Drugs of the Future 1998, 23(6): 655-690

CCC: 0377-8282/98

Information Update

Volume 1-22, Number 6

Estimated developmental phase for this month's updated products:

Preclinical

Emodin (antineoplastic, antibacterial, immunosuppressant; China Pharm. Univ.)
U-73122 (phospholipase C inhibitor; Pharmacia & Upjohn)

Phase I

DX-9065a (anticoagulant, factor Xa inhibitor; Daiichi Pharm., Sanofi)
(–)-Epigallocatechin gallate (antineoplastic, antiviral; Natl. Cancer Center Res. Inst., Pharmamex)

Phase II

N-Acetylcysteine (anti-HIV; Zambon)
E-4031 (antiarrhythmic; Eisai)
Enloplatin (antineoplastic, platinum complex; American Cyanamid, Lederle, Immunex)
Ilmofosine (antineoplastic; Boehringer Mannheim)
JM-216 (antineoplastic, platinum complex; Johnson Matthey, Bristol-Myers Squibb)
Lexacalcitol (antipsoriatic, vitamin D analog; Leo Denmark)
Sulofenur (antineoplastic; Lilly)
Zeniplatin (antineoplastic, platinum complex; American Cyanamid, Lederle)

Phase III

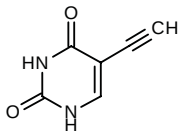
776C85 (dihydropyrimidine dehydrogenase inhibitor, potentiator of 5-FU activity; Glaxo Wellcome)
A-4166 (antidiabetic; Ajinomoto, Novartis, Roussel-Morishita, Yamanouchi)
Azimilide hydrochloride (antiarrhythmic; Procter & Gamble, Tanabe Seiyaku)
Clinprost (platelet antiaggregatory, treatment of peripheral vascular disease; Taisho, Teijin)
Dofetilide (antiarrhythmic; Pfizer)
Homoharringtonine (antineoplastic alkaloid; Chinese Acad. Med. Sci., Natl. Cancer Inst., VivoRx)
Huperzine A (cognition enhancer, acetylcholinesterase inhibitor; Shanghai Inst. Materia Med., Chinese Acad. Med. Sci.)
Liarozole fumarate (antineoplastic; Janssen)
Lubeluzole (neuronal injury inhibitor, glutamate release inhibitor; Janssen, Kyowa Hakko)
Mosapride citrate (gastrointestinal prokinetic, 5-HT_4 agonist; Dainippon, Astra)
Nicaraven (neuroprotectant; Chugai, Novartis)
NS-105 (cognition enhancer, nootropic agent; Nippon Shinyaku)
Osaterone acetate (treatment of BPH, antiandrogen; Taikoku Hormone)
Pirfenidone (agent for cystic fibrosis; Marnac, Synexus, Shionogi)
Prasterone (agent for systemic lupus erythematosus, immunosuppressant; Genelabs Technol., Stanford Univ., Jenapharm, Pharmadigm)
Recombinant human ciliary neurotrophic factor (agent for amyotrophic lateral sclerosis; Amgen, Roche Bioscience, Regeneron, Procter & Gamble)
Rhenium Re-186 etidronate injection (analgesic; Mallinckrodt, Missouri Univ., Univ. Cincinnati, Sloan-Kettering Inst.)
Sabeluzole (cognition enhancer; Janssen)
Ziprasidone hydrochloride (antipsychotic, dopamine antagonist, 5-HT_2 antagonist; Pfizer)

Launched/Year

Cerivastatin sodium (hypolipidemic, HMG-CoA reductase inhibitor; Bayer, Fournier, Takeda, SmithKline Beecham)/1997
Dexketoprofen trometamol (antiinflammatory, analgesic; Menarini, Sepracor, Chiroscience, Lilly)/1996
Dienogest (contraceptive, treatment of osteoporosis; Jenapharm, Schering AG, Innothera, Mochida)/1990
Dolasetron mesilate (antiemetic, 5-HT_3 receptor antagonist; Hoechst Marion Roussel, Abbott)/1997
Faropenem sodium (penem; Suntory, Hoechst Marion Roussel, Wyeth-Ayerst, Yamanouchi)/1997
Gabapentin (anticonvulsant; Warner-Lambert, Fujisawa)/1993
Indinavir sulfate (anti-HIV, HIV-1 protease inhibitor; Merck & Co.)/1996
Lamotrigine (anticonvulsant, glutamate release inhibitor; Glaxo Wellcome, DuPont Merck, Faes)/1990
Loprinone hydrochloride (cardiotonic, PDE III inhibitor; Eisai)/1996
Menatetrenone (treatment of osteoporosis, treatment of vitamin K deficiency; Eisai)/1984
Oxiplatin (antineoplastic, platinum complex; Nagoya Univ., Debiopharm, Sanofi)/1996
Rilmenidine dihydrogen phosphate (antihypertensive; Servier)/1988
Simvastatin (hypolipidemic, HMG-CoA reductase inhibitor; Merck & Co., Mediolanum, Amrad)/1988
Vigabatrin (anticonvulsant, GABA transaminase inhibitor; Hoechst Marion Roussel, Novartis)/1989

776C85 *Dihydropyrimidine Dehydrogenase Inhibitor*
Eniluracil *Potentiator of 5-FU Activity*

EN: 184938



$C_6H_4N_2O_2$ **Glaxo Wellcome**

Administration of GW-776 (0.5 mg/kg) prior to the administration of 5-FU in isolated perfused rat liver produced a 7-fold increase in 5-FU anabolites and a 5-fold increase in fluoronucleotides and 5-fluorouridine-5'-diphosphate sugars. Incorporation of 5-FU into RNA increased as well (1).

A phase I clinical trial evaluated a combination of GW-776 (10 mg q.d.,10 mg b.i.d. or 20 mg b.i.d.) with 5-FU (1.35 or 1.8 mg/m^2 b.i.d.) in 36 adult patients with tumor malignancies. Analysis of 5-FU levels on the second day of treatment yielded concentrations of 0.070 ± 0.013 l/hr.kg (CL/F), 0.45 ± 0.11 l/kg (Vz/F) and 4.6 ± 0.9 h ($t_{1/2}$). A 4-fold change in the dose of GW-776 had no effects on the pharmacokinetic constants of 5-FU and repeated dosing during 28 days produced no unexpected accumulation of 5-FU (2).

GW-766 was evaluated in 24 patients with previously untreated metastatic colorectal cancer and 53 patients refractory to 5-FU/leucovorin treatment. Patients were administered GW-776 (20 mg/day) on days 1-7 and either 5-FU (25 mg/m^2/day p.o.) or 5-FU with leucovorin (20 mg/m^2/day and 50 mg p.o.) on days 2-6, with courses repeated every 28 days. In previously untreated patients, partial response was observed in 2/11 patients treated with the combination of GW-776 and 5-FU, and in 4/12 subjects treated with GW-776, 5-FU and leucovorin. One partial response and 3 stable disease were observed in patients with refractory disease treated with the triple combination regimen. Ten patients treated with the combination of GW-776 and 5-FU demonstrated stable disease, although none demonstrated responses to the treatment. Granulocytopenia was the primary cytotoxicity observed, and 10 subjects were hospitalized with neutropenic fever or sepsis (3).

The safety and efficacy of GW-776 (20 mg) administered together with increasing doses of 5-FU (starting dose 2.5 mg b.i.d.) were evaluated in 11 patients with advanced squamous cell carcinoma of the head and neck receiving twice-daily radiation therapy (75 cGy/dose). Adverse events observed included dose-limiting myelosuppression, both neutropenia and thrombocytopenia, and grade 3 mucositis was observed in 2 patients (4).

Evaluation of toxicity and response to eniluracil with or without 5-fluorouracil (5-FU) in 65 patients with solid tumors refractory to standard therapy showed that bone marrow suppression was the primary and dose-limiting toxicity, while other toxicities included diarrhea, mucositis, anemia, anorexia, nausea, vomiting and fatigue. A 90% inhibition of dihydropyrimidine dehydrogenase activity was also observed in peripheral blood mononuclear cells. Eniluracil given with 5-fluorouracil prolonged the half-life of 5-FU, reduced its clearance and produced linear pharmacokinetics for the drug. Results from this study indicated that the two drugs can be safely administered together, although maximum tolerated doses are much lower due to alterations in the pharmacokinetics of 5-FU (5).

Eniluracil is the new proposed nonproprietary name for 776C85 (6).

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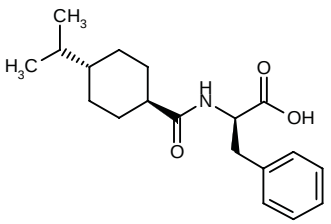
Original monograph - Drugs Fut (Rev Art) 1994, 19: 565.

A-4166 *Antidiabetic*
Nateglinide
Starlix®
Starsis®

EN: 127137



$C_{19}H_{27}NO_3$ **Ajinomoto; Novartis; Roussel-Morishita; Yamanouchi**

In the presence of low glucose concentrations, A-4166 (10-200 μmol) induced a rapid rise in insulin release from perfused rat pancreatic islets, which decreased gradually. The initial insulin release was inhibited by diazoxide, while the sustained release was blunted. In addition, A-4166 blocked the binding of radiolabeled glibenclamide to HIT cell membranes as well as the ^{86}Rb efflux from ATP-depleted or diazoxide treated cells (1).

AY-4166 (3 μM) had no effect on basal insulin secretion in rat pancreas perfused with 5 mM glucose, but increased the first and second phase of insulin secretion following perfusion with 7.5 and 15 mM glucose. In addition, AY-4166 produced a leftward shift of the dose-response curve of insulin secretion induced by glucose.The results indicate that AY-4166 acts as a potentiator of insulin secretion rather than a stimulator of insulin release (2).

The effects of A-4166 (25-100 mg/kg p.o.) on postprandial glycemic increase were evaluated in normal and diabetic rats. In normal rats, the drug rapidly lowered blood glucose levels, although the effect was short-lived. A-4166 also reduced carbohydrate-induced increases in blood glucose in both normal and diabetic rats. Plasma insulin levels in A-4166-treated rats during the first hour following sucrose loading were significantly higher as compared to controls, indicating that the drug blocks postprandial glucose increase in the early phase of insulin secretion (3).

Nateglinide is the new proposed international nonproprietary name for AY-4166 (4).

Yamanouchi has filed for Japanese regulatory approval of the hypoglycemic agent YM-026 (Starsis®), a fast- and short-acting insulin secretion enhancer for the treatment of diabetes (5).

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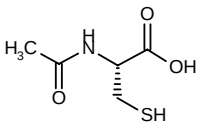
N-Acetylcysteine

Anti-HIV

EN: 091298



$C_5H_9NO_3S$ **Zambon**

N-Acetylcysteine was shown to decrease the invasive ability of vascular and malignant cells *in vitro* (using chemoinvasion and chemotaxis experiments). It was also shown to inhibit angiogenesis *in vivo* (using the Matrigel sponge model and Kaposi's sarcoma cell products) by 70% (1).

A study analyzing the antitumoral activity of *N*-acetylcysteine showed that the drug modulated TNF-α and TNF-R processing, with no evidence of *in vitro* or *in vivo* toxicity (2).

In an isolated, perfused, glutathione-depleted rat liver, preconditioning with *N*-acetylcysteine reduced hepatocellular enzymes and oxidized glutathione levels, while at the same time improving bile production, as compared to livers treated with 5% dextrose. Thus, *N*-acetylcysteine attenuated hepatic injury and improved liver integrity (3).

In rats, *N*-acetylcysteine attenuated increases in intracranial pressure, cerebral spinal fluid white blood cell counts and brain water content caused by experimental pneumococcal meningitis. It did not affect cerebrovascular autoregulatory and cerebral vessel CO_2 reactivity abnormalities (4).

In Sprague-Dawley male rats, *N*-acetylcysteine (0.25-0.50 g/kg b.i.d. x 2 days) was shown to decrease hyperbaric oxygen-induced cardiac ischemia-reperfusion damage when given prior to the hyperbaric oxygen (5).

Following 24 weeks of being fed 0.3% *N*-acetylcysteine, female OF-1 mice showed decreased protein carbonyl content in synaptic mitochondria as compared to age-matched controls (6).

Using a rodent model of lung injury, *N*-acetylcysteine reduced endotoxin (lipopolysaccharide)-induced increases in lung permeability, lowered the endotoxin-dependent elevation of lipid peroxidation and downregulated neutrophil activation without affecting neutrophil influx (7).

Examining the effects of *N*-acetylcysteine (NAC) on ethanol-induced liver damage in female rats, it was observed that NAC-treated rats had decreased activities of serum transaminases and phosphatase, decreased concentrations of thiobarbituric acid reactive substances and free fatty acids in the liver, and the number of litters and average birth weights were similar to those of control animals (8).

N-Acetylcysteine (15 mg/kg i.p.) produced a significant increase in glutathione levels and reduced lipid oxidation after 1 day in lung tissue of thermally injured rats (9).

Administration of *N*-acetylcysteine (1 mmol/kg i.p.) in rats treated with lidocaine produced a significant decrease in monoethylglycinexylidide (MEGX) levels, although no effect on lidocaine levels was observed. The combination of *N*-acetylcysteine and cimetidine markedly decreased lidocaine levels, but had no effect on MEGX levels, indicating that *N*-acetylcysteine may accelerate the metabolism of lidocaine and block the inhibitory effects of cimetidine (10).

In a 6-month, placebo-controlled trial in 41 smokers, bronchoalveolar lavage cell DNA adduct levels were shown to be significantly decreased with *N*-acetylcysteine supplementation (600 mg b.i.d.). Women smoking less than 25 cigarettes per day and having a glutathione-S-transferase M1 negative genotype showed the best responses (11).

A randomized, double-blind, placebo-controlled trial in 262 elderly patients showed that prophylactic treatment with *N*-acetylcysteine (600 mg b.i.d.) for 6 months resulted in fewer influenza-like episodes. Also, there was less severe illness and bed confinement documented in patients who did become infected with influenza. Cell-mediated immunity shifted from anergy to normoergy with *N*-acetylcysteine therapy (12).

N-Acetylcysteine (600 mg t.i.d.) was given to 18 patients with fibrosing alveolitis for 12 weeks as a supplement to their immunosuppressive therapy. Drug treatment resulted in an increase in total glutathione levels and a decrease in Met(O) levels, with an improvement in pulmonary function studies (13).

A retrospective case series analysis from the U.S. Toxic Exposure Surveillance System data sheets showed that, in 76 patients treated with intravenous *N*-acetylcysteine oral solution, only 4 showed adverse events attributable to the drug, none of which involved the pulmonary, cardiovascular or hemodynamic systems. There were no drug-related deaths (14).

