Drugs of the Future 1998, 23(10): 1111-1146

CCC: 0377-8282/98

Information Update

Volume 1-22, Number 10

Estimated developmental phase for this month's updated products:

Preclinical

MDL-74180 (neuroprotectant, antioxidant; Hoechst Marion Roussel)
Neplanocin A (antineoplastic; Toyo Jozo)
Sch-28080 (antiulcerative, H^+/K^+-ATPase inhibitor; Schering-Plough)
SU-840 (antiulcerative; Taisho)

Phase I

GM-611 (gastrointestinal motility stimulant; Chugai)

Phase II

Bisaramil hydrochloride (antiarrhythmic; Gedeon Richter, Taiho)
Interferon-αB/D hybrid (antiviral, antineoplastic; Novartis)
KNI-272 (anti-HIV, HIV-1 protease inhibitor; Japan Energy, Natl. Cancer Inst.)
KW-3902 (diuretic, kidney function improver, adenosine A_1 antagonist; Kyowa Hakko)
Ligustrazine (neuroprotectant; Chinese Univ. Hong Kong, Beijing Med. Univ.)
Losigamone (anticonvulsant; Schwabe)
ML-3000 (antiinflammatory, cyclooxygenase/lipoxygenase inhibitor; Merckle, Alfa Wassermann, Lacer)
MX2 (antineoplastic; Kirin Brewery)
OPC-21268 (vasopressin V_{1A} antagonist, antihypertensive, treatment of congestive heart failure; Otsuka)
Org-9487 (nondepolarizing neuromuscular blocker; Akzo Nobel)
Rupatadine fumarate (antihistamine, PAF antagonist, treatment of allergic rhinitis; Uriach)
Vintoperol (peripheral vasodilator; Gedeon Richter, Takata Seiyaku)
VIP (gastrointestinal motility inhibitor; RTP Pharma)

Phase III

Clinafloxacin (quinolone antibacterial; Kyorin, Warner-Lambert)
Ebselen (antiinflammatory, neuroprotectant, antioxidant; Rhône-Poulenc Rorer, Daiichi Pharm.)
Edaravone (neuroprotectant, antioxidant; Mitsubishi Chem.)
Eliprodil hydrochloride (NMDA antagonist, neuroprotectant; Searle, Synthélabo)
Lidakol™ (antiviral; Lidak, Yamanouchi, Grelan)
Peldesine (immunosuppressant, antiarthritic, purine nucleoside phosphorylase inhibitor, antipsoriatic; BioCryst, Torii)
RSHZ19 (antiviral; SmithKline Beecham)
Saruplase (thrombolytic, treatment of myocardial infarction; Grünenthal)
Sirolimus (immunosuppressant, antifungal; Wyeth-Ayerst, NanoSystems)
Suramin sodium (antineoplastic; Warner-Lambert, Natl. Cancer Inst.)
Telmisartan (antihypertensive, angiotensin AT_1 antagonist; Boehringer Ingelheim, Glaxo Wellcome)
Valspodar (multidrug resistance modulator; Novartis)

