resistant to clindamycin, used as reference (4).

In vitro studies showed that linezolid exhibited good inhibitory activity against various clinical isolates of methicillin-susceptible and -resistant staphylococci (MIC_{90} = 1-4 μg/ml) and vancomycin-susceptible and -resistant enterococi (MIC_{90} = 1-4 μg/ml). Linezolid was bacteriostatic in time-kill studies, demonstrating a postantibiotic effect of 0.8 ± 0.5 h against *Staphylococcus aureus*, *S. epidermidis*, *Enterococcus faecalis* and *E. faecium* (5).

The antibiotic activity of linezolid was evaluated in a mouse model of soft tissue bacterial infections. Linezolid (50 mg/kg p.o.) cured 50% of soft tissue infections with *Staphylococcus aureus*, and yielded an ED_{50} of 11.0 mg/kg against *Enterococcus faecalis*. In polymicrobial soft tissue infections with *Bacteroides fragilis*, *E. coli* and *E. faecalis*, linezolid alone had poor antibiotic activity (ED_{50} = >200 mg/kg), although when used in combination with piperacilin/tazobactam, the infections were cured (ED_{50} =13.6 mg/kg) (6).

In vivo in mice infected with *S. aureus* (MSSA-2 and MRSA-2) and penicillin-susceptible (PSSP-1), -intermediate (PISP-2) and -resistant (PRSP-5) *Streptococcus pneumoniae*, linezolid gave MIC values in the range of 0.5-1.0 and 1.0-4.0 mg/l for *S. pneumoniae* and *S. aureus*, respectively. Based on a pharmacokinetic goal of 40% time above the MIC, a dose regimen of 500 mg i.v. or p.o. b.i.d. was considered to be sufficient for successful treatment of infection with organisms having MICs of up to 4 mg/l (7).

In a preclinical study evaluating the pharmacokinetics and metabolism of linezolid (25 mg/kg p.o. or 10 mg/kg i.v.) in Sprague-Dawley rats, the oxazolidinone showed good bioavailability and wide distribution. Extensive renal tubular reabsorption of the compound was observed, and the drug was excreted primarily in the urine as unchanged compound or as carboxylic acid metabolites with low antibacterial activity (MICs > 16 μg/ml) (8).

The safety, tolerance and efficacy of linezolid were evaluated in 37 patients with multidrug resistant Gram-positive infections. The drug was well tolerated and displayed clinical and antimicrobial efficacy in 63.0 and 55.6% of patients, respectively. No serious therapy-related adverse events were reported. Most common side effects were diarrhea, nausea and elevated liver enzymes (9).

Minimum inhibitory concentrations (MICs) for linezolid, eperezolid and comparators were determined against 103 strains of *Rhodococcus equi* isolated from humans and animals. Linezolid (MIC_{90} = 2.0 μg/ml) was more active than eperezolid (MIC_{90} = 16.0 μg/ml). Differences in antimicrobial activity were not observed against *R. equi* strains isolated from humans or animals. Of the other agents tested, premafloxacin (MIC_{90} = 0.13 μg/ml) was the most active (10).

Pharmacokinetics of linezolid 200, 400 and 600 mg in 48 volunteers with nasal colonization of *Staphylococcus aureus* demonstrated multi-modal within-dose likelihood distributions of K_m and V_{max}, indicating several saturable steps. At the 600-mg dose, the model reached the higher K_m breakpoints more often. However, the nonlinearity observed should not attain clinical significance (11).

The metabolism and excretion of radiolabelled linezolid was evaluated in volunteers receiving single oral doses of 500 mg or two doses of 500 mg b.i.d. five days apart. Radioactivity was excreted rapidly with 80-85% of the original dose detected in urine and 7-12% in feces. The compound was excreted mainly as the parent drug or as morpholine ring-oxidized metabolites with low antibacterial potency. Peak plasma concentration levels averaged 10-15 μg-eq/g in all study groups (12).

Evaluation of pharmacokinetics of linezolid in subjects with various degrees of renal function showed that drug clearance did not change as a function of creatinine clearance, but an increase of 80% was observed in patients on dialysis. The elimination rate constant was not affected by creatinine clearance or dialysis. Thus, patients with decreased renal function do not need to change linezolid dosing, however, in patients on dialysis, administration may need to be delayed until after dialysis, or supplemented with a 200 mg dose at the conclusion of dialysis. (13).

The antibacterial activity of linezolid (200, 400 and 600 mg) was evaluated in 56 patients with nasal colonization with *Staphylococcus aureus*. Bacterial eradication was observed in 94% of the subjects, with a median time to eradication of 36-60 h. No relationship was observed between time to eradication and $AUIC_{24}$, %T>MIC or Peak/MIC. Adverse events observed included headache, vaginal yeast infection, diarrhea, nausea and/or emesis and rash (14).

The pharmacokinetics of linezolid were evaluated in healthy male and female volunteers. Mean clearance following single and multiple i.v. doses was 125 ml/min, with 35% of the parent compound eliminated unchanged in the urine. Renal and nonrenal clearance were about 40 and 100 ml/min, respectively, while mean steady-state volume of distribution was 50 l. Mean elimination half-life was 5-7 h. Following oral administration, C_{max} was reached within 2 h, with an absolute bioavailability of 103%. Administration during fasting and fed conditions did not significantly alter AUC values, indicating that food should not affect the efficacy of the drug (15).

The ability of linezolid to inhibit human MAO A was investigated in a sensitive, linear, flexible and tolerant assay. Linezolid showed weak, competitive (reversible) inhibition of MAO A; however, this has not been observed in phase II and III trials (16).

Pharmacia & Upjohn's linezolid is currently in phase III clinical trials (17).

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Lisinopril
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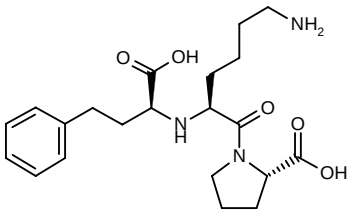
ACE Inhibitor
Treatment of Diabetic Retinopathy and Nephropathy

EN: 090853



$C_{21}H_{31}N_3O_5$ **Zeneca**

Zeneca has introduced lisinopril (Zestril®) in the U.K. for controlling the risk of progression of renal complications of noninsulin-dependent diabetes (1).

The EUCLID study, a 2-year, double-blind, randomized, placebo-controlled trial in 530 patients in a number of European centers, included an assessment of retinopathy after treatment with lisinopril (10-20 mg/day) in nonhypertensive and normoalbuminuric or microalbuminuric patients with type I diabetes. Gradable retinal photographs at baseline and follow-up were available for 354 patients, and retinopathy was present in 103 patients (59%) in the lisinopril group and 117 patients (65%) in the placebo group. Progression of retinopathy by at least 1 level was detected in 21 of 159 lisinopril-treated patients (13.2%) *versus* 39 of 166 placebo-treated patients (23.4%) (unadjusted odds ratio: 0.50). Treatment with lisinopril was also associated with a decrease in progression by two or more grades (unadjusted odds ratio: 0.27) and progression to proliferative retinopathy (unadjusted odds ratio: 0.18). The incidence of retinopathy was also lower in the lisinopril group (13 of 72 patients) *versus* the placebo group (15 of 62 patients), giving an unadjusted odds ratio of 0.69 (2).