In a placebo-controlled, double-blind trial in 60 critically ill patients, *N*-acetylcysteine administered at a dose of 150 mg/kg bolus followed by an infusion of 12 mg/kg/h for 24 h, produced no significant effects on the progress of total antioxidant potential or urinary albumin excretion, as compared to placebo-treated patients (15).

A randomized, multiple-dose, double-masked, parallel-group, phase III pilot study examined the effects of *N*-acetylcysteine (1, 2 and 4 g/d) in 18 patients with chronic atrophic gastritis (but no peptic ulcer) undergoing upper gastrointestinal endoscopy. Improvement on endoscopy after 4 weeks of treatment was seen in 72% of patients, independent of *N*-acetylcysteine dose. Polymorph infiltration was significantly lower with the 2-g dose. Adverse events included constipation, abdominal pain and flatulence (16).

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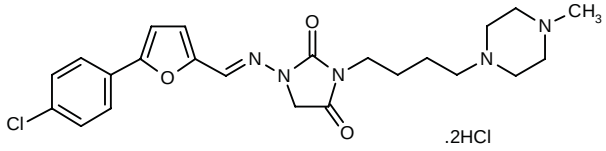
Azimilide Hydrochloride *Antiarrhythmic*
NE-10064
Stedicor®

EN: 195716



$C_{23}H_{28}ClN_5O_3.2HCl$

Procter & Gamble; Tanabe Seiyaku

The effects of azimilide (10 or 20 mg/kg) were evaluated in a canine model of atrial fibrillation. The lower dose did not terminate fibrillation in any subject, while the higher dose did in 3/4 dogs, without affecting conduction velocity. Azimilide at 20 mg/kg showed a tendency to prolong the effective refractory period and the action potential even at shorter cycle lengths, while the 10 mg/kg dose had no effect on these parameters (1).

Single-dose pharmacokinetics of azimilide (50 mg p.o.) were evaluated in 66 healthy volunteers divided into age groups of 18-40, 41-64 and 65 years or older. Ninety-four percent of the drug bound to protein in plasma, and the amount of bound drug was not affected by age or gender. Renal clearance was 19% higher in women than in men, while oral clearance did not differ between sexes. C_{max} was 27% higher in women, while the time to reach C_{max}, C_{max} adjusted to body weight and AUC were the same in both men and women. Age did not affect the pharmacokinetics (2).

A parallel-group safety study of azimilide (4.5, 6, 7.5 and 9 mg/kg i.v.) showed that the pharmacokinetics are dose-proportional and not affected by infusion duration or solution concentration, while the pharmacodynamics are not affected by dose size, infusion duration or solution concentration (3).

The ALIVE (AzimiLide post-Infarct surVival Evaluation) trial, initiated last year in the U.S. and Europe, is designed to evaluate the potential of azimilide to improve survival in postmyocardial infarction patients who are at high risk of sudden cardiac death. The double-blind, placebo-controlled, multinational trial includes male and female adult patients who have a left ventricular ejection fraction of 15-35% and who have recently suffered a heart attack. Patients are being randomized to oral treatment with 75 or 100 mg/day azimilide or placebo. Enrollment is expected to continue for the next 24 months, and treatment will be administered over a 1-year follow-up period (4).

Procter & Gamble and Tanabe Seiyaku have signed an interim agreement by which Tanabe Seiyaku will license Procter & Gamble's experimental antiarrhythmic agent azimilide hydrochloride for selected Asian markets (5).

Azimilide hydrochloride is in phase III testing at Procter & Gamble. The compound acts by blocking both slowly activating ($I\text{-}K_s$) and rapidly activating ($I\text{-}K_r$) components of the delayed rectifier potassium current. Azimilide is designed to prolong time to recurrence of atrial fibrillation, atrial flutter and paroxysmal supraventricular tachycardia, both in patients with heart disease and patients without heart disease. Its potential role in preventing sudden cardiac death in high-risk patients after myocardial infarction is also being evaluated. Azimilide suppressed supraventricular arrhythmias by more than 85% in a variety of models in dogs, completely prevented complex ventricular arrhythmia in infarcted dogs and decreased mortality in a dog model of sudden cardiac death. It demonstrates only minimal effects on blood pressure and heart rate, and does not affect PR or QRS intervals. The compound has a predictable pharmacokinetic profile, with complete absorption that is not affected by food. Once-daily administration is feasible, and dose adjustment is not necessary on the basis of age, gender, hepatic or renal function, or concomitant use of digoxin or warfarin. Safety data obtained in clinical trials, including long-term trials, is favorable (6).

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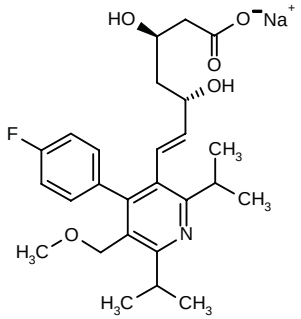

$C_{26}H_{33}FNNaO_5$ **Bayer; Fournier; Takeda; SmithKline Beecham**

Cerivastatin (0.01, 0.03 and 0.1 mg/kg p.o.) administered to beagle dogs was shown to reduce total cholesterol, very low-density and low-density lipoprotein cholesterol levels, while increasing hepatic low-density lipoprotein receptor binding activity and affinity. In Hep G2 cells, cerivastatin increased low-density lipoprotein receptor binding activity in addition to increasing receptor mRNA and protein concentrations, indicating that the drug's plasma cholesterol-lowering effects are a result of low-density lipoprotein receptor expression induction (1).

Absolute bioavailability of cerivastatin was evaluated in 12 healthy, young male volunteers receiving single doses of either 100 μg i.v. bolus or 200 mg p.o. in the form of tablet or as an oral solution. Plasma concentrations following the i.v. dose fit a two-compartment model with a distribution half-life of 3-5 min and an elimination half-life of 1.5-2.4 h. Plasma concentrations *versus* time data following the two oral doses fit a one-compartment pharmacokinetic model with a first-order absorption process. Absolute bioavailabilities for the tablet and oral solutions were 60.0 and 59.6%, respectively, while the relative bioavailability of both solutions was 100.7% (2).

Pharmacokinetic evaluation of cerivastatin in healthy young males receiving single or multiple daily doses of 50-400 μg/day showed that the drug is absorbed rapidly and completely, reaching t_{max} 2-3 h after administration. Plasma concentration *versus* time profiles were identical for tablet and solution formulations, indicating 100% bioavailability. AUC and C_{max} were dose-dependent with low variability in pharmacokinetic parameters. Food and circadian rhythms had no effect on the drug's pharmacokinetics (3).

Long-term administration of BAY-w-6228 (150 or 300 μg/day) was evaluated for efficacy and safety in 91 patients with mild to severe hyperlipidemia. After 48 weeks of treatment, total cholesterol and LDL-cholesterol levels were reduced by 22.5 and 31.3%, respectively. One case of erosive gastritis was reported, while abnor-

mal variations in clinical test values were observed in 16 subjects. General improvement, safety and efficacy rates were reported to be 91.4, 79.3 and 82.3%, respectively. The cholesterol-reducing effects were maintained for more than 48 weeks (4).

The efficacy and safety of BAY-w-6228 were evaluated in 80 young and elderly hyperlipidemic patients. The drug was administered at a dose of 100-300 μg/day during 36 weeks, followed by a 24-week treatment period with 100-150 μg/day. Total cholesterol was reduced by 16.8% in the elderly group and by 18.2% in the younger group after 60 weeks of treatment. No clinical variations were observed between the groups in cortisol and aldosterone blood levels, and efficacy and safety profiles were similar (5).

The efficacy and safety of three different dosing regimens of cerivastatin were assessed in 319 patients with primary hypercholesterolemia. The drug was administered during 4 weeks as regimens of 0.1 mg twice daily, 0.2 mg once daily with the evening meal or 0.2 mg once daily at bedtime. All three regimens produced significant reductions in total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol as compared to baseline values. A reduction in triglycerides was also noted in all three study groups. The drug was well-tolerated in all three dosing regimens and no significant increases in side effects were observed compared to placebo (6).

The efficacy of cerivastatin (0.025, 0.05, 0.1 and 0.2 mg/day) was evaluated in 894 patients for a period of 12 weeks. Total cholesterol, low-density lipoprotein cholesterol and triglycerides were significantly reduced by the treatment, while high-density lipoprotein cholesterol levels increased. Reductions in low-density lipoprotein cholesterol were noted after 1 week of treatment and reached maximal effects after 4 weeks (7).

The efficacy and safety of cerivastatin (0.3, 0.2 0.1 mg) were compared to gemfibrozil (1200 mg) in 751 patients with primary mixed hyperlipidemia. Reductions in low-density lipoprotein cholesterol produced by all regimens of cerivastatin were significantly greater than the reductions achieved with gemfibrozil. Percent of withdrawals due to adverse events was 0.6-4% in the cerivastatin groups compared to 3.8% for gemfibrozil (8).

Cerivastatin (0.1, 0.2 and 0.3 mg) was compared to gemfibrozil (1200 mg) in a randomized, double-blind study in 751 patients with mixed hyperlipidemia for a period of 20 weeks, followed by the addition of resin to the treatment for a period of 16 weeks. Cerivastatin reduced low-density lipoprotein cholesterol by 17.1-23.6%, while gemfibrozil produced an 8.2% reduction. Triglycerides were reduced by 7.6-16.3% with cerivastatin and by 43.8% with gemfibrazil. Cerivastatin was safe and well tolerated, and the incidence of adverse events was similar for both drugs (9).

The efficacy of cerivastatin (0.05-0.3 mg/day) was compared to simvastatin (5-40 mg/day) in a group of 387 adult patients with primary hypercholesterolemia. Reductions in total cholesterol, low-density lipoprotein cholesterol and triglycerides, and an increase in high-density lipoprotein cholesterol were significant in both treatment groups, although changes in lipid parameters produced by cerivastatin occurred at doses 100 times lower than simvastatin. Cerivastatin was well tolerated and adverse events were mild (10).

In 73 patients with highly elevated total cholesterol levels, cerivastatin administered for 12 weeks at doses of 0.15 or 0.3 mg/day reduced total cholesterol, low-density lipoprotein cholesterol and apoB concentrations, while high-density lipoprotein cholesterol levels were increased. Reductions in triglyceride levels were observed in 31 patients with hypertriglyceridemia (11).

Cerivastatin (0.8 mg/day) was evaluated in 41 patients with primary hypercholesterolemia during 28 days. Total cholesterol, low-density lipoprotein cholesterol and triglyceride levels were significantly reduced. The effects of the treatment were noted on day 8 and reached maximal levels by day 22. Cerivastatin at a dose of 0.8 mg/day produced a 44% reduction in LDL-C comparable to higher doses of other statin drugs presently available (12).

The FDA has granted marketing approval for Bayer's cerivastatin sodium (Baycol™) as a dietary adjunct in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson types IIa and IIb) who have not responded adequately to dietary restrictions and other drug therapies (13).

Bayer has introduced cerivastatin sodium (Lipobay®) in Germany for the treatment of primary hypercholesterolemia type IIa and IIb, with or without hypertriglyceridemia, and hypercholesterolemia not responding adequately to dietary measures. The product is available as tablets containing 0.1, 0.2 and 0.3 mg cerivastatin (14).

Bayer has announced a copromotion agreement with SmithKline Beecham for the marketing of their drug Baycol™ in the U.S. The drug is expected to be introduced on the market in early 1998 (15).

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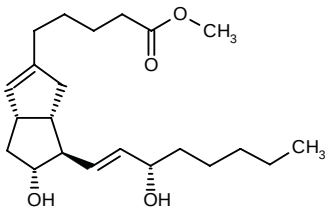

$C_{22}H_{36}O_4$ **Taisho; Teijin**

The cytoprotective potential of TTC-909 was evaluated in a model of middle cerebral artery occlusion in stroke-prone spontaneously hypertensive rats. When injected immediately following middle cerebral artery occlusion, and then daily for 6 consecutive days, TTC-909 (200 ng/kg) significantly prevented the decrease in norepinephrine contents associated with exacerbated cell damage in transient ischemia. These results indicate that TTC-909 may have cytoprotective effects, preventing neuronal damage resulting from ischemia in humans, in addition to its useful therapeutic activity in the treatment of occlusive vascular diseases in general (1).

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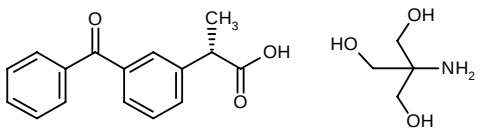


$C_{16}H_{14}O_3.C_4H_{11}NO_3$

Menarini; Sepracor; Chiroscience; Lilly

Menarini has submitted a registration application for dexketoprofen trometamol in all European Union countries under the mutual recognition procedure, with Spain acting as the reference member state (1).

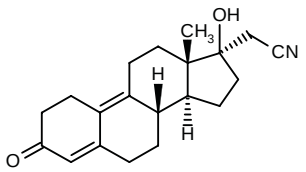
1. *Dexketoprofen trometamol submitted for mutual EC recognition.* Prous Science Daily Essentials October 2, 1997.

Original monograph - Drugs Fut 1996, 21: 585.

Dienogest

Contraceptive
Treatment of Osteoporosis

EN: 090248



$C_{20}H_{25}NO_2$

Jenapharm; Schering AG; Innothera; Mochida

In vivo antitumor and antiuterotropic activity of dienogest was examined in mice and compared with the activity of several progestins. Dienogest showed potent anticancer activity against hormone-dependent cancers at doses at which progestins show no activity (1).

In a randomized, open, multicenter, dose-finding study in 135 healthy women (6 treatment cycles), two combinations of contraceptives were compared with regard to efficacy and tolerability. Combination A contained 0.01 mg ethinylestradiol (EE) + 1 mg estradiol valerate (EV) + 2 mg dienogest (21 days) and combination B contained 0.01 mg EE + 2 mg EV + 2 mg dienogest (21 days). The results showed that the EE dose could be successfully reduced to 0.01 mg by supplementation with 2 mg EV (2).

Dienogest as a progestin without antiestrogen activity was found suitable for maintaining good cycle control in combined oral contraceptives (OC) containing natural estradiol. In an open, randomized, dose-finding study two different regimens containing dienogest and estradiol valerate (EV) as estrogen completely inhibited ovulation. In order to increase both cycle stability and contraceptive efficacy, a novel sequential multiphasic regimen to oral contraception without ethinylestradiol (EE) was tested in a pilot study on 200 healthy females (6 treatment cycles). The results demonstrated that a sequential contraceptive regimen containing EV stepped over 25 days in combination with dienogest as progestin seems to fulfill the demands for a contemporary OC (3).

Results of a phase III uncontrolled, open, multicenter clinical trial in 2290 healthy fertile women (28,183 cycles) from 146 centers in Germany demonstrated very good efficacy (adjusted Pearl index of 0.2) and tolerability of dienogest (4).