Registered/Year

Lobaplatin (antineoplastic, platinum complex; Asta Medica)/1998

Launched/Year

Alteplase (thrombolytic; Genentech, Boehringer Ingelheim)/1987
Amtolmetin guacil (antiinflammatory; Sigma-Tau)/1998
Bupropion (aid to smoking cessation, treatment of male sexual dysfunction, antidepressant, dopamine reuptake inhibitor; Glaxo Wellcome)/1989
Carvedilol (antianginal, α_1-adrenoceptor antagonist, β_1-adrenoceptor antagonist, treatment of congestive heart failure; Roche, SmithKline Beecham)/1991
Cidofovir (antiviral; Gilead, Pharmacia & Upjohn)/1996
Eprosartan (antihypertensive, angiotensin AT_1 antagonist; SmithKline Beecham, Hoechst Marion Roussel)/1997
Etomidate (anesthetic; Abbott, Janssen)/1977
Fexofenadine hydrochloride (antihistamine, treatment of allergic rhinitis; Sepracor, Andrx, Hoechst Marion Roussel)/1996
Loteprednol etabonate (ocular antiinflammatory, topical corticosteroid; Pharmos, Bausch & Lomb)/1998
Mibefradil hydrochloride (antihypertensive, calcium antagonist; Roche, Asta Medica)/1997 (withdrawn)
Montelukast sodium (antiallergic/antiasthmatic, leukotriene $cysLT_1$ antagonist; Merck & Co., Merck Frosst)/1997
Nebivolol (antihypertensive, β-adrenoceptor antagonist; Janssen, Meiji Seika, Menarini)/1997
Nevirapine (anti-HIV, reverse transcriptase inhibitor; Boehringer Ingelheim, Roxane Lab., Glaxo Wellcome)/1996
Riluzole (neuroprotectant, treament of amyotrophic lateral sclerosis; Rhône-Poulenc Rorer)/1996

Alteplase
Actilyse®
Activase®

Thrombolytic

EN: 137796

$C_{2569}H_{3894}N_{746}O_{781}S_{40}$

Genentech; Boehringer Ingelheim

Boehringer Ingelheim has announced preliminary findings from the European Cooperative Acute Stroke Study II (ECASS II) evaluating alteplase in stroke patients. The study showed an unexpectedly low overall mortality as compared to previous stroke trials; however, it also failed to show a statistically significant clinical benefit in patients treated with alteplase as compared to placebo. The study, which was conducted at 108 centers throughout Europe, Australia and New Zealand, involved more than 800 patients with acute ischemic stroke presenting within 0-6 h of symptom onset. The study compared a dose of 0.9 mg/kg alteplase with a maximum total dose of 90 mg. The primary endpoint of the trial – defined as the proportion of patients who had no or minimal functional deficit at day 90 as assessed by the Modified Rankin Scale – did not reach statistical significance. There was an unexpectedly high placebo response, however, which rendered the efficacy evaluation inconclusive. Nevertheless, the observed effects indicated a small but consistent efficacy signal across endpoints. The main safety objective was to reach a mortality rate not greater than that observed in ECASS I, results of which were published in 1995. This objective was clearly achieved, with an overall mortality reduction of about one-half that observed in the first study. There was also no difference between alteplase and placebo in terms of mortality in the ECASS II trial. There was no difference between treatment groups in terms of intracranial hemorrhage (ICH); however, as observed in other trials, including ECASS I, there was an increased frequency of more severe ICHs in the alteplase group (1).

1. *Boehringer Ingelheim reports preliminary findings of ECASS II trial*. Daily Essentials July 27, 1998.

Original monograph - Drugs Fut 1985, 10: 835.

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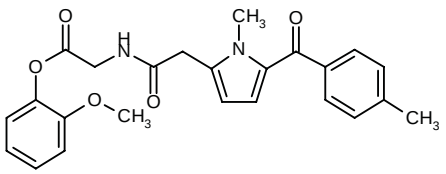
Amtolmetin Guacil

Antiinflammatory

EN: 149069



$C_{24}H_{24}N_2O_5$

Sigma-Tau

Amtolmetin guacyl, as compared to ibuprofen, aspirin and indomethacin, was examined for its gastrolesive properties in isolated gastric fundus, in pylorus-ligated conscious rats and in anesthetized animals with lumen-

perfused stomachs. At 10-100 mg/kg i.g., amtolmetin failed to inhibit histamine- and pylorus ligation-induced acid secretion in intact animals and was ineffective at 0.1-3 μM in isolated gastric preparations. The other reference drugs acted similarly in the various gastric secretory models. Amtolmetin (10-300 mg/kg i.g.) caused a minimal decrease in gastric potential difference (–5 mV), while aspirin (60 mg/kg i.g.) and ibuprofen (60 mg/kg i.g.) caused a significant decline (up to –27 mV). No alteration of the gastric mucosa in rats treated with amtolmetin (up to 300 mg/kg i.g.) was observed (1).