1. *Zestril introduced for new indication in U.K.* Daily Essentials Feb 5, 1998.

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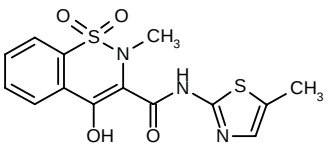
Meloxicam
Mobic®

Antiinflammatory
COX-2 Inhibitor

EN: 100331



$C_{14}H_{13}N_3O_4S_2$ **Boehringer Ingelheim; Almirall Prodesfarma**

Meloxicam demonstrated superior gastrointestinal tolerability and comparable clinical efficacy in studies contrasting its effects to those of two commonly prescribed NSAIDs, piroxicam and diclofenac SR, in patients with osteoarthritis. More than 9000 patients in 27 countries participated in the MELISSA (MEloxicam Large-scale International Study Safety Assessment) study, making it the largest prospective, double-blind trial evaluating

NSAID tolerability to date. Patients in the MELISSA trial received either meloxicam (7.5 mg/day) or diclofenac SR (100 mg/day) during a 28-day treatment period. Results showed 32% fewer meloxicam-treated patients had gastrointestinal adverse effects compared to patients on diclofenac. Additionally, only 3 patients in the meloxicam group spent a total of 5 days hospitalized for GI side effects, compared to 10 patients in the diclofenac SR group who spent a total of 21 days in the hospital. Findings from the MELISSA study are consistent with those reported in the SELECT (Safety and Efficacy Large-scale Evaluation of COX-inhibiting Therapies) study, the second largest prospective trial conducted to date for purposes of evaluating NSAID tolerability. The 8500 osteoarthritis patients in 12 countries who participated in SELECT were randomized to treatment with meloxican (7.5 mg/day) or piroxicam (20 mg/day) for 28 days. In this study, 33% fewer meloxicam-treated patients had adverse gastrointestinal effects than patients on piroxicam (1).

In a double-blind, randomized trial in 513 patients with osteoarthritis of the knee, once-daily treatment with meloxicam (7.5 and 15 mg) was more effective than placebo with respect to pain on movement and pain at rest in the target joint, with the 15-mg dose reaching statistical significance. Both doses also demonstrated a significant difference on outcome measures of global efficacy and were well tolerated (2).

Boehringer Ingelheim's meloxicam (Mobic®) has been cleared for use in the U.K. for the symptomatic treatment of ankylosing spondylitis. The drug was originally approved for the short-term treatment of osteoarthritis and the long-term treatment of rheumatoid arthritis (3).

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Midazolam Maleate
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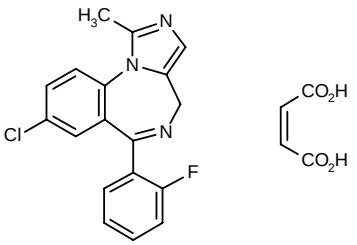
EN: 091131



$C_{18}H_{13}ClFN_3.C_4H_4O_4$ **Roche**

The FDA has granted additional exclusivity to Roche for midazolam hydrochloride (Versed®) through June 2000. This protection was granted in recognition of the studies conducted for Versed® Syrup, a pediatric formulation for alleviating anxiety before a diagnostic or therapeutic medical procedure or before the induction of general anesthesia (1).

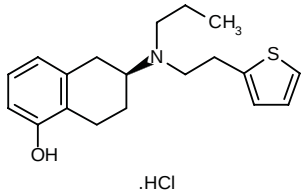
1. *Roche granted additional exclusivity for Versed from FDA*. Daily Essentials Oct 23, 1998.

Original monograph - Drugs Fut 1978, 3: 822.

N-0923

Antiparkinsonian
Dopamine D_2 Agonist

EN: 171120



$C_{19}H_{25}NOS.HCl$ **Discovery Therapeutics; Yoshitomi; Schwarz**

Discovery Therapeutics has reported that preliminary analysis of a double-blind, placebo-controlled, multicenter North American phase IIb clinical trial showed significant efficacy and reduced side effects in the treatment of patients with mild to severe Parkinson's disease using the company's once-a-day N-0923 transdermal patch. The patch reduced daily levodopa in the three highest dose groups by more than 30%. All evaluable patients were able to completely eliminate the use of oral agonists for the full 21-day study and 27% were able to reduce their levodopa intake to less than the minimum daily dose (300 mg). The multicenter North American study tested the patch in a total of 82 patients in 5 dosage arms, including 1 placebo group, for 21 days. Patients were taken off their regular dopamine agonist and levodopa therapy the night before starting treatment with the patch. If needed, levodopa was then added back into the regimen to maintain control of symptoms. All patients tolerated the immediate transition to N-0923 patch well, without the need for a gradual dose escalation typically required of oral agonists. The adverse effect rate, especially nausea, was notably lower than that associated with oral agonists and only 2 of 82 patients were discontinued because of adverse effects (1).

Schwarz and Discovery Therapeutics will codevelop Discovery Therapeutics' once-daily transdermal patch, N-0923, for the treatment of Parkinson's disease. The patch will be marketed worldwide by Schwarz except in Japan, where it will be marketed by Yoshitomi (2).

1. *Parkinson's patch yields positive results*. Daily Essentials Feb 16, 1998.

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Nacolomab Tafenatox
LS-4565
PNU-214565

Antineoplastic
Immunomodulator

EN: 229757

Pharmacia & Upjohn

The safety and efficacy of PNU-214565 was evaluated in 27 patients with advanced gastrointestinal malig-

nancies receiving 4 consecutive daily 3-h infusions of 0.15, 0.5, 1.5, 2.75 or 3.5 ng/kg. Partial response was observed in 1 patient with pancreatic cancer and liver metastasis, with fever and hypotension being the most common dose-limiting toxicities observed. Dose escalation was discontinued due to dose-limiting toxicity observed at the 4 ng/kg level. Considering the weight and anti-SEA concentration in a given patient, it was possible to assign a dose that produced cytokine-release without therapy-related toxicity (1).

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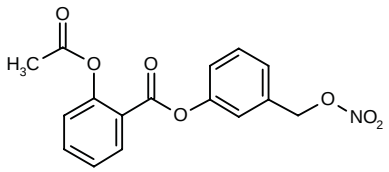
NCX-4016

Antithrombotic
Antiinflammatory
Analgesic

EN: 252036



$C_{16}H_{13}NO_7$ **NicOx; Bayer**

NCX-4016 has been evaluated in a rabbit model of platelet thromboembolism. Both NCX-4016 and aspirin at equimolar doses significantly inhibited thrombin-induced platelet accumulation, while neither inhibited platelet accumulation induced by ADP. Both drugs decreased collagen-induced platelet accumulation to a significant degree, but the effects of NCX-4016 were more potent (1).