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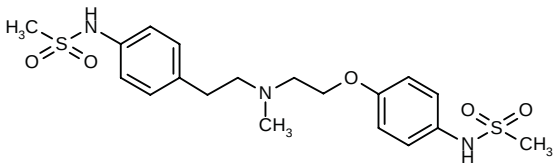

$C_{19}H_{27}N_3O_5S_2$ **Pfizer**

Using microelectrode techniques at different stimulation frequencies in guinea pig papillary muscle, it was found that the action potential duration (APD) prolonging effect of dofetilide was reverse frequency-dependent. Modulation of L-type calcium currents with diltiazem led to a decrease in the change of APD at 0.5 Hz but not at 3 Hz, while Bay K 8644 prolonged the APD further at 3 Hz but not at 0.5 Hz (1).

Using whole cell patch-clamp experiments in isolated guinea pig cardiomyocytes, it was found that dofetilide's block of the delayed rectifier potassium current was decreased with elevated extracellular potassium and increased by hypokalemia (2).

The effects of dofetilide on the human atrium have been investigated by comparing Doppler echocardiographic images from patients with atrial fibrillation treated with 500 μg b.i.d. of the active drug (51 patients) or placebo (54 patients) in a double-blind, randomized trial. Dofetilide was found to increase A wave height following cardioversion. The absence of effects on heart rate and deceleration time suggest that the compound exerts an atrial positive inotropic effect rather than altering ventricular hemodynamics (3).

In anesthetized dogs undergoing vagal stimulation, dofetilide was effective in prolonging sinus cycle length, right atrial effective refractory period (AERP) and ventricular effective refractory period in a dose-dependent manner. It also inhibited SCL prolongation and potentiated AERP shortening during cervical vagus stimulation-induced prolongation of SCL (4).

The effectiveness of dofetilide in preventing sudden death in patients at high risk is being studied in patients with congestive heart failure (CHF, n = 1518) and acute myocardial infarction (MI, n = 1510) with LVEF of ≤ 35%. Patients were randomized to treatment with either dofetilide or placebo. At minimum follow-up of 1 year, overall mortality was 28% for CHF and 22% for MI patients (5).

A randomized, crossover study in 20 subjects showed that food ingestion had a modest effect on dofetilide pharmacokinetics and pharmacodynamics (lower C_{max}, later t_{max}, no change in mean $t_{1/2}$), although the effect was not clinically significant (6).

In a study of the clinical and electrophysiologic effects of dofetilide in recent onset (< 7 days) atrial fibrillation (AF) and paroxysmal supraventricular tachycardia (PSVT), dofetilide converted 7 of 13 patients with AF and 4 of 6 with PSVT. Dofetilide also lengthened the effective refractory period in the ventricle, atrium and accessory pathways with no effect on intracardiac conduction (7).

A randomized, double-blind, placebo-controlled trial of dofetilide (125, 250 and 500 μg b.i.d.) given following cardioversion of atrial fibrillation/flutter in 326 evaluable patients showed that dofetilide was effective in maintaining normal sinus rhythm up to 6 months in 70% of patients compared to 26% of patients on placebo. The maximum effect was seen with the highest dose. Dofetilide appeared safe and no cases of Torsades de Pointes were reported (8).

A randomized, double-blind, placebo-controlled trial comparing dofetilide (8 μg/kg i.v.) to procainamide (15 mg/kg i.v.) for the conversion of atrial fibrillation/flutter in 190 patients showed that both drugs were effective in conversion within 3 h of start of infusion. There were 7 proarrhythmic events with dofetilide and 1 with procainamide. The infusion was stopped in 8 procainamide patients and 17 dofetilide patients (9).

A randomized, multicenter, placebo-controlled, double-blind trial in 96 patients showed that dofetilide (6 μg/kg i.v. infusion for 15 min) was effective ($p < 0.001$) in terminating paroxysmal supraventricular tachycardia (81% conversions) compared to placebo (38%), and the time to conversion was shorter ($p < 0.0001$). No serious adverse events or proarrhythmias occurred (10).

A randomized, placebo-controlled study of dofetilide (0.25-1 mg/d) in 1518 patients with congestive heart failure (LVEF ≤ 0.35) failed to show any improvement in all cause mortality compared to placebo after a minimum follow-up of 1 year (11).

In a randomized, placebo-controlled, double-blind study in 1518 patients with congestive heart failure (LVEF under 35%), dofetilide significantly decreased hospital admissions for worsening CHF as compared to placebo ($p < 0.001$), with a risk reduction of 0.75. This effect was independent of the presence of atrial fibrillation (12).

In a study in 30 patients with congestive heart failure (LVEF 19 ± 8%), intravenous amiodarone, but not dofetilide, significantly increased cardiac sympathetic drive, as shown by increases in aortic and coronary sinus norepinephrine and doubling of the transcardiac norepinephrine spillover (13).

A randomized, placebo-controlled trial in 15 male patients with Wolff-Parkinson-White syndrome showed that dofetilide 2.5 μg/min i.v. for 15 min terminated induced supraventricular arrhythmias in 2 of 5 patients, while 4 of 5 patients responded to 4.0 μg/min. With a second dose of 4.0 μg/min, 11 of 15 patients responded. No serious adverse events occurred (14).

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Dolasetron Mesilate

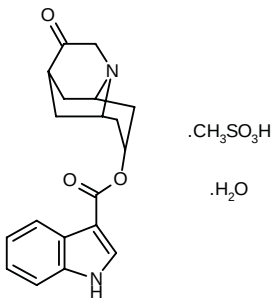
Anemet®

Anzemet®

Antiemetic

5-HT_3 Receptor Antagonist

EN: 151754



$C_{19}H_{20}N_2O_3.CH_4O_3S.H_2O$

Hoechst Marion Roussel; Abbott

A randomized study compared the combined use of oral dolasetron (200 mg) and dexamethasone (20 mg) given as 3-day and 6-day courses to 83 cancer patients treated with high-dose cisplatin. Both treatment regimens were equally effective in delaying emesis (complete response of 70% for all patients). Adverse events included constipation, headache, diarrhea, dizziness, dyspepsia and hiccup (1).

A randomized, double-blind study was done in 30 patients receiving high-dose cisplatin chemotherapy. Results showed that the antiemetic effect of dolasetron as a single intravenous dose (0.6 mg/kg) before chemotherapy was as effective as a 3-dose regimen. Mild headache and diarrhea were the most common adverse events (2).

A randomized, double-blind, placebo-controlled, multicenter trial evaluating the use of dolasetron (12.5, 25, 50 and 100 mg i.v.) administered after cessation of anesthesia to 281 women having gynecological surgery showed that all doses of the drug decreased emetic episodes and

increased the likelihood of the patient having no nausea. Adverse events were mild, and no changes were seen in laboratory tests, vital signs or ECG (3).

A randomized, double-blind, placebo-controlled, multicenter trial in 514 patients compared dolasetron (25 and 50 mg) and ondansetron (4 mg) at induction of anesthesia. Results showed that both ondansetron and the 50-mg dose of dolasetron significantly reduced postoperative nausea and vomiting, and were equally well tolerated and safe (4).

A randomized, double-blind, placebo-controlled study of oral dolasetron (25, 50, 100 and 200 mg) administered 1-2 h prior to anesthesia in 374 women undergoing total abdominal hysterectomy showed that the 100-mg and 200-mg doses significantly reduced postoperative nausea and vomiting for 24 h after surgery, with the effect showing a linear dose-response relationship across treatment groups (5).

A phase III randomized, double-blind, parallel-group study evaluated the antiemetic effects of dolasetron and ondansetron, both alone and combined with dexamethasone for 7 days, in 696 patients treated with moderately emetogenic chemotherapy. At 24 h, ondansetron alone was more effective than dolasetron alone, while at 7 days there was no difference. Dexamethasone improved the efficacy of both drugs at 24 h and over 7 days (6).

A double-blind, placebo-controlled, parallel-group study in 49 healthy nonsmoking males showed that the pharmacokinetics of intravenous dolasetron (50, 100 and 200 mg/min) were unaffected by infusion rates. Dolasetron was well tolerated with no differences in adverse events or vital signs with different rates of infusion (7).

Dolasetron mesilate (Anemet®) has been launched in Germany by Hoechst Marion Roussel for the treatment of postoperative nausea and vomiting and chemotherapy-induced nausea and vomiting. For postoperative use it is supplied as tablets, 50 mg equiv. to 37 mg dolasetron, and ampules, 12.5 mg equiv. to 9.3 mg dolasetron. For use in chemotherapy, it is supplied as tablets, 200 mg equiv. to 148 mg dolasetron, and ampules, 100 mg equiv. to 74 mg dolasetron (8, 9).

Hoechst Marion Roussel and Abbott have signed a multiyear agreement to market the injectable form and promote the oral form of dolasetron mesilate (Anemet®, Anzemet®) for postoperative nausea and vomiting (10).

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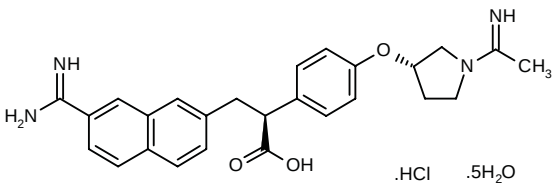
DX-9065a

Anticoagulant
Factor Xa Inhibitor

EN: 199880



$C_{26}H_{28}N_4O_3.HCl.5H_2O$ **Daiichi Pharm.; Sanofi**

The antithrombotic and hemorrhagic effects of DX-9065a, argatroban and ATIII-dependent anticoagulants were compared in a rat model of thrombosis and hemostasis. DX-9065a (0.1-1 mg/kg/h i.v.), argatroban (0.1-1 mg/kg/h i.v.), low-molecular-weight heparin (25-100 anti-XaU/kg/h i.v.), unfractionated heparin (25-100 anti-XaU/kg/h i.v.) and danaparoid sodium (30-300 anti-XaU/kg/h i.v.) administered for 1 h all dose-dependently inhibited thrombus formation and increases in plasma thrombin-ATIII complex in the copper wire arteriove-

nous shunt model in rats. Whereas DX-9065a did not prolong bleeding time at doses well above those active in the thrombosis model, the other compounds prolonged bleeding time at doses only slightly higher than effective doses (1).

DX-9065a in pooled human, monkey, rabbit and dog plasma preparations was shown to inhibit coagulation in a concentration-dependent manner, without affecting thrombin time values. Comparison of DX-9065a with heparin-pentasaccharide in human plasma systems produced IC_{50} values of 6.8 and 2.5 μg/ml, respectively, although assay-dependent variations were noted (2).

In a tissue factor-induced disseminated intravascular coagulation (DIC) model in monkeys, DX-9065a dose-dependently reduced elevations of plasma TAT, D-dimer, serum FDP and consumption of platelets, while in an endotoxin-induced rat model of DIC, the drug demonstrated protective effects. The concentration required to block DIC had no effects on bleeding time (3).

In a thromboplastin-induced monkey model of disseminated intravascular coagulation (DIC), DX-9065a (5 mg/kg i.v.) administered 1 min before thromboplastin suppressed plasma thrombin-AT III complex, D-dimer and platelet consumption. The elevation of F1+2 was also blocked, suggesting that DX-9065a prevents progression of thromboplastin-induced DIC by blocking thrombin generation in this particular model (4).

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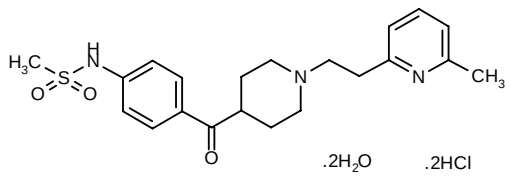
E-4031

Antiarrhythmic

EN: 159932



$C_{21}H_{27}N_3O_3S.2HCl.2H_2O$ **Eisai**

Channel affinity for E-4031 was reduced by elevation of $[K^+]_o$ in the wild-type channel, independently of C-type channel inactivation effects. Removal of C-type inactivation by extracellular residue mutation decreased E-4031 affinity by more than one order of magnitude (1).

Using autonomically decentralized hearts of open-chest anesthetized dogs, E-4031 (1-2 μmol/kg i.v.) increased sinus cycle length and SA node recovery time dose independently, and decreased SA conduction time dose dependently. Corrected SA node recovery time was decreased at low pacing rates or with low numbers of pacing stimuli, but was unaffected with sufficient pacing stimuli. E-4031 selectively inhibited SA nodal region stimulation-induced sinus cycle length prolongation (2).

Results of experiments using the patch-clamp technique demonstrated that E-4031, at concentrations of 10-30 μM, had no significant effect on the amplitude of protein kinase A-activated chloride current in guinea pig ventricular myocytes (3).

Perfusion of rat hearts in the presence of E-4031 (0.1 μM) slowed the heart rate, increased myocardial Ca^{2+} uptake and reduced the loss of K^+ during ischemia. E-4031 also reduced ischemia-induced ventricular tachyarrhythmias, whereas those induced by reperfusion were sustained longer by E-4031. Furthermore, administration of the compound prior to ischemia prevented the loss of high-energy phosphates, but blocked their recovery during reperfusion (4).

In anesthetized dogs undergoing vagal stimulation, E-4031 prolonged sinus cycle length (SCL), right atrial effective refractory period (AERP) and ventricular effective refractory period (VERP) in a dose-dependent fashion. The drug also inhibited SCL prolongation and potentiated AERP shortening during cervical vagus stimulation-induced prolongation of SCL, but had no effect on atrio-His interval and VERP prolongations (5).

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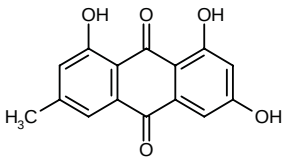
Emodin

Antineoplastic
Antibacterial
EN: 237157 *Immunosuppressant*



$C_{15}H_{10}O_5$ **China Pharm. Univ.**

Emodin blocked endotoxin-induced secretion of inflammatory cytokines in mononuclear phagocytes. The compound also stimulated inflammatory cytokine secretion in mononuclear phagocytes, although the stimulation was less than that observed with endotoxin (1).

Pretreatment of isolated rat liver cells with emodin significantly increased intracellular free Ca^{2+} levels with or without the addition of $CaCl_2$ or KCl to the cell suspension prior to emodin treatment, as compared to controls (2).

In vitro, emodin exhibited antiproliferative effects on cultured smooth muscle cells by blocking the transition from the G_0 to S phase of the cell cycle (3).

In isolated rabbit aorta strips, emodin increased the amplitude of contraction induced by KCl and NE, and produced a leftward shift in the corresponding dose-response curve. In the presence of high concentrations of K^+ and NE, the drug produced a decrease in the amplitude of contraction and a rightward shift in the dose-response curve, indicating Ca^{2+}-agonistic activity at low concentrations and Ca^{2+}-chelating properties at high concentrations (4).