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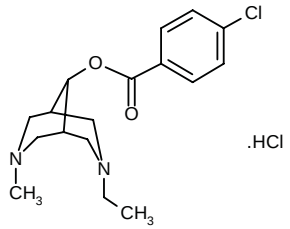
Bisaramil Hydrochloride
Yutac®

Antiarrhythmic

EN: 107350



$C_{17}H_{23}ClN_2O_2.HCl$ **Gedeon Richter; Taiho**

Bisaramil hydrochloride has been compared to the class Ib antiarrhythmic agent lidocaine for its effects on heart, skeletal muscle and brain Na^+ channels expressed in *Xenopus oocytes*. A concentration-dependent tonic block of Na^+ channels, particularly cardiac channels, was observed with both compounds, although bisaramil was more potent. Whereas bisaramil produced a marked frequency-dependent block of cardiac channels and mild frequency-dependent block of skeletal muscle and brain channels, lidocaine induced marked frequency-dependent block of all channels. It is concluded that selective tonic and frequency-dependent blockade of heart Na^+ channels may explain the potent *in vivo* antiarrhythmic effects of bisaramil, and this profile also suggests that it may be associated with reduced CNS toxicity compared to standard antiarrhythmic agents (1).

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Original monograph - Drugs Fut 1985, 10: 837.

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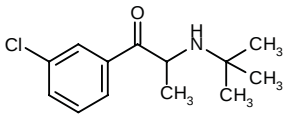

$C_{13}H_{18}ClNO$ **Glaxo Wellcome**

Bupropion has been assessed for its effects on sexual function in 14 diabetic men with somatic erectile dysfunction in a single-blind, prospective study in which the patients received placebo for 2 weeks and bupropion for 6 weeks following a 2-week baseline period. As measured by both subjective and objective parameters, bupropion did not produce worsening in sexual functioning, but rather showed a trend for improvement in several measures. Treatment had no effect on diabetic control. These results suggest that bupropion may be an attractive alternative for the treatment of depression in diabetic men or others with sexual dysfunction (1).

1. Rowland, D.L., Myers, L., Culver, A., Davidson, J.M. *Bupropion and sexual function: A placebo-controlled prospective study on diabetic men with erectile dysfunction*. J Clin Psychopharmacol 1997, 17(5): 350.

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Glaxo Wellcome's R&D pipeline remains full and diverse. Daily Essentials Jan 21, 1998.

Smoking cessation treatment launched in the U.S. Daily Essentials July 10, 1997.

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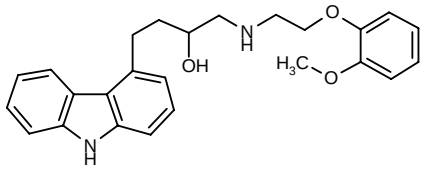

$C_{24}H_{26}N_2O_4$ **Roche; SmithKline Beecham**

Roche has commenced copromotion with SmithKline Beecham of carvedilol (Coreg®) for the treatment of congestive heart failure (CHF). This copromotion is a result of Roche's acquisition of Corange, the parent company of Boehringer Mannheim (1).

1. *Roche now copromoting Coreg with SKB*. Daily Essentials May 8, 1998.

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COHERE will track long-term effects of β-blockade in heart failure. Daily Essentials Oct 14, 1998.

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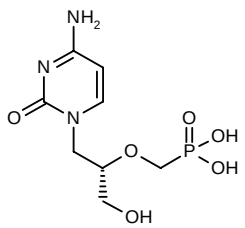

$C_8H_{14}N_3O_6P$

Gilead; Pharmacia & Upjohn

A 12-week, double-blind, placebo-controlled study evaluated daily application of 1% cidofovir gel in 31 immunocompetent patients with human papillomavirus-associated genital warts. Forty-seven percent of patients had complete clearance and 80% had a complete or partial response. Reversible application site reactions occurred in 65% of the patients, although no signs of systemic toxicity were observed (1).