NCX-4016 has been compared to aspirin *in vitro* and *in vivo* for its effects on cytokines, ICE-like proteases and the gastric mucosa. In contrast to aspirin, NCX-4016 did not induce tumor necrosis factor (TNF-α) release from murine macrophages. Aspirin administration (150 mg/kg orally) in rats produced gastric mucosal damage and upregulated gastric mucosa ICE/caspase activity. An equimolar dose of NCX-4016 did not induce gastric damage and significantly increased plasma nitrite/nitrate levels and inhibited aspirin-induced upregulation of ICE/caspase activity. Unlike aspirin, NCX-4016 inhibited TNF-α-induced apoptosis in human endothelial cells in a concentration-dependent manner, and it also inhibited IL-1β release from endotoxin-stimulated macrophages. These results provide evidence implicating modulation of ICE-like proteases and IL-1β release in the antiinflammatory and gastric mucosal protective effects of *N*-releasing NSAIDs (2).

The dual pharmacological properties of NCX-4215 and NCX-4016 on platelet function and gastrointestinal tolerability were examined *in vitro* and *in vivo*. Both compounds inhibited platelet COX activity and agonist-induced platelet aggregation while intracellular soluble guanylyl cyclase was activated. The agents exhibited superior gastrointestinal tolerability as compared to acetylsalicylic acid. NCX-4215 and NCX-4016 were also more potent than acetylsalicylic acid as inhibitors of thrombin-induced platelet aggregation *in vitro* and *in vivo*. Inhibition of thrombin-induced aggregation was suggested to involve nitric oxide (NO) release since aggregation was suppressed by NO scavengers and NCX-4215 and NCX-4016 stimulated NO release *in vivo* and *in vitro*. Platelet adhesion, expression of adhesion molecules and arachidonic-induced aggregation were also inhibited by both compounds with a greater potency noted for NCX-4215 on the latter effect. Cumulative doses of NCX-4016 inhibited the production of platelet thromboxin *in vivo* (3).

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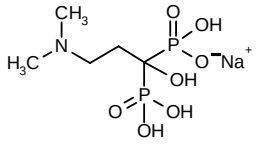
Original monograph - Drugs Fut 1997, 22: 1231.

Olpadronic Acid Sodium Salt

Treatment of Osteoporosis

EN: 159103



$C_5H_{14}NNaO_7P_2$ **Henkel; Gador**

A study of the effects of olpadronate in ovariectomized thyroxine-treated rats showed that the drug prevented increased hydroxyproline excretion and maintained bone mineral density and bone mineral content at the same level as in sham control rats (1).

Three boys with severe osteogenesis imperfecta type III and vertebral deformities were treated with continuous oral olpadronate for 5-7 years. The patients showed reduced bone fractures, increased calcification of long bones and improvement in vertebral shape. No side effects were reported (2).

Olpadronate (100-200 mg/day) was given to 37 patients with Paget's disease for 0.5-13 months. Patients with no previous treatment showed normalization of alkaline phosphatase levels, as did 21 of 25 patients previously treated with other drugs, including pamidronate in 14 cases (3).

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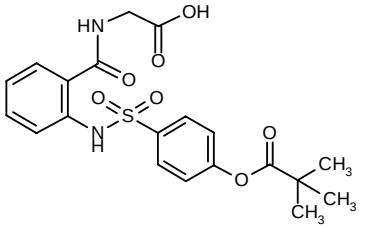
Ono-5046
Sivelestat
EI-546
Elaspol®

Elastase Inhibitor

EN: 157441



$C_{20}H_{22}N_2O_7S$ **Ono; Cortech**

The *in vitro* effects of Ono-5046 on proinflammatory cytokine production by human monocytes in a neutrophil-free system were investigated. Results suggest that Ono-5046 can inhibit cytokine production at clinically available concentrations, thus indicating that the drug could act as a dual inhibitor of neutrophils and moncytes in inflammatory tissue destruction (1).

Results of *in vitro* studies using the Capan-1 pancreatic carcinoma cell line have shown that Ono-5046 (1, 10 and 100 μg/ml) significantly suppressed proliferation, motility and chemotaxis, indicating that the drug may function as an anticancer agent by preventing the progression and metastasis of pancreatic carcinoma cells (2).

Two minutes after administration of Ono-5046 (1 and 5 mg/kg i.v. bolus) to male rats, respective plasma concentrations of unchanged drug reached levels of 10.33 and 33.61 μg/ml. The concentrations did not increase dose-dependently, and both doses had a $t_{1/2}$ of 7 min. However, the increases in total clearance and steady-state volume were dose-dependent. After administration of 1 and 5 mg/kg i.v. bolus to male dogs, the $t_{1/2}$ was 5 min and the AUC did not increase with dose. In rats, intravenous infusion (1 and 10 mg/kg/h for 2 h) produced dose-dependent, steady-state levels of 2.29 and 22.05 μg/ml, respectively, within 1 h. Administration of a similar regimen in dogs produced respective steady-state plasma concentrations of 1.14 and 13.24 μg/ml 30 min after administration. Total clearance of the drug in dogs was 2-fold higher than in rats (3).

In a rat model of nephrotoxic serum nephritis (NTS), intraperitoneal administration of Ono-5046 at 3 h and 1, 2, 3, 4, 5 and 6 days after injection of NTS dose-dependently decreased proteinuria and hematuria and inhibited the formation of crescentic glomeruli. These results suggest that neutrophil elastase degrades glomerular basement membrane proteins in NTS, and that Ono-5046 arrests elastase-induced crescentic formation and glomerular injury (4).

Results of *in vivo* studies in mice transplanted with human lung carcinoma cell line EBC-1 showed that daily injections of Ono-5046 (50 mg/kg i.p.) completely suppressed tumor growth when treatment was begun on day 1 of tumor implantation, and caused a significant delay in tumor growth when treatment began 14 days after tumor implantation. Both regimens completely inhibited the appearance of metastatic loci in the lungs 8 weeks post-transplantation. The results indicate that Ono-5046 inhibits both primary and metastatic growth of non-small cell lung cancers (5).

The general pharmacological properties of Ono-5046 have been investigated in various animal species, including mice, rats, dogs and guinea pigs. Overall results showed that Ono-5046 caused a decrease in blood pressure that was associated with an increase in mesenteric blood flow. These changes were temporary and reversible, indicating a very low risk of serious adverse events in clinical use (6).