In a suspension of macrophages, emodin increased intracellular free Ca^{2+} concentrations and produced an additional increase in intracellular free Ca^{2+} concentrations after the addition of CaCl to the suspension. The results indicate that emodin can induce the release of intracellular Ca^{2+}, as well as the influx of extracellular Ca^{2+} (5).

Emodin increased intracellular free Ca^{2+} concentrations in cultured rat myocytes after the addition of $CaCl_2$, suggesting that the drug promotes influx of extracellular Ca^{2+} in myocytes (6).

Emodin was shown to suppress *c-myc* RNA overexpression induced by LPS in rat glomerular mesangial cells, reaching maximum suppression after 2.5 h and lasting for 6 h (7).

Recent studies have shown that water extracts from rhubarb, such as emodin, can scavenge oxygen free radicals, including $O_2^{\cdot}$ and H_2O_2, and prevent lipid peroxidation, demonstrating antioxidant activity (8).

In rats, emodin blocked endotoxin-induced secretion of multiple cell factor from Kupfer cells in a dose-dependent manner (9).

Results from studies in rats showed that emodin dose-dependently inhibited LTB_4 synthesis (by 88.0%) when administered in the range of 0.5-5 μM, with an IC_{50} of 1.2 μM (10).

In rats with acute hemorrhagic-necrotizing pancreatitis and significantly reduced pancreatic blood flow, emodin reversed the reduction in blood flow. This effect may be partly attributed to its potential to reduce elevated eicosanoid synthesis, as well as its cytoprotective properties in acini cells (11).

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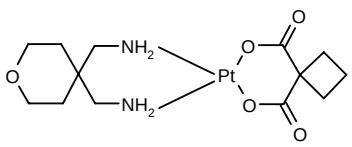
Enloplatin

Antineoplastic
Platinum Complex

EN: 135140



$C_{13}H_{22}N_2O_5Pt$ **American Cyanamid; Lederle; Immunex**

In a phase II study in 18 patients with platinum refractory ovarian cancer, intravenous enloplatin produced a median survival of 9.4 months. Neutropenia was the dose-limiting toxicity, while nephrotoxicity was manageable. The parent compound was the major free form in plasma, although 13.5 h postadministration, 85% of the compound was protein bound. Elimination was mainly through the urine, and pharmacokinetics of the drug were similar to carboplatin (1).

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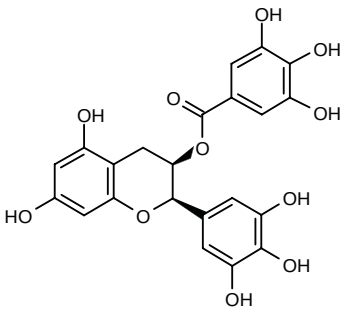
(–)-Epigallocatechin Gallate

Antineoplastic
Antiviral

EN: 183411



$C_{22}H_{18}O_{11}$ **Natl. Cancer Center Res. Inst. (JP); Pharmamex**

The effects of green tea polyphenols (GTP) on apoptosis and regulation of the cell cycle were assessed in a human epidermoid carcinoma cell line. Apoptosis was observed up to 10 h after exposure of cells to 20 μg of GTP, while exposure to 80 μg/ml induced the formation of internucleosomal DNA fragments. Treatment also produced altered distribution of cells in different phases of the cell cycle. Most of these effects were attributed to (–)-epigallocatechin gallate (1).

(–)-Epigallocatechin gallate was shown to have better antioxidant activity in oxidized corn oil triglycerides than epicatechin and catechin, while in a corn oil-in-water emulsion, the compound was a prooxidant. (–)-Epigallocatechin gallate was a better antioxidant than gallic acid, catechin, epicatechin and propyl gallate in oxidized soya lecithin liposomes, whereas in liposomes oxidized in the presence of cupric acetate, it promoted lipid oxidation (2).

(–)-Epigallocatechin gallate and other polyphenolic components of green tea demonstrated antibacterial activity against 20 strains of *Helicobacter pylori*. Eradication of the bacteria was observed in 6 out of 34 patients treated with the compound (3).

(–)-Epigallocatechin gallate demonstrated a sensitiz-

ing effect in doxorubicin-resistant murine sarcoma and human colon carcinoma cell lines, suggesting that the compound inhibits protein kinase C. This inhibition may downregulate the expression of certain proteins related to drug resistance (4).

(–)-Epigallocatechin gallate induced apoptosis in human carcinoma cell lines A431 (epidermoid), HaCaT (keratinocyte), L5178Y (lymphoma) and DU145 (prostate) but not in normal human epidermal keratinocytes (5).

Treatment of human epidermoid carcinoma cells A431 with (–)-epigallocatechin gallate (100 μM) for 24 h caused a significant and dose-dependent reduction (42%) in the constitutive NFκB/p65 nuclear protein, and an inhibition of tumor necrosis factor α-mediated activation of NFκB in the nucleus (6).

(–)-Epigallocatechin gallate at a concentration of 1-20 μM inhibited AP-1 activity by 30-80% in a mouse epidermal cell line transfected with a mutant Ha-ras gene (IC_{50} = 5 μM). Colony formation in this cell line was also reduced following drug treatment (7).

(–)-Epigallocatechin gallate (EGCG) inhibited growth of human lung cancer cell lines H661 and H1299 (IC_{50}s = 22 μM), although IC_{50}s estimated in H441 lung cancer and HT-29 colon cancer cell lines were 2-3 times higher. The compound (30 μM) also induced apoptosis in H661 cells with an apoptosis index of 23%, which was completely blocked by the addition of catalase. EGCG also induced H_2O_2 production in H661 cells, which may be a mechanism for the induction of apoptosis (8).

UVB irradiation-induced AP-1 activation and *c-fos* gene transcription was inhibited by (–)-epigallocatechin gallate in the HaCaT human keratinocyte cell line in a dose-dependent manner, as was c-fos protein accumulation (9).

Evaluation of (–)-epigallocatechin gallate in A431 human squamous carcinoma cells and human prostate cancer PC3 and DU145 cells showed that the drug inhibits growth of all three cell types in a dose-dependent and biphasic manner, with growth stimulation at low concentrations and inhibition at high concentrations. No treatment-induced changes in cell cycle distribution were observed in PC3 cells (10).

Incubation of (–)-epigallocatechin gallate (EGCG) in human saliva and murine stomach juice caused rapid disappearance of the compound, and analysis of the saliva mixture revealed 8 new products. Incubation of EGCG with tyrosinase produced red pigmentation identified as theaflavins. Topical application of EGCG to a substrate containing human keratinocytes and melanocytes, followed by UVB irradiation, produced red-brown pigmentation similar to melanin formation induced by *l*-dopa-tyrosinase in melanocytes (11).

Incorporation of [^{3}H]-(–)-epigallocatechin gallate in PC-9 cells was blocked by unlabeled (–)-epigallocatechin gallate (EGCG) in a dose-dependent manner. Furthermore, a combination of epicatechin and EGCG induced apoptosis, while neither compound alone could produce this effect, indicating that the effects of EGCG are potentiated by epicatechin (12).

Recent *in vitro* studies have shown that epigallocatechin gallate (EGCG) exhibits greater protective effects against cellular DNA damage than vitamins C and E or red wine. In the Ames test, EGCG had potent antioxidant effects, providing 63% protection against peroxide-induced DNA damage; specifically, it was 100 times more effective than vitamin C, 25 times more effective than vitamin E and almost twice as effective as red wine (13).

(–)-Epigallocatechin gallate (0.1%) was found to reduce cell proliferation by 34% in mice with NNK-induced hyperproliferation of bronchial epithelium, indicating the involvement of antiproliferative activity in the compound's anticarcinogenic activities (14).

Results of studies in mice with experimental duodenal carcinogenesis showed that decaffeination of (–)-epigallocatechin gallate may help alleviate the side effects of epigastric discomfort and sleeplessness observed in the clinical use of the compound (15).

Maximum concentrations of (–)-epigallocatechin gallate (EGCG) in plasma and bile were observed after oral administration of 100 mg/kg of the compound in rats. Theasinensin A and a dimer of EGCG were identified as degradation products after incubation of EGCG in bile. Both compounds inhibited hydroxy and alkoxy radical-induced oxidative damage *in vitro* and may contribute to the bioantioxidant effects of EGCG (16).

(–)-Epigallocatechin gallate was found to inhibit prostate tumor growth and to rapidly reduce tumor size in male castrated athymic mice with prostate tumors induced by the injection of the human prostate cancer cell line LNCaP 104-S (17).

A 5% dispersion of (–)-epigallocatechin applied topically to the dorsal epidermis in mice inhibited thymidine dimer formation by 34% as compared to controls following exposure to UVB, and reduced edema in a dose-dependent manner, suggesting that the compound may inhibit UVB-induced skin cancer through a general sunscreen action and a DNA photoprotective mechanism (18).

Pharmacokinetic studies of [^{3}H]-(–)-epigallocatechin gallate (2.2 μmol, 50 μCi) administered to male rats by gavage showed that the compound is absorbed rapidly reaching a peak plasma level at 0.5 h, with an elimination half-life of 0.5 h. High concentrations of radiolabeled compound were detected in the small intestine, stomach, liver, kidneys, esophagus, lungs, cecum and skin, while intermediate levels were observed in the colon and pancreas, and very low levels were detected in brain, spleen, eyes and thymus. A second peak was observed in the plasma and several major organs between 8-48 h. Peak concentrations in the digestive tract were detected at 8 h or earlier, and vanished completely within 24 h. [^{3}H]-EGCG was excreted in the feces and urine, with a distribution of 59.4 and 18.1%, respectively (19).

Maximum tolerated dose of (–)-epigallocatechin gallate (EGCG) was estimated to be 75 mg/kg after i.p. administration in mice. Lethality induced by higher doses was mainly due to hepatotoxicity which was not cholesta-

tic. Acute doses of 125 mg/kg i.p. produced significant increases in liver weight and reduced total body weight by 10.3%. Only minor antitumor activity was observed in the Lewis lung carcinoma model. Topical application of 7.5 mg EGCG in hydrophilic ointment produced gross toxicity in the form of erythema and papular lesions in hairless mice, as opposed to a study in which 50 mg was applied topically in acetone in mice and produced no dermal toxicity. These results indicate that EGCG-induced toxicity depends on the formulation and route of administration (20).

(–)-Epigallocatechin gallate showed significant antitumor-promoting activity against fumonisin B1-induced skin carcinogenesis in mice (21).

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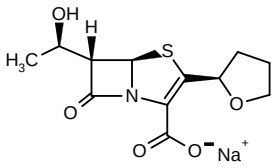

$C_{12}H_{14}NNaO_5S$ **Suntory; Hoechst Marion Roussel; Wyeth-Ayerst;Yamanouchi**

Based on time-kill kinetics and measurement of postantibiotic effect, faropenem was shown to be bactericidal against *B. fragilis*, *E. coli*, *S. aureus*, *H. influenzae*, *M. catarrhalis* and *S. pyogenes*. A postantibiotic effect was evident against all bacteria except for *H. influenzae* (1).

Using the agar dilution method and 500 bacterial clinical isolates, faropenem was shown to be active against *Staphylococcus*, *Streptococcus* and *Enterococcus*. Penicillin-resistant *S. pneumoniae* were susceptible under 0.4 μg/ml. While showing similar activity to levofloxacin against *Enterobacteriaceae*, it was less effective against *Citrobacter* and *Enterobacter* strains. MIC_{90} for faropenem against *B. fragilis* and *Peptostreptococcus* was 0.39 μg/ml and against *Propionibacterium acnes* was 0.05 μg/ml (2).

In a study in rats, the AUC of faropenem administered orally was increased (from 2.90 μg.h/ml to 8.79 μg.h/ml) by the intravenous injection of cilastatin. This effect appeared to result from cilastatin suppressing faropenem metabolism in the lung, kidney and intestinal tract (3).

Faropenem, when given to beagle dogs as a single intravenous dose of 500 mg/kg, caused necrosis and degeneration of proximal tubules, with elevation of BUN and creatinine. However, after 48 h, regeneration was seen, with BUN and creatinine returning to normal. With oral dosing of 2000 mg/kg for 4 weeks, evidence of renal damage was seen early in the trial, but this subsided and was considered to be slight at the end of 4 weeks (4).

Faropenem has properties similar to cephems and penicillins, showing a wide spectrum of activity. $T_{1/2}$ following oral administration is 0.9 h, with C_{max} reached at 1 h (prolonged if administered postprandially). Protein binding is 89.8%, mostly reversible. Because of its high efficacy against anaerobes, soft stools and diarrhea occur slightly more often than with other cephems. Clinically, faropenem is highly efficacious against pneumonia, pharyngitis, tonsillitis and acute bronchitis (5).

In a study of 40 pediatric infections, primarily respiratory, faropenem was shown to have a clinical efficacy rate of 94.6%. No serious side effects were observed. Combination treatment with Enteronon-R reduced the frequency of loose stools from 94.7% to 63.2% of cases. Four strains of pencillin-resistant *S. pneumoniae* were isolated, against which faropenem was effective (6).

In a study of 494 pediatric cases, faropenem showed an efficacy rate of 91.9% in 295 cases where bacteria were isolated and 93.0% in 199 cases where no causative agent was isolated. Clinical efficacy was high against penicillin-resistant *S. pneumoniae*. Adverse events, none of which were serious, occurred in 6.6% of 548 cases evaluated for safety (diarrhea, loose stool, gluteal candidiasis, urticaria and rash); abnormal laboratory findings occurred in 37 cases. Palatability of the drug was rated as more than moderate by 99.3% of patients (7).

Faropenem (Farom®) has been launched in Japan by Suntory and Yamanouchi for the treatment of faropenem-susceptible bacterial infections. It is supplied as tablets, 150 and 200 mg (8).

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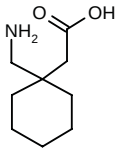

$C_9H_{17}NO_2$ **Warner-Lambert; Fujisawa**

In a placebo-controlled, double-blind, crossover trial in 40 patients with painful diabetic neuropathy, patients were randomized to treatment with gabapentin (900 mg/day) or placebo for 6 weeks, followed by a 3-week washout period and crossover to the other treatment arm. Pain as judged by the McGill Pain Questionnaire (MPQ), Visual Analogue Pain Scale (VAS) and Present Pain Intensity (PPI) scale decreased significantly following treatment with gabapentin, although VAS scores also indicated improvements with placebo treatment. MPQ score decreased by a mean of 8.9 points in the gabapentin group, and 17 of 40 patients reported moderate to excellent pain relief with gabapentin (1).