Seventy-six patients with AIDS and cytomegalovirus retinitis participated in a nonrandomized study to analyze adverse events after consecutive intravitreous injections of cidofovir (30 μg). 93 eyes with 246 injections were followed up for 1 month or longer. 18 eyes of 9 patients were studied at autopsy. Postinjection chronic hypotony, which was associated with permanent visual loss, constituted the most severe adverse event (in 3% of eyes), followed by transient hypotony in 14% of eyes (2).

As cidofovir has been shown to suppress the growth of papillomavirus-induced tumors, its efficacy in 17 patients with severe respiratory papillomatosis was evaluated. Patients were treated with cidofovir at a concentration of 2.5 mg/ml injected directly into the laryngeal papillomatous lesions during microlaryngoscopy. Fourteen patients had complete disappearance of the disease, and 4 of these relapsed but were successfully retreated with cidofovir. One patient showed progression following an initial marked response, 1 patient had a partial remission and remained stable for over 1 year after the last injection, and 1 patient was lost to follow-up. No serious side effects were reported (3).

Pharmacia & Upjohn, Gilead's licensee and marketing partner, has launched cidofovir (Vistide®) in Spain for the treatment of CMV retinitis in patients with AIDS and normal renal function (4).

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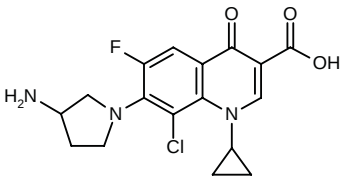
Clinafloxacin

Quinolone Antibacterial

EN: 127085



$C_{17}H_{17}ClFN_3O_3$ **Kyorin; Warner-Lambert**

In a mouse model of deep-seated *Pseudomonas aeruginosa* renal abscess, administration of oral clinafloxacin (50 mg/kg b.i.d for 5 days) resulted in a 4 log decrease in mean bacterial count. Complete bacterial eradication was found in 88% of the kidneys tested (1).

Mean maximum plasma concentrations of clinafloxacin were 1.34 μg/ml at 1.8 h following the administration of a single 200-mg dose in 9 healthy male volunteers. C_{max} in cantharidin-induced inflammatory fluid measured 3.8 h postadministration was 1.3 μg/ml, with a penetration rate of 93.1%. Elimination half-life in plasma was 5.65 h; 24-h and 48-h recovery rates of the drug in urine were 58.8 and 71.8%, respectively (2).

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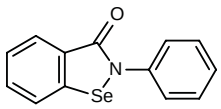
Ebselen

Antiinflammatory
Neuroprotectant
Antioxidant

EN: 090700



$C_{13}H_9NOSe$ **Rhône-Poulenc Rorer; Daiichi Pharm.**

Ebselen inhibited IL-1-induced proteoglycan degradation (IC_{50} = 4.7 μM) and cartilage PGE_2 release (IC_{50} = 6.2 μM) in organ culture cartilage. This inhibition of cartilage proteoglycan breakdown without inhibiting proteoglycan synthesis may result in a new mechanism of cartilage matrix protection in arthritic joints (1).

Leukocyte accumulation in the whole lung and airway mucosa was used to determine the effects of ebselen against antigen-induced lung inflammation in the rat. Ovalbumin-sensitized Brown Norway rats received ebselen (3, 10 or 30 mg/kg) or vehicle i.p. 30 minutes before and 4 and 12 h after inhaled antigen challenge. Lungs were removed 24 h after antigen challenge and total eosinophils, neutrophils and monocytes/macrophages were counted. Total eosinophils, activated eosinophils

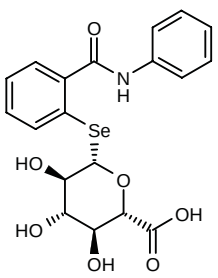
and total monocytes/macrophages in the airway mucosa were calculated from prepared lung tissue sections from other mice. Ebselen suppressed eosinophilia and eosinophil activation but failed to inhibit the accumulation of neutrophils and monocytes/macrophages. Although an observed potentiated neutrophilia requires further investigation, these results suggest an eosinophil-specific mechanism of action (2).