The effects of Ono-5046 (5, 10 and 30 mg/kg/h) on endotoxin-induced liver mitochondrial dysfunction were assessed in guinea pigs. Data showed that Ono-5046 had dose-dependent benefical effects on oxygen uptake, respiratory control ratio and adenosine triphosphate synthesis, and at the highest dose, significantly improved mean blood pressure (7).

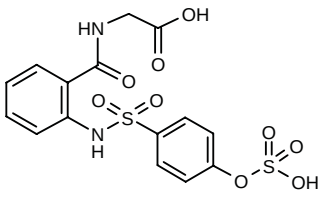
The effects of Ono-5046 (20 mg/kg/h) on acute lung injury caused by TNF-α and PMA-activated neutrophils have been investigated in isolated perfused rabbit lungs.

Results showed that Ono-5046 inhibited the alveolar epithelial and vascular endothelial injury caused by activated neutrophils, thus attenuating acute lung injury (8).

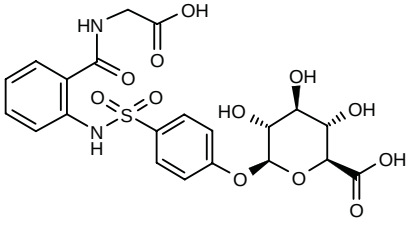
Metabolism studies of single doses of [^{14}C]-Ono-5046 were carried out in rats of both sexes. Elimination half-lives were 163.61-192.72 min after i.v. administration of 0.1-100 mg/kg, and did not differ between sexes. The AUC increased dose-dependently at doses up to 1 mg/kg. At doses of 0.1, 1 and 10 mg/kg/h, steady-state plasma concentrations were reached within 1.5 h, with elimination half-lives of 232.29-631.63 min. At a dose of 1 mg/kg, sex-related differences were observed in the rates of biliary excretion (33.0% in males *vs.*14.0% in females), as well as fecal and urinary excretion (24.0 and 73.1% in males *vs.* 90.2 and 8.2% in females) (9).

The metabolic profile of [^{14}C]-Ono-5046 after repeated administration (1 mg/kg/day i.v. for 7 days) and its effect on metabolizing enzyme activities were evaluated in rats. Pharmacokinetic parameters did not differ from those after single administration, and radioactivity in most organs diminished rapidly, which was similar to patterns after single dosing. Administration of Ono-5046 (1, 10 and 30 mg/kg/day) for 7 days had no effects on microsomal protein content or hepatic drug metabolizing enzyme activities (10).

The metabolism and binding to serum protein of Ono-5046 (1 mg/kg) were examined in various animal species. The structures of the main metabolite (M-1) and the sulfate [I] and glucuronide of M-1 [II] were identified in rats. After i.v. administration of [^{14}C]-Ono-5046 to male and female rats, the parent compound and M-1 accounted for 25.5-26.5 and 56.6-67.5% of plasma radioactivity, respectively. Male rats had a 10-fold higher plasma concentration and a 3.5-fold higher rate of urinary excretion of the M-1 sulfate than female rats. Biliary excretion accounted for < 0.1% of the dose. Serum protein binding of [^{14}C]-Ono-5046 (10 μg/ml) was 99.6, 96.7, 99.6 and 99.6% in rats, dogs, hamsters and humans, respectively (11).



[I]



[II]

After a single bolus administration of [^{14}C]-Ono-5046 (1 mg/kg i.v.) to pregnant rats, the radioactivity in the fetus was 0.004 times higher than in plasma at 30 min postdose, declining to a level below the detection limit at 4 h postdose. In lactating rats, the maximum level of radioactivity was lower in the milk than in the plasma (12).

Ono-5046 was shown to decrease the physiologic changes induced by instillation of phosphate buffered saline into the right lower lobes of rabbit lungs. It also produced neutrophil elastase blockade, but did not change neutrophil sequestration in the lungs. Measurements of lung injury were improved by Ono-5046 following hydrochloric acid instillation into the lungs (13).

Ono-5046, injected intraperitoneally into severe combined immunodeficiency mice that had been transplanted with 2 non-small cell lung cancer lines (EBC-1 and PC-3), caused complete growth suppression of EBC-1, but only delayed growth of PC-3 (14).

The effects of Ono-5046 (30 and 100 mg/kg), anti-CD18 MAb (0.5 and 1 mg/kg) and pentoxifylline (200 mg/kg) on the transition phase from acute gastric mucosal damage to gastric ulceration was investigated in a rat gastric ulcer model. The ulcer area was significantly reduced by all three drugs 72 h after ischemia-reperfusion. Leukocyte infiltration into damaged tissue was also inhibited by all three regimens. Furthermore, Ono-5046 (30 mg/kg) in combination with omeprazole (10 mg/kg) also significantly reduced the ulcer area as compared to omeprazole alone (15).

Sivelestat is the new proposed international nonproprietary name for Ono-5046 (16).

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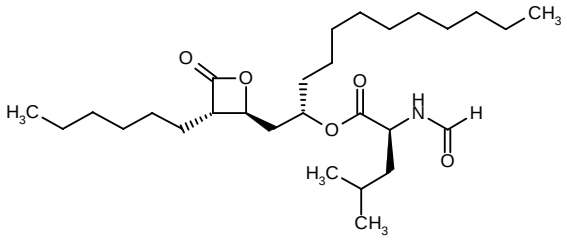
Orlistat
Xenical®

Antiobesity
Pancreatic Lipase Inhibitor

EN: 110823



$C_{29}H_{53}NO_5$

Roche

The effects of orlistat on lipid levels and blood pressure were assessed using data from 5 large, randomized, double-blind, placebo-controlled trials in the U.S. and Europe. Under a mildly hypocaloric diet, 1561 patients received orlistat 120 mg t.i.d. and 1119 patients received placebo t.i.d. Patients in the orlistat group had significantly better improvement in serum lipid levels and significant reductions in blood pressure compared with placebo (1).

The efficacy and tolerability of orlistat was evaluated in 676 obese male and female subjects randomized to receive orlistat 30, 60, 120 and 240 mg during meals for a period of 24 weeks. Subjects on active treatment demonstrated a greater mean body weight loss as compared to placebo, with the greatest body weight reductions observed in the group receiving orlistat 120 mg. The drug was well tolerated, and the optimum dose was determined to 120 mg t.i.d (2).

Results from a double-blind, multicenter, randomized, placebo-controlled, parallel-group-designed study indicated that orlistat (120 mg, t.i.d.) with an appropriate diet promoted significant weight loss and prevented weight regain as evaluated in 688 patients over a 2-year period. The orlistat group lost more body weight and regained half as much weight as the placebo group. In addition, total cholesterol, low-density lipoprotein (LDL) cholesterol, LDL/high-density lipoprotein cholesterol ratio and glucose and insulin concentrations were lowered more in the orlistat group than with placebo. Gastrointestinal adverse events were more common in the orlistat group (3) (Box 1).