In an open-label comparative study enrolling 25 elderly patients with painful diabetic neuropathy, the efficacy and safety of gabapentin were assessed and compared to amitriptyline. Patients with pain and paresthesia of at least 6 months duration were treated with gabapentin (400 mg/day, titrated every 3-5 days to up to 2400 mg/day) or amitriptyline (10 mg/day, titrated every 3-5 days to up to 90 mg/day) for 12 weeks, and pain was assessed weekly. In this study, pain relief and reduction of paresthesia were significantly greater in the gabapentin arm than in the amitriptyline arm, and side effects were less frequent (2).

Patients with symptoms of diabetic neuropathy of 1-5 years duration were enrolled in a double-blind, placebo-controlled, parallel-group study. These patients were treated with gabapentin or placebo for 8 weeks, with dose escalation over the first 4 weeks to a target dosage of 3600 mg/day. Pain relief was shown to be significantly greater with gabapentin than with placebo, as judged by patient diaries of pain and sleep interference (3).

Gabapentin was compared to carbamazepine in the treatment of idiopathic trigeminal neuralgia, with the study drug used both as first-line therapy and as an alternative to carbamazepine in nonresponders. At a mean dose of 1107 mg/day (range 600-2000 mg/day), pain response with gabapentin was rated as excellent in 3 of 6 and 1 of 7 nonpretreated and carbamazepine-pretreated patients, respectively; pain response was rated as good in 2 of 6 and 3 of 7 patients, respectively. No significant side effects were reported with gabapentin. Overall, gabapentin was effective in 83% of patients receiving the drug as first-line therapy and in 57% of patients not responding to carbamazepine (4).

Forty-nine patients with chronic pain resulting from a variety of conditions were treated with gabapentin, in most cases following the failure of first-line analgesic therapy. Clinical improvements were obtained in 77.5% of these patients, while 20.4% showed no change and only one worsened with gabapentin. Seventeen of 21 patients suffering from postherpetic neuralgia, 3 of 7 patients with central pain and 4 of 7 with trigeminal neuralgia showed clinical improvement following treatment with gabapentin. Side effects of drowsiness and myoclonus, although not serious, led to interruption of gabapentin therapy in 10% of all treated patients (5).

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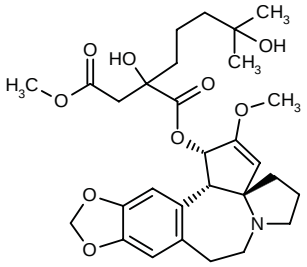
Homoharringtonine

Antineoplastic Alkaloid

EN: 090682



$C_{29}H_{39}NO_9$ **Chinese Acad. Med. Sci.; Natl. Cancer Inst. (US); VivoRx**

Homoharringtonine (2.5 mg/m^2/d) and ara-C (7.5 mg/m^2/d) were given as a continuous i.v. infusion for 14 days to 44 patients with chronic myelogenous leukemia. Complete hematologic remission occurred in 93% of patients; at 6 months, 44% of all patients had cytogenetic improvement. All patients receiving homoharringtonine as first therapy had complete remission initially, and at 6 months 84% had cytogenetic improvement. The drug

combination was well tolerated; adverse events included nausea and/or fatigue, intravenous line infection and thromboses (1).

A combination of homoharringtonine (2.5 mg/m^2/d by continuous infusion for 5 days) and ara-C (15 mg/m^2/d s.c., in 2 divided doses for 5 days) was given every month to 50 patients with Ph-positive chronic myelogenous leukemia (median age 50 years). CHR occurred in 70%, with PHR in 16% and major Ph suppression in 26%. Adverse events included infections (4%), mild to moderate diarrhea (24%) and moderate to severe headache (8%) (2).

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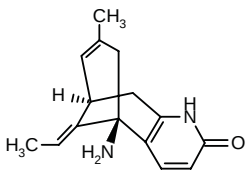
Huperzine A

Cognition Enhancer
Acetylcholinesterase Inhibitor

EN: 122853



$C_{15}H_{18}N_2O$ **Shanghai Inst. Materia Med.; Chinese Acad. Med. Sci.**

In a study in rats, huperzine A (0.1-0.4 mg/kg p.o.) was shown to reverse scopolamine-induced memory deficits as tested using a radial maze task, and was significantly better than E-2020 (0.5-1.0 mg/kg p.o.) and tacrine (1.0-2.0 mg/kg p.o.). Huperzine A was also the most selective acetylcholinesterase inhibitor (1).

In a study in Sprague-Dawley rats, huperzine A (0.1-0.4 mg/kg i.p.) was shown to increase the learning process in adult and aged rats and to ameliorate the scopolamine-induced impairment of consolidation in active avoidance responses. Huperzine A was more potent than tacrine (6-12 mg/kg i.p.) (2).

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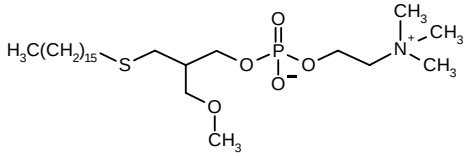
Ilmofosine

Antineoplastic

EN: 118807



$C_{26}H_{56}NO_5PS$ **Boehringer Mannheim**

In vitro experiments revealed that certain multidrug-resistant cell lines showed cross-resistance to ilmofosine, and that ilmofosine was not a substrate for P-glycoprotein. Resistance to ilmofosine appears to result from MDR1-associated membrane lipid alteration (1).

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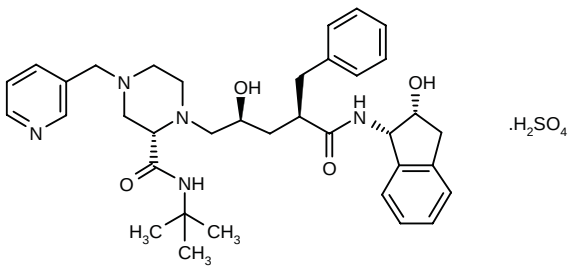

$C_{36}H_{47}N_5O_4.H_2SO_4$ **Merck & Co.**

The efficacy of indinavir in combination with one or two nucleoside analogs was evaluated in 177 protease inhibitor-naive patients with advanced HIV disease. The treatment decreased HIV viral load and raised the CD4 count, indicating that indinavir in combination with reverse transcriptase inhibitors may be highly efficient in patients with advanced HIV infection (1).

The antiviral activity and safety of indinavir (800 mg q8h, 1000 mg q12h and 1200 mg q12h) were assessed in 87 HIV-1 infected patients who were 3TC and protease inhibitor naive. Preliminary results from 46 patients after 20 weeks of therapy indicated that the reduction in viral RNA and the increase in CD4 counts were comparable in all three groups, and that all dosing regimens were well tolerated (2).

Monitoring of creatinine levels, analysis of urine and urologic symptoms during administration of indinavir in 72 patients for a period of 44 weeks showed that median creatinine levels increased at weeks 12 and 24. Elevated creatinine levels were found more frequently in women with pyuria, hematuria, renal colic with or without nephrolithiasis, and flank or back pain. Elevated creatinine levels continued for more than 4 months in 1 male and 4 female patients. All patients experienced mild to moderate hair loss, while a decrease in HIV RNA levels was also observed. The frequency of nephrotoxicity in this group of patients may have been due to factors other than treatment with indinavir (3).

Evaluation of indinavir treatment in 500 pretreated HIV patients during 10 months indicated that changing combined NRTI at the start of indinavir therapy improves virological results independently of baseline CD4 count and viral load (4).

Two cases of oliguric acute renal failure associated with indinavir treatment have been reported. Renal failure was resolved in both cases by administration of intravenous fluids, although urologic intervention was required in 1 patient in order to relieve bilateral ureteral obstruction (5).

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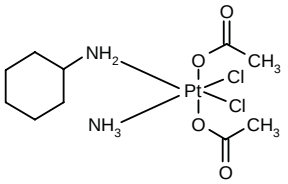
JM-216
BMS-182751

Antineoplastic
Platinum Complex

EN: 185356



$C_{10}H_{22}Cl_2N_2O_4Pt$

Johnson Matthey; Bristol-Myers Squibb

Loss of DNA mismatch repair activity on sensitivity to JM-216 was evaluated in 3 pairs of cell lines proficient or deficient in this function. There was no difference in sensitivity between the DNA mismatch repair-proficient and -deficient cell lines, indicating that loss of this mechanism does not result in resistance to the drug (1).

The synergistic effects of JM-216 given together with VP-16 were evaluated in tumor-bearing mice. The drugs were administered daily for 5 days starting on day 4 or 5 after tumor implantation and again on days 11 or 12. The maximum tolerated dose for the combination treatment was much less than the dose observed for each drug alone. Additional experiments in a P388 leukemia model supported the existence of a synergistic effect with the combination regimen, although repetition of the experiments in a sarcoma model did not support this conclusion (2).

Results of disposition studies of [^{14}C]-JM-216 and its metabolite [^{14}C]-JM-118 in rats and dogs indicated that JM-216 was absent from dog plasma ultrafiltrate and JM-118 accounted for only a portion of the plasma ultrafiltrate platinum content. Furthermore, cyclohexylamine was separated from the platinum part of JM-216 and represented the major urinary metabolite in both rat and dog (3).

A phase I study evaluated JM-216 in 23 patients with advanced cancer refractory to standard treatment. Administration of 50-120 mg/m^2/day during 5 days every 4 weeks yielded a maximum tolerated dose of 120 mg/m^2/day. Total and unbound plasma concentrations were lower on day 1 than on day 5, while the AUC of unbound drug correlated better to the decrease in neutrophils than to total drug concentrations. A minor response was observed in 1 patient with breast cancer, but the disease continued to progress before the patient recovered from hematological toxicities. Recommended dose was determined to be100 mg/m^2/day for 5 days in previously treated patients (4).

A phase I study evaluated a combination regimen of JM-216 (5, 10 and 20 mg/day), uracil/ftorafur (300 mg/day) and leucovorin (90 mg/day) in 11 cancer patients for toxicity and disease response. Patients received the combination for 14 days of a 28-day cycle. One patient with refractory endometrial cancer demonstrated stable

disease after 4 cycles of therapy, and 1 patient with advanced prostate cancer demonstrated significantly decreased serum PSA. Toxicities observed included nausea, emesis, fatigue and thrombocytopenia (5).

Pharmacokinetics of JM-216 (10-50 mg/m^2/day p.o.) were evaluated in 45 patients with solid tumors treated daily for 2 weeks every 4-5 weeks. At a dose of 45 mg/m^2, mean C_{max} values of total and free JM-216 were 145 ± 18 and 40 ± 10 ng/ml on day 1, respectively, and 400 ± 53 and 54 ± 20 ng/ml on day 14, respectively. Mean AUCs were estimated to be 1900 ± 410 and 409 ± 106 ng/ml.h on day 1, respectively, and 833 ± 442 ng/ml.h on day 14. Toxicities included dose-limiting thrombocytopenia, nausea, vomiting, diarrhea and fever. The maximum tolerated dose in untreated and pretreated patients appeared to be 50 and 35 mg/m^2, respectively, administered every 5 weeks (6).

A phase II trial of JM-216 (120 mg/m^2/day x 5 days every 28 days) with oral ondansetron in 15 patients with hormone refractory prostate cancer with progressive disease after antiandrogen withdrawal has shown the drug to be active and convenient against the disease. Treatment produced 1 partial response in 2 patients with measurable disease. One patient showed a normalization of PSA levels, 2 patients experienced reductions in serum PSA greater than 50%, 3 patients stabilized their PSA levels, and 2 patients showed increased PSA levels. Hematological toxicities included neutropenia, thrombocytopenia and anemia, while nonhematologic toxicities were fatigue, nausea, diarrhea and elevated bilirubin (7).

JM-216 (120 mg/m^2/day x 5 days every 3 weeks) was evaluated as a first-line therapy in a phase II trial in 17 patients with non-small cell lung cancer. No sustained objective responses were observed, although 1 patient demonstrated stable disease and partial response after 3 cycles, but continued to progress after 4 cycles. Stable disease was observed in an additional 5 patients. Side effects included nausea, vomiting, diarrhea, constipation and asthenia (8).

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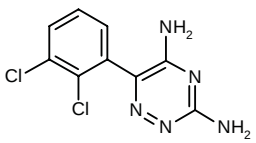

$C_9H_7Cl_2N_5$ **Glaxo Wellcome; DuPont Merck; Faes**

A nonrandomized, open-label, first-line, add-on study investigated the addition of lamotrigine to carbamazepine over a 5-month period in epileptic patients. Lamotrigine's cognitive profile appeared similar to that of carbamazepine, with no significant changes in cognitive testing. However, patients complained less after treatment with lamotrigine (1).

A 16-week, double-blind, placebo-controlled trial examining the use of lamotrigine in 169 patients with Lennox-Gastaut syndrome showed that lamotrigine resulted in a reduction of at least 50% in the frequency of seizures in 33% of patients compared to 16% of placebo-treated patients. Colds and viral illnesses, however, were more common in the lamotrigine group (2).

In an ongoing open trial in depressed outpatients, 5 of 6 patients with recurrent major depressive episodes treated with low doses (50-100 mg/day) of lamotrigine had considerable clinical improvement without significant side effects (3).

The potential psychotropic activity of lamotrigine has been evaluated in a placebo-controlled study involving a group of 35 children with autism. Lamotrigine was administered as daily divided doses of 0.5 mg/kg/day p.o. for 2 weeks, followed by dosing at 1.0 mg/kg/day p.o. for another 2 weeks. Dose incrementation continued up to a final dose of 5 mg/kg/day p.o., which remained constant

for 4 weeks before tapering down to a drug-free period of 4 weeks. Results in the 28 subjects completing the trial indicated that lamotrigine did not significantly improve behavior in this group of autistic children (4).

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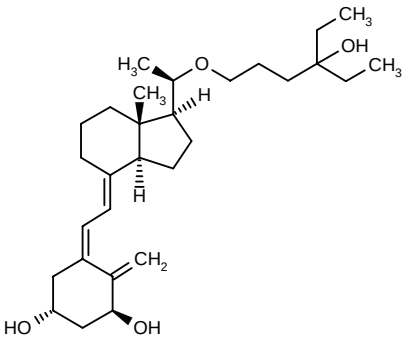
Lexacalcitol

Antipsoriatic
Vitamin D Analog

EN: 166325



$C_{29}H_{48}O_4$ **Leo Denmark**

In vitro evaluation of vitamin D_3 analogs MC-1288 and KH-1066 on keratinocyte stem cells showed that both compounds inhibited clonal keratinocyte growth more efficiently than 1,25-dihydroxyvitamin D_3, with KH-1060 being more potent than MC-1288 (1).

KH-1060 alone was shown to inhibit clonal growth of an acute promyelocytic leukemia cell line (NB4) with an ED_{50} of 80 pM, while the combination of KH-1060 with 9-*cis*-RA synergistically enhanced this effect, with an ED_{50} of 5 pM. Neither compound markedly induced cell differentiation (2).