In a rat model of lung inflammation, ebselen administered i.p. at 0, 4 and 12 h after sephadex particle administration dose-dependently arrested lung edema (ED_{50} = 4.6 mg/kg), and at 10 and 30 mg/kg significantly inhibited BAL TNF-α levels. These findings suggest that ebselen may be effective in a variety of lung pathologies when bronchiolar inflammation is present (3).

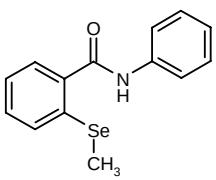
Inorganic selenium was not released from ebselen during its metabolism and subsequent elimination from the rat body (4).

The effects of ebselen (10 or 30 mg/kg by gavage) on the volume of infarction were investigated in a rodent model of permanent focal cerebral ischemia. Peak plasma levels of 0.68 and 0.84 μg/ml were reached 1 h following administration of the 10 and 30 mg/kg doses. The 10 mg/kg dose was associated with 31.8 and 36.7% reductions of the volume of infarction in the cerebral hemisphere and the cerebral cortex, respectively, while the 30 mg/kg dose was associated with 23.7 and 27.5% reductions in the respective areas. The results indicate that the antioxidative effects of ebselen effectively attenuate free radical-induced damage in models of maintained ischemia (5).

The pharmacokinetic parameters of ebselen were determined in fasted rats after single (50 mg/kg) and multiple dose (21 days; 50 mg/kg/day) oral administration. The peak plasma levels (C_{max}) were 15 μg/ml within 1 h (t_{max}) after drug administration. Ebselen followed a two compartment model, appeared to undergo biliary recycling, and was found to be highly protein-bound (more than 99%). The two distribution phases were completed in about 12 h, and the elimination half-life values were 2.1 h (range 1-3 h) for $t_{1/2\alpha}$ and 6.6 h (range 4-8 h) for $t_{1/2\beta}$. In 96 h, the drug was mainly excreted in urine as metabolites (60%) and the remaining 40% was excreted in feces. The major metabolites in rat plasma were a selenium-glucuronide [I], its polar metabolites and the methylated selenol [II] (6).



[I]



[II]

After multiple administrations, the excretion patterns of ebselen in rat urine and feces remained the same. The steady-state concentration observed after the 17th dose of repeated administration was approximately 4 times higher than that observed after the first dose. The peak concentration after 21st dose was about 1.6 times higher than that after the 1st dose, and the rate of elimination decreased after 21 doses, as compared to the rate of elimination observed after single-dose administration (7).

The effect of ebselen on outcome in patients with subarachnoid hemorrhage was assessed in a multicenter, placebo-controlled, double-blind clinical trial involving 286 subjects with aneurysmal subarachnoid hemorrhages of Hunt and Kosnic grades II-IV. Subjects were given ebselen granules suspended in water (150 mg b.i.d.) for a period of 2 weeks immediately after admission. Intent-to-treat analysis showed that the incidence of clinically diagnosed delayed ischemic neurological deficits was unchanged by the treatment; 52 patients receiving ebselen and 58 patients on placebo had delayed deficits. However, ebselen treatment resulted in a significantly better clinical outcome than placebo treatment, with a corresponding decrease in the incidence and extent of low-density areas on postoperative computed tomographic scans (8).

An NDA has been submitted by Daiichi Pharmaceutical in Japan for ebselen for use in the treatment of subarachnoid hemorrhage and acute stroke (9).