Box 1: Efficacy and tolerability of orlistat in obese patients (3) [Prous Science CTLine database].

Study Design	Multicenter, randomized, double-blind, placebo-controlled, parallel clinical trial	
Study Population	Patients with body mass index 28-47 kg/m^2 (n = 743)	
Intervention Groups	Orlistat (O), 120 mg t.i.d. x 1 year → orlistat 120 mg t.i.d. or placebo x 1 year Placebo (P) x 1 year → placebo or orlistat 120 mg t.i.d. x 1 year	
Withdrawals	During year 1 P = 83 O = 61	During year 2 P+P = 24 P+O = 25 O+P = 21 O+O = 21
Results	Mean decrease in body weight at 1 year: O = 10.2%, P = 6.1% Body weight decrease > 20% at 1 year: O = 9.3%, P = 2.1% Maintained weight loss > 5% at 2 years: O = 57.1%, P = 37.4%	
Conclusions	Orlistat significantly promoted weight loss and prevented regain over a 2-year period. Use of orlistat beyond 2 years necessitates monitoring	

The effects of orlistat 120 mg t.i.d. on glycemic control was assessed in 855 normal, 63 impaired and 44 diabetic individuals, as defined by the oral glucose tolerance test. More patients in the orlistat-treated group improved their glucose tolerance status as compared to placebo-treated patients. Changes in AUC were greater in the group receiving active treatment, as compared to the group receiving placebo. Thus orlistat in combination with a weight loss program and behavioral modification reduces the risk of glucose tolerance deterioration in patients at risk of developing diabetes mellitus (4).

An overview of the safety profile of orlistat, taken for 1 year in combination with a low-fat, moderately caloric diet, has shown that the drug produced significant weight loss, reductions in waist circumference, and improvements in serum lipid profiles and glucose tolerance test results. The most common adverse events were gastrointestinal, but were generally mild and transient. No clinically relevant changes in hematology, blood chemistry or urinalysis parameters were reported (5).

The effect of orlistat (120 mg t.i.d.) on diabetic status was evaluated according to data gathered from 5 phase III studies. 1629 obese patients enrolled in these studies. It was concluded that orlistat may postpone the onset of type II diabetes in high-risk obese patients (6).

The effects of orlistat and weight loss on cardiovascular risk factors were evaluated in 321 obese diabetic patients on a mildly hypocaloric diet. Reductions in total cholesterol were observed in patients treated with orlistat, and HbA1c decreased progressively over patient weight-loss categories. A similar effect was observed with systolic blood pressure. Gastrointestinal-related side effects were mild and transient, and the drug was generally well tolerated (7).

The effects of oral orlistat (120 mg q.i.d.) on weight loss, glycemic control and serum lipid levels were evaluated in 391 obese patients with type-2 diabetes treated with sulfonylurea-containing medications. Treatment with orlistat produced significant reductions in weight loss and improved glycemic control as compared to patients treated with placebo, allowing dosage reductions of sulfonylurea medications. Significant improvements in lipid parameters were also observed (8).

The FDA has deemed the NDA for orlistat (Xenical®) for the treatment of obesity approvable. Final approval is subject to certain conditions, including submission of follow-up safety data from ongoing clinical trials and agreement on final labeling (9, 10).

Roche has launched orlistat (Xenical®) in New Zealand, the drug's first market. Orlistat, available since June 1, 1998, is indicated for the long-term treatment of significantly obese patients, including patients with risk factors associated with obesity, in conjunction with a mildly hypocaloric diet. The drug is available in 120-mg capsules (11).

The European Commission has approved orlistat (Xenical®) for marketing in the member countries of the European Union. The first European launches of the lipase inhibitor will take place in September in Germany, France, the U.K., Austria and Finland, with launches in other EU countries to follow (12).

Roche has introduced orlistat (Xenical®) in the U.K., where it is indicated for use in conjunction with a mildly hypocaloric diet in obese patients with a body mass index ≥30 kg/m^2, or in overweight patients (BMI ≥28 kg/m^2) with associated risk factors (13).

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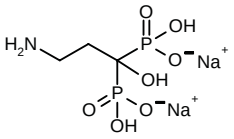
Pamidronate Sodium
Aminomux®
Aredia®

Bisphosphonate
Treatment of Bone Disease

EN: 090842



$C_3H_9NNa_2O_7P_2$

Henkel; Novartis; Almirall-Prodesfarma

A U.S. phase III trial of pamidronate disodium (Aredia®) injection has enrolled approximately 50 patients with advanced prostate cancer to determine if a reduction in pain with stable or reduced analgesic use occurs as a result of treatment with pamidronate. A secondary objective of the study is to determine if there is a decrease in skeletal-related events, such as fractures, spinal cord compression or need for surgery or radiation to bone (1).

Novartis has launched pamidronate disodium (Aredia®) in Spain for the treatment of Paget's disease, hypercalcemia of malignancy and osteolytic bone metastases in patients with certain cancers (2).

1. *Novartis begins phase III trial with Aredia in prostate cancer patients*. Daily Essentials May 12, 1998.

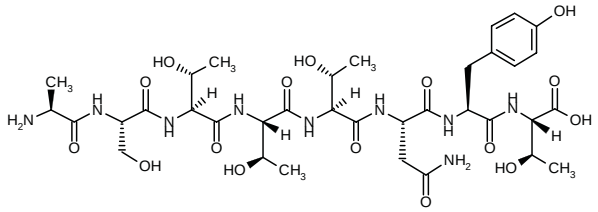
2. *Another market introduction for Novartis bisphosphonate*. Daily Essentials Oct 14, 1998.

Original monograph - Drugs Fut 1979, 4: 781.

Peptide T

Antiviral
Anti-HIV
Antiinflammatory

EN: 130170



$C_{35}H_{55}N_9O_{16}$

Karolinska Inst.; Natl. Inst. Health (US); Peptech

A multicenter, double-blind, placebo-controlled trial was performed to evaluate the ability of intranasal peptide T to improve cognitive function in HIV-positive patients with cognitive impairment. Patients were randomized to receive intranasal placebo or peptide T (2 mg t.i.d. x 6 months), and those completing baseline and final neuropsychological evaluations after at least 4 months of treatment were included in the efficacy analysis. No significant differences were observed between the groups as regards changes in the global neuropsychological score derived from a battery of tests, individual domain scores

and deficit scores of global and domain performance. However, adjustment for baseline $CD4^+$ cell counts indicated greater improvement in the peptide T group, and subgroup analysis indicated a beneficial effect for peptide T in patients with baseline $CD4^+$ cell counts above 200 cells/ml and in those with baseline global deficit scores of at least 0.5 (1).