Treatment of NB4 cells with KH-1060 inhibited clonal growth with an ED_{50} of 50 pM, and the addition of 9-*cis*-RA synergistically and irreversibly enhanced this inhibition. Neither compound induced differentiation significantly. An increase in apoptosis was only observed after treatment with 9-*cis*-RA alone or concomitantly with KH-1060. Levels of bcl-2 protein in wild-type NB4 cells decreased from 100% to 2% after treatment with KH-1060 in combination with 9-*cis* RA, while bax protein levels increased from 50% to 92%. These findings were confirmed in acute promyelocytic leukemia cells from one individual (3).

In vivo and *in vitro* studies of KH-1060 metabolism revealed the existence of multiple side-chain hydroxylated metabolic products as well as side-chain truncated forms. Inhibition of cytochrome P450 blocked the metabolism of the drug. Certain metabolic species had significant biologic activity when evaluated in a vitamin D-dependent reporter gene system and showed superior biological activity in native gene expression systems in vitamin D target cells as compared to 1α,25-dihydroxyvitamin D_3 (4).

KH-1060 significantly inhibited growth of $CD34^-$ acute promyelocytic leukemia cells as compared to $CD34^+$ samples, while 9-*cis*-RA had no effect. KH-1060 at a dose of 1 μM completely inhibited $CD34^-$ growth, while an equal dose of 9-*cis*-RA reduced the number of colonies to 11% of control values. Flow cytometry analysis showed that KH-1060 also downregulated bcl-x expression in both $CD34^+$ and $CD34^-$ cells, which may increase the sensitivity of leukemic cells to cytotoxic drugs (5).

Metabolic studies have shown that KH-1060 was rapidly metabolized in HPK1A-ras cells and hepatocytes to yield 22 different metabolites, although the proportions between metabolites differed in the two cell types. Metabolism was inhibited by ketoconazole, indicating a cytochrome P450-mediated process. Evaluation of the metabolites showed that they were gene- and cell-specific in their effects on vitamin D responsive gene products. Accumulation of active metabolites was observed in both cell types, indicating that the metabolic products may be responsible for increasing the potency of KH-1060 (6).

Application of topical KH-1060 (0.2 μg/ml in isopropanol) or KH-1060 after betamethasone 17-valerate treatment (2 mg/ml in isopropanol) to the backs of hairless mice during 4 weeks increased the number of dermal fibroblasts. The fibroblasts contained a high number of normal mature secretory components in the cytoplasm, and the cells degranulated after disintegration. Extrusion of nondisintegrated granules was not observed. The number of collagen fibrils increased as well as their thickness, although the content of type I collagen remained the same, while the appearance of glycosaminoglycan figures was altered (7).

Administration of KH-1060 (450 ng/kg/day) in X-linked hypophosphatemic mice raised plasma phosphate, improved femoral mineralization and reduced osteoid content, although bone length was not improved as compared to 1, 25-dihydroxyvitamin D_3 (8).

Administration of KH-1060 in combination with ciclosporin in spontaneous diabetic NOD mice significantly reduced IL-12 and Th1 cytokine levels, and increased the level of Th2 cytokines, as compared to control. In addition, the treatment significantly prolonged syngeneic islet graft survival, possibly by inducing an immune shift from Th1 to Th2 (9).

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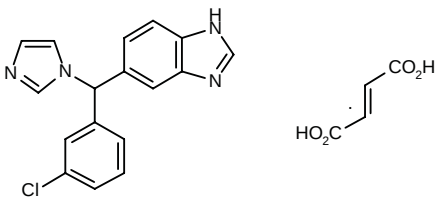

$C_{17}H_{13}ClN_4.3/2C_4H_4O_4$ **Janssen**

Liarozole has been shown to inhibit the breakdown of endogenous retinoic acid, which is also mediated by retinoic acid-4-hydroxylase, a cytochrome P450 enzyme, indicating that the antitumor activity exhibited by liarozole could be due to an accumulation of retinoic acid (1).

The effects of liarozole were evaluated in healthy male subjects administered doses of 75 mg or 150 mg b.i.d. Labeling index changed significantly as compared to placebo, although changes in mean epidermal thickness or differentiation were not observed. Concentrations of the drug in subcutaneous fat were 25-30% of those in skin and plasma, indicating that the tendency of accumulation in subcutaneous fat is low (2).

Liarozole was evaluated in 55 patients with hormone-resistant prostate cancer at doses of 300 mg b.i.d., or starting at a dose of 150 mg b.i.d. increased to 300 mg b.i.d. after 4-8 weeks. Improvement in pain score was noted in 23/42 patients, and a 1-point improvement of WHO performance status was seen in 11 patients. A 41% PSA response rate was observed, with 15 patients having a 50% or more reduction in PSA levels. Side effects were similar to retinoic acid toxicity and included nausea, fatigue and slight alopecia (3).

In 2 open-label pilot studies involving 100 patients with progressive prostate cancer that had relapsed in spite of prior androgen ablation, liarozole (150-300 mg) was administered twice daily for periods of at least 1

month. PSA serum levels decreased in 15/30 patients in 1 study and in 10/55 patients in the other study as a result of treatment with the compound. Patients with PSA response also demonstrated more significant reductions in prostatic acid phosphatase, alkaline phosphatase and bone pain symptom scores, as well as significantly better improvements in general well-being, than did PSA nonresponders. Treatment with the drug did not affect plasma levels of adrenal androgens or cortisol or androgen response to the ACTH stimulation test, although cortisol response to the ACTH stimulation test decreased slightly. The drug was generally well tolerated, although some patients experienced dermatological adverse effects that could be related to intracellular increases in retinoic acid (4).

The effects on plasma pharmacokinetics following continuous administration of liarozole (150-300 mg p.o. b.i.d.) were evaluated in 11 patients with advanced non-small cell lung cancer, and who were nonresponsive to initial chemotherapy. Mean AUC of all-*trans* retinoic acid increased from a baseline value of 395 ng.h/ml to 428 ng.h/ml by week 2, and to 602 ng.h/ml by week 4. The mean change from baseline AUC of all-*trans* retinoic acid was 30 ng.h/ml at week 2 and 229 ng.h/ml at week 4. Antitumor response was not observed in this group of subjects (5).

Observed toxicities during a phase II trial of liarozole in patients with metastatic squamous cell carcinoma of the cervix resembled those described in hypervitaminosis A syndrome. Four cases of dermatologic toxicity in the form of macular, desquamating and pruritic skin rash grade 1-3 were also recorded. Treatment of liarozole-associated toxicities with α-tocopherol produced alleviation in 1 case and complete resolution of skin rash in 3 cases, indicating that α-tocopherol may effectively reduce liarozole-induced dermatologic toxicities (6).

A phase II study evaluated liarozole (150 mg p.o. b.i.d.) in 84 postmenopausal patients with metastatic breast cancer. The treatment produced responses in 10 patients and stable disease in 10 patients. Soft tissue metastasis was observed in 8 responders and 6 patients with stable disease. Toxicities were mild to moderate and resembled hypervitaminosis A syndrome. Plasma estrogen levels were undetected after 2 weeks of treatment (7).

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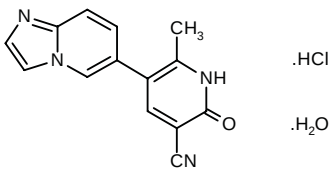

$C_{14}H_{10}N_4O.HCl.H_2O$ **Eisai**

Olprinone (0.3 μg/kg/min) significantly increased the cardiac output and hepatic venous oxygen saturation (from 49.3 to 57.6%) in 20 patients subjected to elective cardiac surgery, indicating that the drug may facilitate splanchnic blood flow and protect splanchnic organs following surgery (1).

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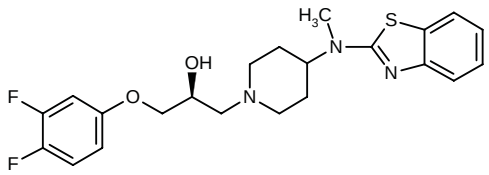

$C_{22}H_{25}F_2N_3O_2S$ **Janssen; Kyowa Hakko**

Lubeluzole (0.3 μM) prevented bovine chromaffin cell death due to Ca^{2+} overload in a concentration-dependent manner, and at 10 μM reduced lesions produced by free radicals in cells following exposure to 6-OH-dopamine. These observations indicate that its cytoprotective properties may be a result of its potential to block high threshold voltage-dependent Ca^{2+} channels (1).

The effects of lubeluzole on whole-cell currents were evaluated in voltage-clamped chromaffin cells. The drug blocked peak IBa (IC_{50} = 1.94 μM) in a time- and concentration-dependent manner, and a 10 min exposure of the drug augmented current inactivation. Peak current inactivation was more pronounced at more depolarizing holding potentials, while a more pronounced inactivation of the current occurred at more hyperpolarizing holding potentials (2).

In studies using primary rat hippocampal neurons, lubeluzole not only directly prevented nitric oxide-induced programmed cell death, but also reversed the induction of cell death during the critical 4-h period following exposure to NO (3).

Evaluation of the pharmacokinetic parameters of lubeluzole in normal subjects and in patients with mild, moderate and severe renal impairment demonstrated no differences between the groups in regard to AUC, C_{max}, renal CL and $t_{1/2}$. Plasma protein binding to lubeluzole was significantly lower in patients with moderate and severe renal impairment as compared to normal subjects. The results suggest that renal impairment does not appear to affect the pharmacokinetics of lubeluzole (4).

A 12-week, multicenter, double-blind, placebo-controlled trial evaluated lubeluzole in 725 patients with acute ischemic stroke. The drug was administered within 6 h of the onset of symptoms in doses of 7.5 mg for 1 h, followed by 10 mg/day for 5 days. Initial analysis of mortality rates indicated no differences between the group receiving lubeluzole and the placebo-treated group. However, when patients over 75 years of age having a severe Clinical Global Impression of Stroke rating were excluded from the analysis, lubeluzole was found to significantly reduce mortality (5).

Lubeluzole (7.5 mg for 1 h, followed by 10 mg/day x 5 days) was evaulated in a 12-week, multicenter, randomized, double-blind, placebo-controlled trial in 700 patients with a clinical diagnosis of acute ischemic stroke. The results demonstrated that the drug significantly reduced mortality and improved the Barthel Index for functionality, the NIH Stroke Scale for neurologic recovery and the Rankin Scale for disability. No safety issues were raised during the treatment (6).

Administration of intravenous lubeluzole in 721 patients within 6 h of the onset of ischemic stroke at a dose of 7.5 mg for 1 h, followed by 10 mg/day for 5 days, had no significant effects on mortality or improved clinical outcome as compared to placebo (7).

Evaluation of lubeluzole treatment (7.5 mg i.v. over 1 h followed by 10 mg/day x 5 days) within 6 h of acute ischemic stroke in 1375 patients showed that the drug reduced the risk of mortality in the mild to moderate CGI class by 51%, while in the severe CGI class this effect was nonsignificant. In addition, the drug also increased the risk of patients being in the lower dependency class by 22%. The exclusion of patients recognized to have a poor diagnosis reduced the mortality risk by 37% and significantly improved the chances of being in a lower dependency and disability class (8).

Results of randomized, placebo-controlled studies evaluating single escalating doses of lubeluzole (5-15 mg) in 22 patients with acute ischemic stroke showed that the drug had no significant effects on any cardiovascular variables when compared with placebo. No electroencephalogram abnormalities were observed, and epileptiform discharges were not detected in any patient. Drug plasma concentrations decayed biphasically with distribution half-lives of 46.3-101.0 min and terminal half-lives of 20.8-27.7 h, while comparison of dose-normalized values of plasma concentrations indicated linear kinetics over the dose ranges evaluated (9).

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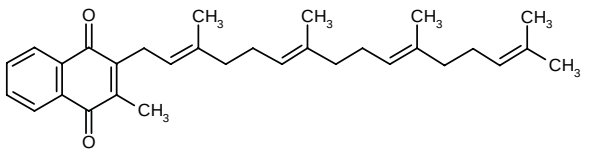

$C_{31}H_{40}O_2$ **Eisai**

Menatrenone, given in doses of 1, 10 and 100 mg/kg/day to rabbits fed a 0.5% cholesterol diet for 10 weeks, prevented atherosclerotic plaque progression, intimal thickening and pulmonary atherosclerosis. It also decreased factor X activity and ester-cholesterol aortic deposition (1).

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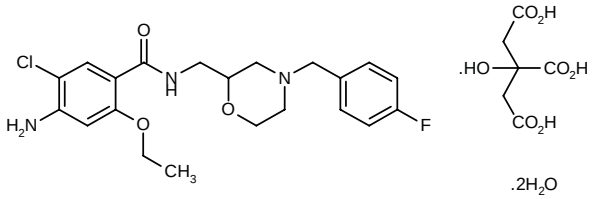

$C_{21}H_{25}ClFN_3O_3.C_6H_8O_7.2H_2O$ **Dainippon; Astra**

Mosapride citrate (0.3-3 mg/kg i.v.) stimulated antral motility in conscious dogs with implanted force transducers without affecting colonic motility, an effect which was antagonized by pretreatment with the selective 5-HT_4 receptor agonist GR-113808. *In vitro*, mosapride citrate blocked the binding of GR-113808 to the 5-HT_4 receptor in guinea pig striatum (IC_{50} = 113 nM) and relaxed carbachol-precontracted rat esophagus, augmented electrically induced contractions of guinea pig ileum and induced contractions in the guinea pig distal colon, with respective EC_{50}s of 208, 73 and 3029 nM (1).

In 21 patients with gastroesophageal reflux disease, mosapride citrate (40 mg/day) significantly decreased the total number of reflux episodes, the total number and duration of reflux episodes of more than 5 min, and the amount of daytime with an intraesophageal pH below 4 (2).

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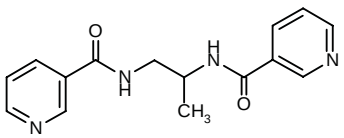

$C_{15}H_{16}N_4O_2$ **Chugai; Novartis**

Results of an *in vitro* study of oxidative stress using ring segments of pig epicardial right coronary arteries indicated that nicaraven (100 and 10 μM) had a protective effect on hydroxy radical-induced endothelial dysfunction (1).

In a controlled study examining the effect of nicaraven on conserved extracted kidneys subjected to simple cooling, peak levels of creatinine reached 10-12 mg/dl in the nicaraven-treated group, demonstrating the drug's protective effect (2).