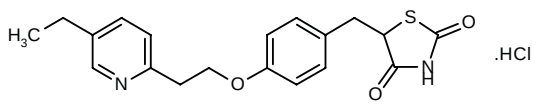
1. Heseltine, P.N.R. et al. *Randomized double-blind placebo-controlled trial of peptide T for HIV-associated cognitive impairment*. Arch Neurol 1998, 55(1): 41.

Original monograph - Drugs Fut 1989, 14: 1049.

Pioglitazone Hydrochloride Actos®

Antidiabetic

EN: 164965



$C_{19}H_{29}N_2O_3S.HCl$ **Takeda**

Incubation of human vascular smooth muscle cells with TNF-α (20 ng/ml) and pioglitazone (10, 100 and 1000 μM) for 16 and 24 h resulted in suppression of plasminogen activator inhibitor-1 (PAI-1) secretion by 76.55 and 55.37% of control, respectively. The results indicate that pioglitazone may be beneficial in treating diabetic macroangiopathy by suppressing PAI-1 expression (1).

In vitro studies on mouse aortic endothelial cells demonstrated that treatment with pioglitazone had very little effect on direct endothelial cell proliferation. Basic fibroblast growth factor-induced endothelial cell mitogenesis was significantly inhibited, whereas insulin-mediated proliferation was not affected (2).

The *in vitro* effects of troglitazone, pioglitazone and vitamin E were assessed on thrombin-induced platelet aggregation, metabolism of phosphoinositide, protein phosphorylation, protein kinase C-α and -β and phosphatidylinositol 3-kinase activation in human platelets. Troglitazone and vitamin E showed potent inhibitory effects on platelet aggregation via suppression of the thrombin-induced activation of phosphoinositide signaling in human platelets. Troglitazone's inhibitory effect may be due to its chemical structure which contains vitamin E (3).

The antidiabetic effects of pioglitazone alone or in combination with voglibose were studied in genetically obese diabetic Wistar fatty rats. In male rats receiving pioglizatione (1 mg/kg/day p.o.) for 2 weeks, plasma glucose and triglyceride levels decreased by 61 and 45% of control levels, respectively. Administration of pioglitazone with voglibose (0.3 or 0.7 mg/kg/day, p.o.) for 2 or 3 weeks normalized plasma glucose levels and muscular hexosamine content, lowered the plasma triglyceride level and greatly improved oral glucose intolerance (4).

The effect of pioglitazone on the development of multiple low-dose streptozotocin (MD-STZ)-induced autoimmune diabetes was examined in mice. Diabetes development was prevented in CD-1 mice pretreated with pioglitazone (0.01% food admixture) 7 days prior to STZ treatment (40 mg/kg/day x 5 i.p.). The agent was found to block infiltration of mononuclear cells into the islets of MD-STZ-treated mice (5).

Administration of pioglitazone (3 mg/kg/day) for 2 weeks to genetically obese and diabetic fatty rats caused hyperglycemia and hypertriglyceridemia to disappear and TNF-α levels in muscle to decrease in a time-dependent manner. These results indicate that increased production of TNF-α causes metabolic abnormalities in obesity and diabetes and that there is a close correlation between the antidiabetic activity of pioglitazone and the suppression of TNF-α production (6).

The effects of pioglitazone 30 mg once daily on insulin resistance were evaluated in 21 patients with NIDDM. Patients treated with pioglitazone during 12 weeks demonstrated significant increments in mean glucose infusion rate prior to oral glucose loading and increased splanchnic glucose uptake. Thus, pioglitazone may effectively ameliorate insulin resistance in patients with NIDDM (7).

Sixteen normal volunteers participated in a 2-period, crossover study to evaluate the effects of multiple doses of pioglitazone on steady-state glipizide levels and the safety of concomitant administration of the two drugs. Subjects received either placebo and glipizide (5 mg) or pioglitazone (45 mg) and glipizide (5 mg) for 7 days followed by another 7 days of alternative treatment. The pharmacokinetic and statistical analyses indicated that coadministration of pioglitazone did not affect the disposition or steady-state pharmacokinetics of glipizide. No serious adverse events were observed (8).

The effects of pioglitazone on insulin-stimulated glucose disposal, and carbohydrate and lipid metabolism was assessed in 20 patients with non-insulin dependent diabetes mellitus (II). Patients receiving pioglitazone 30 mg/day for 77-97 days significantly improved insulin-stimulated glucose disposal and significantly reduced fasting plasma glucose levels. Fasting serum insulin, C peptide, triglyceride and free fatty acid levels decreased, while HDL-cholesterol levels increased. The results indicate that administration of pioglitazone enhanced the effects of insulin in patients with NIDDM, enhancing both plasma glucose levels and lipid profiles (9).

Takeda is currently in negotiations with Lilly regarding a U.S. marketing agreement for pioglitazone which is now in phase II/III in that country. A previous codevelopment agreement with Pharmacia & Upjohn has been discontinued (10).

Takeda plans to establish an independent pharmaceutical marketing company soon in the U.S. to market and sell pioglitazone hydrochloride (Actos®) upon approval. The company will be known as Takeda

Pharmaceuticals America and will be a wholly owned subsidiary of Takeda America Holdings, which in turn is a wholly owned subsidiary of Takeda. The company has also signed a memorandum of understanding with Lilly for the copromotion of pioglitazone (11).

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2. Gralinski, M.R., Rowse, P.E., Breider, M.A. *Effects of troglitazone and pioglitazone on cytokine-mediated endothelial cell proliferation in vitro*. J Cardiovasc Pharmacol 1998, 31(6): 909.

3. Ishizuka, T., Itaya, S., Wada, H., Ishizawa, M., Kimura, M., Kajita, K., Kanoh, Y., Miura, A., Muto, N., Yasuda, K. *Differential effect of the antidiabetic thiazolidinediones troglitazone and pioglitazone on human platelet aggregation mechanism*. Diabetes 1998, 47(9): 1494.

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5. Ando, H. et al. *Pioglitazone prevents mice from multiple low-dose streptozotocin-induced insulitis and diabetes*. 34th Annu Meet Eur Assoc Study Diabetes (Sept 8-12, Barcelona) 1998, Abst 624.

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9. Yamasaki, Y. et al. *Pioglitazone (AD-4833) ameliorates insulin resistance in patients with NIDDM*. Tohoku J Exp Med 1997, 183(3): 173.

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11. *Takeda establishes independent U.S. company, begins partnership with Lilly*. Daily Essentials May 26, 1998.

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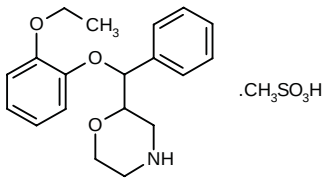
Yoshimoto, T. et al. *Vasculo-protective effects of insulin-sensitizing agent pioglitazone in neointimal thickening and chronic hypertension*. J Hypertens 1998, 16(Suppl. 2): Abst P20.09.

Reboxetine Mesilate *Antidepressant*
Norebox® *Norepinephrine Reuptake Inhibitor*
Edronax®

EN: 090985



$C_{19}H_{23}NO_3.CH_4O_3S$ **Pharmacia & Upjohn**

Results from a questionnaire survey evaluating reboxetine in the treatment of depression in 250 patients showed that a clinical response rated 'good' was reported by 60% of the patients. Symptomatic improvements rated 'good/very good' were reported in 76% of the patients, and 73% reported comparable improvements in daily activities. Side effects were reported in 33% of the patients (1).

Data from 8 clinical trials involving 1959 hospitalized or outpatients diagnosed with major depression has shown that reboxetine was at least as efficacious as tricyclic antidepressants and selective serotonin reuptake inhibitors. Additional benefits of the drug consisted of effective long-term treatment, efficacy in all levels of depression and specific advantages on social functioning (2).

Results from a comparative study of reboxetine 4-8 mg with desipramine 100-200 mg in 258 patients with major depression showed that the therapeutic effects following administration of reboxetine were observed earlier as compared to the effects observed after administration of desipramine. Patients in the reboxetine-treated group

also scored higher on the CGI-Efficacy Index than patients treated with desipramine or placebo. Thus, daily doses of reboxetine 4-8 mg administered during 4 weeks appeared to be effective in the treatment of patients with major depression (3).

Pharmacia & Upjohn has submitted an NDA with the FDA seeking approval for reboxetine mesilate tablets for the treatment of depression (4).

Reboxetine mesilate has been launched in Germany as Edronax® and in Spain as Norebox® for the treatment of depression. It is supplied as tablets, 4 mg (5, 6).

1. Baldwin, D. *Reboxetine in the treatment of depression: Early clinical experience in the United Kingdom*. J Psychopharmacol 1998, 12(3, Suppl. A): Abst 56.

2. Montgomery, S.A. *Reboxetine: Additional benefits to the depressed patient*. J Psychopharmacol 1997, 11(4, Suppl.): S9.

3. Ban, T.A., Gaszner, P., Aguglia, E., Batista, R., Castillo,A., Lipcsey, A., Macher, J.P., Torres Ruiz, A., Vergara, L. *Clinical efficacy of reboxetine: A comparative study with desipramine, with methodological considerations*. Hum Psychopharmacol - Clin Exp 1998, 13(Suppl. 1): S29.

4. *Pharmacia & Upjohn submits NDA for Edronax*. Daily Essentials May 12, 1998.

5. *Pharmacia & Upjohn launches new antidepressant in Germany*. Daily Essentials Oct 15, 1998.

6. *Pharmacia & Upjohn's reboxetine now available in Spain.* Daily Essentials Nov 23, 1998.

Original monograph - Drugs Fut 1985, 10: 905.

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Silva, J.C. *The role of reboxetine, a selective noradrenaline reuptake inhibitor, in the treatment of depression - Proceedings of a Satellite Symposium to the European Congress of the World Psychiatric Association, Geneva, 1997 - Conclusion*. Hum Psychopharmacol - Clin Exp 1998, 13(Suppl. 1): S41.

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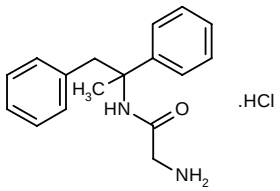
Pharmacokinetics, efficacy and tolerability of reboxetine. Daily Essentials Jun 3, 1997.

Remacemide Hydrochloride

Anticonvulsant
NMDA Antagonist

EN: 152057



$C_{17}H_{20}N_2O.HCl$ **Astra**

Results of a randomized study in patients with refractory epilepsy being treated with at least one enzyme-inducing antiepileptic drug showed that adjunctive therapy with remacemide 1200 mg/day was well tolerated by most patients, and some patients tolerated doses up to 2400 mg/day. The most frequent dose-related adverse events were dizziness, nausea, vomiting, abdominal pain and somnolence (1).

In a randomized, placebo-controlled study the effects of remacemide hydrochloride (600 mg/day) on neuropsychological sequelae of coronary artery bypass surgery (CABS) were evaluated in 170 patients. Subjects (n = 87) received drug for 5 days pre- and postsurgery. Cognitive function was assessed 1 week before and 8 weeks after CABS on 9 neuropsychological tests. At week 8, 12% on placebo and 9% on drug showed deficits in 2 or more tests. Improvement due to learning was greater with remacemide hydrochloride using a global Z score, thus suggesting the drug has neuroprotective properties in this context and that CABS may aid in screening such compounds (2).

The cognitive effects of remacemide were assessed in 16 healthy volunteers receiving single oral doses of 100, 200 and 400 mg. Evidence of impairment and reductions in alertness were reported by the 400-mg group 2 and 4 h after administration. Quality of sleep was not affected at any dose levels. Administration of the highest dose produced upper limit plasma concentrations observed in patients with epilepsy. The lower doses of the drug were well tolerated, although the 400 mg dose produced a higher incidence of upper gastrointestinal and neuropsychiatric symptoms (3).

1. Privitera, M.D. et al. *Tolerability and safety of high dose remacemide hydrochloride as adjunctive therapy in patients with refractory epilepsy*. 50th Annu Meet Amer Assoc Neurol (April 25-May 2, Minneapolis) 1998, Abst S64.002.

2. Harrison, M.J., Newman, S.P., Arrowsmith, J., Stygall, J., Timberlake, N., Shah, T., Pugsley, W. *Effect of remacemide on neuropsychological sequelae of coronary artery bypass surgery (CABS)*. Stroke 1998, 29(10): 2238.

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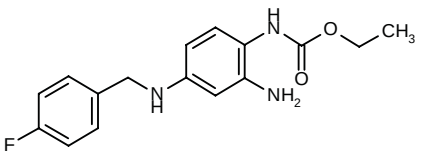
Retigabine
D-23129

Anticonvulsant

EN: 227505



$C_{16}H_{18}FN_3O_2$ **Arzneimittelwerk Dresden; Asta Medica; Wyeth-Ayerst**

In a hippocampal slice model of drug-resistant epilepsy, retigabine was shown to concentration-dependently block all types of epileptiform discharges, indicating its potential in the treatment of patients with drug-resistant epilepsy (1).

1. Rundfeldt, C., Armand, V., Heinemann, U. *The anticonvulsant D-23129 (Retigabine(pINN)) is effective in a hippocampal slice model of drug resistant epilepsy*. Soc Neurosci Abst 1997, 23(Part 2): Abst 840.2.

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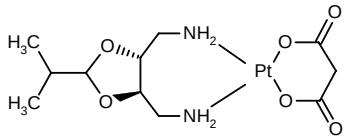
SKI-2053R
NSC-D-644591
NSC-644591

Antineoplastic
Platinum Complex

EN: 210284



$C_{11}H_{20}N_2O_6Pt$ **Sunkyong**

SKI-2053R at doses of 0.75 and 1.5 mg/kg/day in rats did not cause maternal toxicity or embryotoxicity. At a dose of 3.0 mg/kg/day, the drug caused reduced food intake, reduced body weight and decreased liver weight in dams, as well as visceral and skeletal malformations in fetus (1).