Using a rat experimental model of subarachnoid hemorrhage to evaluate the effects of nicaraven, angiography and blood-brain barrier Evans Blue permeation assessment was carried out on 4 groups of 10 rats each. Based on intragroup mean vessel diameters of the anterior cerebral artery, middle cerebral artery and basilar artery, it was seen that nicaraven significantly decreased subarachnoid hemorrhage-induced vasospasm and blood-brain barrier opening (3).

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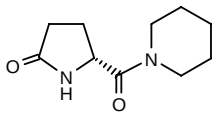

$C_{10}H_{16}N_2O_2$ **Nippon Shinyaku**

NS-105 (0.1-10 μM) blocked forskolin-stimulated cAMP formation in cultured neurons of the mouse cerebral cortex, but produced an opposite effect in neurons pretreated with pertussis toxin. The latter effect was reversed by cholera toxin, while L-AP3 blocked both effects produced by NS-105 on cAMP formation. NS-105 also intensified isoproterenol- and adenosine-stimulated cAMP formation, but had no effect on phosphoinositide hydrolysis (1).

Administration of NS-105 (1-100 mg/kg p.o) in rats significantly reduced the immobility time in the forced swimming test. Repeated administration reversed the failure to escape in the shuttle-box test by rats previously given an inescapable foot shock and increased the number of $GABA_B$ receptors in the cerebral cortex. *In vitro* monoamine uptake and concentrations in brain tissues or extracellular fluids were not affected by the compound (2).

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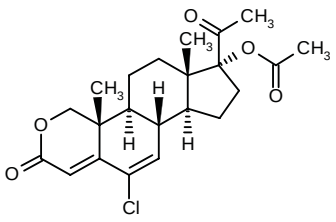

$C_{22}H_{27}ClO_5$ **Teikoku Hormone**

The effects of osaterone acetate and 17β-estradiol on long bone structure, strength and turnover have been compared in ovariectomized female rats administered the compounds every other day for 12 weeks starting at 12 weeks of age. The results demonstrated that osaterone increases the dimension, bone mineral density and physical strength of long bones by enhancing cortical bone formation, whereas 17β-estradiol maintains trabecular bone mineral density by inhibiting bone resorption, suggesting the potential of osaterone in the treatment of osteoporosis with reduced cortical bone formation (1).

Teikoku Hormone has signed an agreement with Wyeth-Ayerst granting the latter an option to license Teikoku's tissue-selective antiandrogen osaterone acetate. An NDA for the compound is under review in Japan for the indication of benign prostatic hyperplasia (2).

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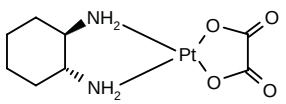

$C_8H_{14}N_2O_4Pt$

Nagoya Univ (JP).; Debiopharm; Sanofi

Oxaliplatin (130 mg/m^2 q3weeks) and 5-FU plus folinic acid was given to 21 advanced colorectal cancer patients. Plasma levels of 5-FU increased at days 8 and 15 compared to day 1, while 5-FUH2 and UH2 plasma levels decreased. Oxaliplatin clearly influenced 5-FU metabolism (1).

Oxaliplatin (130 mg/m^2 2-h i.v. infusion every 3 weeks) was given alone (13 patients) or with 5-FU (12 patients) to patients with 5-FU-resistant metastatic colorectal cancer. Neurological toxicity was the most common adverse event. Oxaliplatin alone was not effective, but in combination with 5-FU resulted in a partial response rate of 16% (2).

Oxaliplatin (130 mg/m^2 over 2 h every 3 weeks) pharmacokinetics, when combined with weekly 5-FU and leucovorin, was studied in 16 patients with metastatic colorectal carcinoma. C_{max} (total and ultracentrifugable platinum) was constant, with a platinum $t_{1/2}$ of 9 days; no significant plasma accumulation occurred following 4 cycles. Platinum accumulated significantly in RBCs after 3 cycles, with the half-life equal to the RBC half-life (3).

Oxaliplatin (130 mg/m^2 i.v. infusion every 3 weeks) was given to 14 patients with anthracycline-resistant metastatic breast cancer. After a median number of 3 courses, 3 partial responses, 1 stable disease and 9 progressions were seen. Major toxicities included acute dysesthesia (3) and thrombocytopenia (1), with 4 patients each having grade 1 and 2 neurological cumulative toxicity (4).

In a phase I trial, the combination of oxaliplatin (85-110 mg/m^2) and CPT-11 (150-200 mg/m^2) was studied in 16 patients with gastrointestinal cancers. Results showed that the combination was both feasible and highly active (5).

In a multicenter, phase II trial, oxaliplatin (130 mg/m^2/d 2-h i.v. infusion q3weeks) was given as first-line therapy to 39 patients with metastatic colorectal carcinoma. With 27 patients evaluable and a median of 5 cycles/patient, the response rate was 24%, with a median time to progression and median duration of stabilization of 4 months. Oxaliplatin was well tolerated with no functional impairment and no grade 3-4 neurotoxicity (6).

The combination of oxaliplatin (25 mg/m^2/d), folinic acid (300 mg/m^2/d) and 5-FU (700-1000 mg/m^2/d) was studied in a multicenter, phase II trial in 90 patients with previously untreated metastatic colorectal carcinoma. At a minimum follow-up of 2 years, the objective response rate was 67% on CT scan, with a median survival of 19 months. Toxicity was considered acceptable (7).

In a multicenter, phase II study in 44 evaluable patients with progressing metastatic colorectal cancer, low-dose oxaliplatin (85 mg/m^2 2-h i.v. day 1) added to leucovorin and 5-FU was confirmed to show synergism, with an overall response rate of 27% (8).

The combination of oxaliplatin (130 mg/m^2 on day 1), folinic acid (500 mg/m^2 over 1 h) and 5-FU (2.6 g/m^2 over 24 h on day 1 and 8) every 3 weeks was evaluated as second- or third-line treatment in 34 patients (median age 60 years) with advanced colorectal carcinoma. Tumor growth was controlled in 42% of patients with a 7-month median duration. Toxicity was moderate, with neurotoxicity being the main adverse event (9).

A feasibility study of the combination of 5-FU (420 mg/m^2) and folinic acid (20 mg/m^2) administered on days 1-5 by i.v. short infusion every 28 days and oxaliplatin (80 mg/m^2) administered on day 1 and 14 by 2-h i.v. infusion in 7 patients with first-line advanced colorectal carcinoma showed that this regimen was feasible and had a low toxicity (10).

In a study involving 38 patients (mean age 66 years) with 5-FU refractory advanced colorectal cancer, the combination of 5-FU and oxaliplatin (130 mg/m^2 q3weeks by 2-h i.v. infusion) was shown to have synergistic activity with only mild toxicity. Mean response duration was 6 months, with a median overall survival of 7.6 months. After 12 months, 9 patients remained alive (11).

Treatment with oxaliplatin (120 mg/m^2 as 2-h i.v. infusion every 21 days) as a first-line chemotherapy in a phase II trial in 25 patients with metastatic colorectal cancer produced an overall response rate of 20% and stable disease status in 32% of the patients. Median progression-free survival was 4 months and the median overall survival was 14.5 months. Neuropathy and laryngopharyngeal dysesthesia were major adverse effects observed, and gastrointestinal and hematological toxicities were mild (12).

A multicenter, randomized phase II-III trial comparing cyclophosphamide (1000 mg/m^2 i.v.) combined with either oxaliplatin (130 mg/m^2 i.v. every 3 weeks x 6) or cisplatin (100 mg/m^2 i.v. every 3 weeks x 6) in 182 cases of advanced ovarian cancer showed that oxaliplatin was significantly better tolerated and showed equal activity to full dose cisplatin (13).

Sanofi has received approval in France for a new indication for oxaliplatin (Eloxatin®) in the first-line treatment of metastatic colorectal cancer in association with fluoropyrimidines, and as monotherapy in patients in whom administration of fluoropyrimidines is not appropriate. The company is conducting clinical trials on the platinum complex in the U.S. and expects to file for marketing approval in the U.S. as well as in the rest of Europe before the end of 1998 (14).

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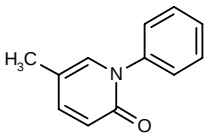

$C_{12}H_{11}NO$ **Marnac; Synexus; Shionogi**

In an *in vitro* study, pirfenidone was shown to inhibit myometrial and leiomyoma cell proliferation (using tritiated thymidine incorporation assays and cell number changes) and reduce mRNA levels of collagen (types I and III) in a dose-dependent fashion (measured by densitometric analysis of Northern blots). No cytotoxic effects

were seen with lactate dehydrogenase assays and trypan blue exclusion measurements (1).

Using murine C57BL/6 peritoneal macrophages stimulated with either lipopolysaccharide (LPS) or mannosylated bovine serum albumin, pirfenidone was shown to decrease TNF-α production. *In vivo*, pirfenidone (200 mg/kg) completely inhibited LPS-induced endotoxin shock when administered simultaneously with LPS, and partially inhibited it when administered before or after LPS (2).

Pirfenidone (0.05 mg) administered intraperitoneally did not reduce dermoid cyst fluid-induced adhesion formation in intact rats or in rats with standardized injury to the right uterine horn (3).

Results of a disposition study of radiolabeled pirfenidone in mice revealed a plasma half-life of 12.5 min with monophasic kinetics, and a peak plasma concentration appearing after 5 min following i.v. administration. The tissues with highest to lowest amount of radioactivity were kidney, liver, ventricle, lung, spleen, pancreas, testicle, GI tract, skeletal muscle, adrenal gland and epididymal fat pad. Ninety-seven percent of the dose was recovered in the urine, all of which was associated with metabolites presumed to be glucuronic acid and sulfate conjugates (4).

A prospective, open-label, phase II trial of pirfenidone in the treatment of idiopathic pulmonary fibrosis was carried out on 47 patients who failed, could not tolerate or refused current conventional therapy. One-year survival was 85%. Prednisone was tapered off in 80%, and minimal adverse events were seen (gastrointestinal in 9, skin rash in 8) (5).

In a placebo-controlled study of the effects of pirfenidone treatment for 8 weeks on renal lesions in rats with 5/6 nephrectomies, pirfenidone-treated rats had better renal function, excreted less urinary protein, had lower glomerular matrix scores and less severe interstitial lesions, and had less expression of TGF-β, collagen (types I and IV), fibronectin and α-SM-actin (6).

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3. Al-Took, S., Murray, C., Tulandi, T. *Effects of pirfenidone and dermoid cyst fluid on adhesion formation.* Fertil Steril 1998, 69(2): 341.

4. Giri, S.N., Wang, Y., Chang, A., Buckpitt, A.R., Margolin, S.B. *Pharmacokinetics of a novel antifibrotic drug pirfenidone, in mouse following intravenous administration.* Amer J Respir Crit Care Med 1998, 157(3): A279.

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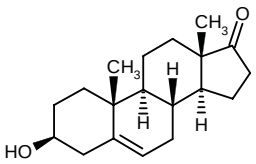
Prasterone *Agent for Systemic Lupus Erythematosus*
Dehydroepiandrosterone *Immunosuppressant*

EN: 213244



$C_{19}H_{28}O_2$ **Genelabs Technol.; Stanford Univ.; Jenapharm; Pharmadigm**

Dehydroepiandrosterone therapy (200 mg/day) in conjunction with corticosteroids with or without immunosuppressive agents was evaluated in a double-blind, placebo-controlled study in 21 patients with severe lupus erythematosus during 6 months. Eleven patients achieved the primary goal defined as quantitative improvement in principal lupus manifestation, while 7 patients reached 2 out of 3 secondary goals. Drug-induced side effects included acne and mild hirsutism (1).

Neuroscience Pharma has initiated a double-blind, placebo-controlled Canadian phase II/III trial to evaluate the efficacy of dehydroepiandrosterone (DHEA) for the treatment of memory deficits associated with Alzheimer's disease (2).

Genelabs Technologies has completed patient enrollment in its second phase III clinical trial evaluating the efficacy of GL-701 (DHEA) in women with systemic lupus erythematosus (SLE). The double-blind, randomized, placebo-controlled, multicenter trial is designed to determine whether GL-701 can improve clinical outcome or disease symptoms in patients with SLE receiving either 200 mg of active drug or placebo daily. Patient enrollment was completed on schedule, with more than 370 women with SLE enrolled for a 12-month treatment period. The study is expected to be completed at the end of March 1999. Results from Genelabs' first phase III trial demonstrated that a beneficial effect was most evident in the patients with active disease who received 200 mg of GL-701 daily. Based on discussions with the FDA, the company intends to file an NDA if results from the second phase III trial confirm the beneficial effect of GL-701 in patients with active SLE (3).

1. Genovese, M.C., Hendrickson, C.L., Park, J., Powell, M.J., McGuire, J.L., van Vollenhoven, R.F. *Dehydroepiandrosterone (DHEA) in severe systemic lupus erythematosus. Results of a double-blinded, placebo controlled pilot study.* Arthritis Rheum 1997, 40(9, Suppl.): Abst 168.

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3. *Patient enrollment complete for phase III trial of GL-701 in SLE.* Prous Science Daily Essentials May 6, 1998.

Original monograph - Drugs Fut 1995, 20: 575.

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Kurzman, I.D. et al. *The effect of dehydroepiandrosterone combined with a low-fat diet in spontaneously obese dogs: A clinical trial.* Obes Res 1998, 6(1): 20.

Mao, X.R., Barger, S.W. *Neuroprotection by dehydroepiandrosterone-sulfate: Role of an NFκB-like factor.* Neuroreport 1998, 9(4): 759.

Khalil, A. et al. *Dehydroepiandrosterone protects low density lipoproteins against peroxidation by free radicals produced by gamma-radiolysis of ethanol-water mixtures.* Atherosclerosis 1998, 136(1): 99.

Recombinant Human Ciliary Neurotrophic Factor

Agent for Amyotrophic Lateral Sclerosis

EN: 197381

Amgen; Roche Bioscience; Regeneron; Procter & Gamble

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

Regeneron and Procter & Gamble have expanded their previously announced 10-year collaborative agreement to include ciliary neurotrophic factor (CNTF) (2).

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

2. *Regeneron and P&G joint development program for obesity.* Prous Science Daily Essentials October 3, 1997.

Original monograph - Drugs Fut 1994, 19: 557.

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Kalra, S.P. et al. *Cilliary neurotropic factor is a potent anorectic cytokine acting through hypothalamic neuropeptide Y.* Soc Neurosci Abst 1996, 22(Part 2): Abst 536.13.

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Rhenium Re-186 Etidronate Injection

Analgesic

EN: 183269

Mallinckrodt; Missouri Univ.; Univ. Cincinnati; Sloan-Kettering Inst.

^{186}Re-HEDP treatment significantly improved symptom free survival of rats with induced prostate tumor skeletal metastasis. Histological examination revealed a decrease in detectable tumor tissue in the lumbar vertebrae, and autoradiography showed that radioactivity accumulated in lumbar areas of bone formation and turnover (1).

Sixteen prostate cancer patients with osseous metastatic lesions were treated with ^{186}Re-HEDP. Three patients experienced loss of pain, while 8 demonstrated obvious improvement and 2 some improvement. Adverse effects included decreased platelet and polymorphonuclear white blood cell counts and peripheral neuropathy. Thus, the compound appears to be useful in alleviating pain in prostate cancer patients with painful bone metastases (2).

^{186}Re-HEDP was evaluated for pain relief in 20 patients taking analgesics with multiloculated osteoblastic metastases originating from hormone-resistant prostate cancer. One injection of 1295 MBq of the compound produced responses in 75% of the patients and complete pain relief in 25% without the need for analgesics. The response lasted from 1-32 weeks, with mild and reversible hemotoxicity (3).

^{186}Re-HEDP was evaluated for the relief of pain in 50 patients with disseminated bone metastases due to prostate or breast cancer. Response was observed in 32 patients and lasted from 1-32 weeks, with 9 responders experiencing complete pain relief without analgesic therapy. Severe side effects were absent, although some patients experienced leukocytopenia and thrombocytopenia. Hemotoxicity was reversed within 10-14 days after drug withdrawal (4).

1. Geldof, A.A., Van den Tillaar, P.L.M., Newling, D.W.W., Teule, G.J.J. *Radionuclide therapy prolongs symptom-free survival in experimental prostate cancer lumbar metastasis.* Proc Amer Assoc Cancer Res 1997, 38: Abst 1682.

2. Limouris, G.S., Shukla, S.K., Manetou, A., Kouvaris, I.,Plataniotis, G., Triantafyllou, N., Rigas, A.V., Vlahos, L. *Rhenium-186HEDP palliative treatment in disseminated bone metastases due to prostate cancer.* Anticancer Res 1997, 17(3B): 1699.

3. Schoeneich, G., Palmedo, H., Heimbach, D., Biersack, H.J., Muller, S.C. *Advanced prostate cancer: Systemic radiopharmaceutical therapy of metastatic prostate cancer with rhenium-186 hydroxyethylidene diphosphonate.* Onkologie 1997, 20(4): 316.

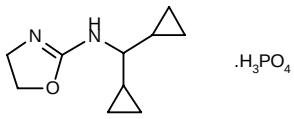
4. Schoeneich, G., Palmedo, H., Müller, S.C., Biersack, H.J. *Systemic radionuclide therapy of painful bony metastases with rhenium-186 hydroxyethylidine diphosphonate (Re-186 HEDP).* Eur Urol 1998, 33(Suppl. 1): Abst 188.

Original monograph - Drugs Fut 1993, 18: 520

Rilmenidine Dihydrogen Phosphate Hyperium®

Antihypertensive

EN: 090333



$C_{10}H_{16}N_2O.H_3PO_4$ **Servier**

A randomized, placebo-controlled, double-blind study evaluated rilmenidine (1 mg/d for 3 months) in 41 patients with typical rosacea. No statistical differences were seen in relation to reduction of papules and pustules, variation of facial redness and variation in number of flushes (1).

1. Grosshans, E., Michel, C., Arcade, B., Cribier, B. *Rilmenidine in rosacea: A double-blind study versus placebo.* Ann Dermatol Venereol 1997, 124(10): 687.

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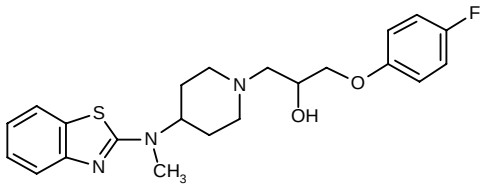
Ozog, M.A. et al. *Rilmenidine effects of astrocyte calcium levels and ischemic neurons in vitro.* Soc Neurosci Abst 1997, 23(Part 1): Abst 213.3.

Sabeluzole
Reminyl®

Cognition Enhancer

EN: 121491



$C_{22}H_{26}FN_3O_2S$ **Janssen**

A placebo-controlled trial of sabeluzole (5 or 10 mg b.i.d. for more than 1 year) in patients with Alzheimer's disease showed that sabeluzole-treated patients had greater stability in some cognitive measures. Computerized tomographic images showed some weak associations between relative cognitive function preservation and smaller structural abnormalities in the third ventricle and hippocampus (1).

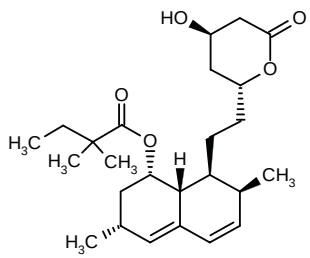
1. Mohr, E., Nair, N.P.V., Sampson, M., Murtha, S., Belanger, G., Pappas, B., Mendis, T. *Treatment of Alzheimer's disease with sabeluzole: Functional and structural correlates.* Clin Neuropharmacol 1997, 20(4): 338.

Original monograph- Drugs Fut 1988, 13: 529.

Simvastatin
Zocor®

Hypolipidemic
HMG-CoA Reductase Inhibitor

EN: 122234



$C_{25}H_{38}O_5$ **Merck & Co.; Mediolanum; Amrad**

Simvastatin has been assessed for *in vitro* and *in vivo* activity against gliomas. The compound inhibited growth in all human glioma cell lines tested, an effect which was reversed by the addition of exogenous mevalonic acid. An additive effect on glioma cell growth was observed with simvastatin and peroxidized LDL. In nude mice, intratumoral injection of simvastatin and peroxidized LDL also inhibited the growth of gliomas (1).

In vivo in rats subjected to focal cerebral ischemic damage, simvastatin upregulated endothelial NOS, thus protecting against acute cerebral ischemia. If these data can be confirmed, a new use may be found for statins in preventing major stroke in patients at risk (2).

The efficacy and safety of simvastatin and pravastatin were evaluated and compared in heart transplant patients. Forty-nine heart transplant recipients with sustained elevations in LDL cholesterol levels were randomized to treatment with pharmacologically equivalent doses of pravastatin or simvastatin for at least 6 months. Simvastatin was found to be more potent than pravastatin in reducing total cholesterol and LDL cholesterol levels in these patients. No significant differences in safety were observed (3).

The FDA has approved simvastatin (Zocor®) for reducing the risk of first stroke or transient ischemic attack (TIA) in people with high cholesterol and coronary heart disease. The new indication is based on the landmark Simvastatin Survival Study (4S), which showed that among 4444 patients in the study, those treated with simvastatin (20 or 40 mg once daily) had 28% fewer fatal or nonfatal strokes and TIAs than patients administered a placebo, as well as 42% fewer deaths from heart disease and 30% fewer deaths from any cause (4).

1. Kikuchi, T., Nagata, Y., Abe, T. *In vitro and in vivo antiproliferative effects of simvatatin, an HMG-CoA reductase inhibitor, on human glioma cells.* J Neuro-Oncol 1997, 34(3): 233.

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3. Vivekananthan, K., Uber, P.A., DeGruiter, H., Solis, S.,Kapoor, C., Dumas-Hicks, D., Mehra, M.R. *A randomized controlled comparison of the efficacy and safety of pravastatin and simvastatin in heart transplantation.* Transplantation 1998, 65(8, Suppl.): Abst 627.

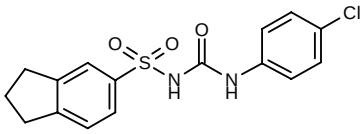
4. *Another statin approved for stroke prevention indications.* Prous Science Daily Essentials May 4, 1998.

Original monograph - Drugs Fut 1988, 13: 531.

Sulofenur

Antineoplastic

EN: 133601



$C_{16}H_{15}ClN_2O_3S$ **Lilly**

Escalating doses of sulofenur (250-700 mg/m^2 p.o. x 28 days) were evaluated in a phase I trial in 38 patients with advanced solid malignant tumors. Tumor regression was not achieved but 1 patient had stable disease throughout 9 courses. Marked hemolytic anemia, the main side effect, occurred at doses of 600 and 700 mg/m^2. Moderate methemoglobinemia and 1 case of reversible toxic hepatitis was also reported. Maximum

plasma levels reached 348 μg/ml and the maximal tolerated dose was determined to be 600 mg/m^2 (1).

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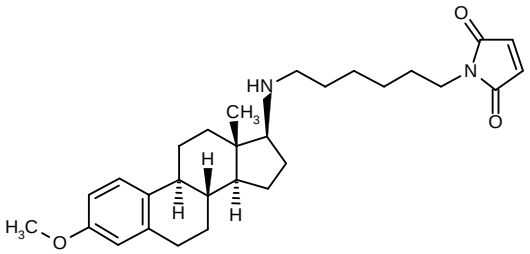
U-73122

Phospholipase C Inhibitor

EN: 165099



$C_{29}H_{40}N_2O_3$ **Pharmacia & Upjohn**

The effects of U-73122 and neomycin on Ins(1,4,5)P_3 production, intracellular Ca^{2+}, Ca^{2+}-activated K^+ current and M current were evaluated in differentiated NG108-15 neuroblastoma x glioma cells. Ins(1,4,5)P_3 generation and increase in Ca^{2+} induced by bradykinin was partially suppressed by preincubation with 1 or 5 μM U-73122, while the resting levels of Ins(1,4,5)P_3 were unaffected. Bradykinin-induced Ca^{2+}-activated K^+ current was reduced by 80% after pretreatment of whole-cell clamped cells with 1 μM U-73122, and was completely inhibited by 5 μM of the drug. U-73122 and its inactive analog U-73343 at 5-10 μM irreversibly reduced the holding current as well as the M current. Neomycin at 1 or 3 mM had no effect on bradykinin-induced Ins(1,4,5)P_3 generation and increase in Ca^{2+}, although 3 mM neomycin reduced the bradykinin-induced Ca^{2+}-activated K^+ current to 20% of its normal size (1).

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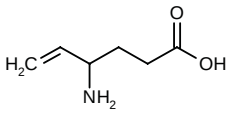
Vigabatrin
Sabril®
Sabrilex®

Anticonvulsant
GABA Transaminase Inhibitor

EN: 090252



$C_6H_{11}NO_2$ **Hoechst Marion Roussel; Novartis**

Vigabatrin (40-100 mg/kg/d for 2 weeks) was given to 25 infants (mean age 5.1 months) with infantile spasms. EEG improvement was evident in 78.9% of the 19 symptomatic patients and in 50% of the 6 cryptogenic patients. Clinical improvement was seen in 84.2% and 66.6%, respectively. Deterioration was observed at higher doses (1).

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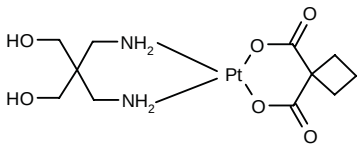
Zeniplatin

Antineoplastic
Platinum Complex

EN: 135141



$C_{11}H_{20}N_2O_6Pt$ **American Cyanamid; Lederle**

In phase II studies, zeniplatin (125 mg/m^2 i.v. bolus injection every 3 weeks) produced objective responses in 3/21 patients with advanced malignant melanoma and no responses in the 4 evauable patients with renal cancer. Leukopenia, nausea and vomiting were the main non-hematological toxicities. Nephrotoxicity, which was not prevented by hyperhydration, was observed and was serious enough to terminate the studies (1).

1. Aamdal, S., Bruntsch, U., Kerger, J., Verweij, J., Huinink, W.T., Wanders, J., Rastogi, R., Franklin, H.R., Kaye, S.B. *Zeniplatin in advanced malignant melanoma and renal cancer: Phase II studies with unexpected nephrotoxicity.* Cancer Chemother Pharmacol 1997, 40(5): 439.

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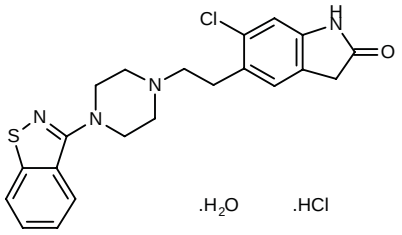
Ziprasidone Hydrochloride
Zeldrox®

Antipsychotic
Dopamine Antagonist
5-HT$_2$ Antagonist

EN: 199378



$C_{21}H_{21}ClN_4OS.HCl.H_2O$ **Pfizer**

The steady-state pharmacokinetics of ziprasidone were compared in healthy young and elderly male and female subjects. Mean pharmacokinetic variables (AUC, C_{max}, t_{max} and $t_{1/2}$) did not vary significantly according to age or gender, indicating that dose adjustment will not be necessary (1).

In a study in healthy young volunteers, no clinically significant pharmacokinetic interactions were observed between ziprasidone and Maalox® or cimetidine (2).

The pharmacokinetics of radiolabeled ziprasidone 20 mg p.o. were evaluated in 4 male volunteers. Eleven days following dosing, 20.3% of the radioactivity was collected in the urine and 66.3% in the feces. The drug was rapidly absorbed and C_{max} for the parent compound and its metabolites was reached 2-6 h after dosing. Peak serum concentration of the drug was 45 ng/ml and the mean AUC was 3357 ng.h/ml. Maximum concentration of total radioactivity reached 91 ng-eq/ml with a mean AUC of 724.6 ng-eq.h/ml, indicating that approximately 46% of radioactivity detected was attributed to unmetabolized compound. Ziprasidone was almost completely metabolized, with only 5% of the parent compound excreted, producing 12 detectable metabolites which accounted for more than 90% of the total radioactivity detected in urine (3).

The effects of a high-fat meal on the pharmacokinetics and pharmacodynamics of ziprasidone (20 mg) were assessed in 8 healthy male volunteers. Ziprasidone administered directly after a standard high-fat breakfast resulted in increased AUC and a reduced half-life, indicating that administration following a high-fat meal results in an increased systemic exposure to the drug (4).

In clinical trials in patients with acute exacerbations of schizophrenia and schizoaffective disorders, ziprasidone (80-160 mg/day) has been shown to be significantly more effective than placebo in improving positive, negative and depressive symptoms. A dose of 160 mg/day was comparable to haloperidol 15 mg/day in improving positive symptoms. The most frequent side effects of ziprasidone were somnolence, constipation, nausea and dyspepsia, with a low incidence of movement disorders being reported (5).

1. Tensfeldt, T.G., Wilner, K.D., Baris, B., Smolarek, T.A., Turncliff, R.Z., Colburn, W.A., Hansen, R.A. *Steady-state pharmacokinetics of ziprasidone in healthy elderly and young volunteers.* Biol Psychiatry 1997, 42(1, Suppl.): Abst 14-116.

2. Wilner, K.D., Hansen, R.A., Folger, C.J., Geoffroy, P. *Effects of cimetidine or Maalox® on ziprasidone pharmacokinetics.* Biol Psychiatry 1997, 42(1, Suppl.): Abst 14-118.

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