1. Chung, M.K., Kim, J.C., Roh, J.K. *Embryotoxic effects of SKI 2053R, a new potential anticancer agent, in rats*. Reprod Toxicol 1998, 12(3): 375.

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Additional Reference

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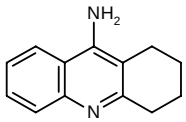
Tacrine
Cognex®

Cognition Enhancer
Acetylcholinesterase Inhibitor

EN: 129666



$C_{13}H_{14}N_2$ **Warner-Lambert; Alza**

Results from a comparative study of tremor and salivation following intraperitoneal and oral administration of tacrine, donepezil and NXX-066 showed that tacrine possessed comparatively poor selectivity for centrally- (tremor) *versus* peripherally- (salivation) mediated effects. In order to achieve a similar degree of tremor, substantially higher doses of tacrine are needed when it is administered orally *versus* i.p. Donepezil's tremorogenic effect was relatively short when given orally (1).

The potency of tacrine, donepezil, rivastigmine and metrifonate to induce overt cholinergic responses after oral administration was examined as well their duration of action in rats. Compared to the other compounds, tacrine demonstrated poor selectivity for centrally- (tremor) ver-

sus peripherally-mediated effects (salivation and lacrimation). Metrifonate possessed low potency and a brief duration of action (2).

1. Murray, T.K., Snape, M.F., Cross, A.J., Green, A.R. *Comparison of the time course of the tremorogenic effect of tacrine, donepezil and NXX-066 in rats*. Br J Pharmacol 1998, 124(Suppl.): Abst 47P.

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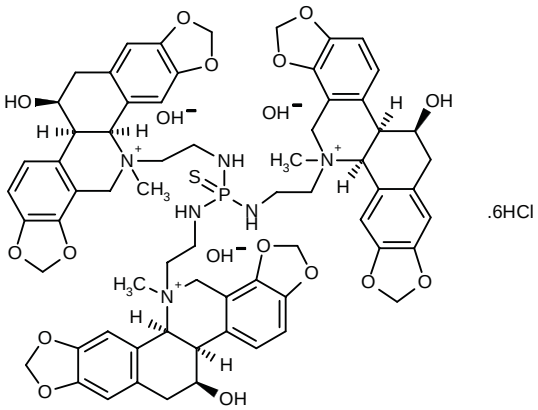
Original monograph - Drugs Fut 1987, 12: 1032.

Ukrain

Antineoplastic Alkaloid
Immunomodulator

EN: 196926



$C_{66}H_{75}N_6O_{18}PS.6HCl$ **Ukranian Anti-Cancer Inst. (AT); Nowicky Pharma.**

In a study in 21 patients with advanced colorectal, lung, breast, bladder or ovarian cancer, treatment with Ukrain (5 mg i.v. every 2 days for 10 injections) resulted in significant increases in peripheral T-lymphocyte formation and lymphocyte proliferative response, as well as distinct improvement in suppressor T-cell activity. The results suggest that Ukrain would be useful in restitution therapy in patients with cancer-induced depressed cellular immunity (1).

Exposure to Ukrain (50 μg/ml for 48 h) resulted in growth inhibition of human cervical (52.8%) and esophageal (49.1%) carcinoma cell lines, whereas growth of normal equine lung cells was unaffected. Ukrain also reduced the number of G_2M cells in both malignant cell lines, and morphological studies revealed the presence of abnormal mitotic spindles and apoptotic cells. The toxicity of Ukrain in malignant cells appears to be induced by a metaphase block producing micronuclei and apoptosis (2).

The efficacy of Ukrain was evaluated in a study in which patients with recurrent urinary bladder cancer were administered Ukrain (10 mg i.v. injection every 2 days for 3 months) following tumor removal. Eleven patients did not exhibit recurrent growth 10-12 months following therapy. Only one patient had recurrent growth 6 months after treatment. Since recurrence was effectively decreased, Ukrain therapy may reduce the need for radical surgical removal of the bladder in these patients (3).

A clinical study has examined the efficacy of Ukrain as neoadjuvant chemotherapy for patients with T1NOMO urinary bladder cancer. Twenty-eight patients were administered Ukrain (10 mg/day x 10) for up to 3 courses. In patients who received 2 courses of treatment, one complete tumor regression, 4 partial regressions, and 5 stabilization of tumor progress were observed. After three courses, 2 complete regressions, 6 partial regressions and 1 stabilization of tumor progress were observed. Ukrain therapy was determined to cause complete or partial regression in approximately 61% of the cases and the optimal regimen was determined to be 3 courses at 2-week intervals (4).

Ukrain® was launched in February 1996, in the Republic of Belarus for the treatment of adenocarcinomas. It is supplied as ampoules containing 5 mg *Chelidonium majus L*. alkaloid-thiophosphoric acid derivative in 5 ml bidistilled water for injection (5).

1. Dabrowska-Bernstein, B.K., Brzosko, W.J., Nowicky, I.W. *Cell mediated immunity in patients with cancer*. 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 332.

2. Panzer, A., Seegers, J.C. *Ukrain, a semisynthetic alkaloid of Chelidonium majus, is selectively toxic to malignant cells by causing a metaphase block which results in apoptosis*. Proc Amer Assoc Cancer Res 1998, Abst 2183.

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Vapreotide
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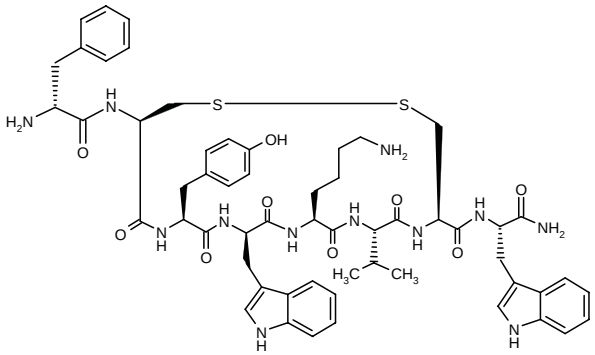

$C_{57}H_{70}N_{12}O_9S_2$ **Tulane Univ. (US); Debiopharm**

In a phase II trial, 20 patients with progressive, hormone-refractory prostate cancer received outpatient treatment with vapreotide (3 mg/day by continuous s.c. perfusion) for 3 months. Although the treatment was well tolerated, it had only limited activity, with 1 patient achieving a partial response and 2 subjects disease stabilization (1).

An injectable biodegradable depot formulation of vapreotide has been developed, which can maintain satisfactory peptide blood levels for up to 250 days. The addition of a wear coating may minimize the initial release burst (2).

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