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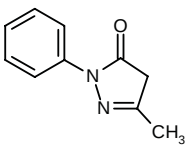
Edaravone

Neuroprotectant
Antioxidant

EN: 129588



$C_{10}H_{10}N_2O$ **Mitsubishi Chem.**

MCI-186 (3 mg/kg i.v. as 30-min infusion) administered twice after induction of rat middle cerebral artery occlusion significantly reduced the size of cerebral damage 24 h after occlusion and reduced hydroxyl radical concentrations (1).

Intravenous administration of MCI-186 (0.5 mg/kg b.i.d. x 2 days) in 7 healthy elderly and 7 healthy young subjects resulted in respective C_{max} values of 1040.7 and 887.6 ng/ml measured 12 h after administration. The difference observed was not statistically significant (2).

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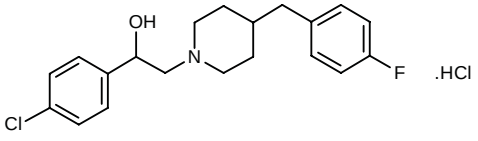
Yokota, S. et al. *A pharmacokinetic study of MCI-186, a novel drug for cerebrovascular disease in elderly and young healthy subjects*. Jpn J Clin Pharmacol Ther 1997, 28(3): 693.

Eliprodil Hydrochloride

NMDA Antagonist
Neuroprotectant

EN: 212381



$C_{20}H_{23}ClFNO.HCl$ **Searle; Synthélabo**

The efficacy of eliprodil alone or in combination with alteplase has been investigated in a rat embolic stroke model. Eliprodil (1 mg/kg i.v.) reduced the neurological deficit by 54% and the total volume of the brain lesion by 49%. Treatment with alteplase (2.5 mg/kg i.v.) reduced the neurological deficit by 48% and the size of the total infarct by 55%. Neurological and histological outcomes showed that combination therapy drastically improved the degree of neuroprotection (70% and 89% improvement in neurological and histological parameters, respectively. (1).

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Additional Reference

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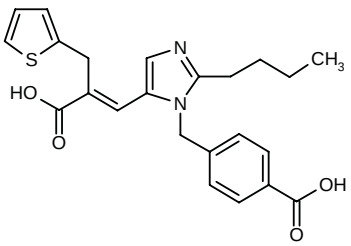
Eprosartan
SK&F-108566
Teveten™

Antihypertensive
Angiotensin AT_1 Antagonist

EN: 168384



$C_{23}H_{24}N_2O_4S$ **SmithKline Beecham; Hoechst Marion Roussel**

The effects of eprosartan on the steady-state anticoagulant activity of warfarin were evaluated in 18 healthy male volunteers. Warfarin doses were titrated over 9 days to reach a stable international normalized ratio (INR) of 1.3-1.6 by day 14. According to the measured INR, eprosartan (300 mg b.i.d. for 7 days) had no effect on the anticoagulant effect of warfarin (1).

The incidence of cough was evaluated in 528 hypertensive patients administered either eprosartan (200 mg/day titrated to 300 mg/day) or enalapril (5 mg/day titrated to 20 mg/day). Results of both patient and investigator reports demonstrated a 3.45-fold increase in the incidence of cough in enalapril-treated patients (2).

Eprosartan has been evaluated in a total of 27 clinical pharmacology studies involving 485 hypertensive patients and 144 healthy volunteers. Safety in volunteers was demonstrated at doses of up to 800 mg (single doses) and at 300 mg b.i.d. for 8 days; in patients with essential hypertension, the compound was safe at up to 1200 mg once daily for 1 week or at 300 mg b.i.d. for 28 days. In contrast to losartan, eprosartan (single or multiple doses) did not produce uricosuric effects in healthy volunteers or patients with essential hypertension or with renal insufficiency. No effects on effective renal plasma blood flow, glomerular filtration rate or sodium excretion have been observed in response to single or multiple doses of the compound in volunteers and patients (3, 4).

An 8-week, double-blind, parallel-group, multicenter trial was performed in 538 patients with mild to moderate essential hypertension. After a 4- to 6-week, single-blind, placebo run-in period, subjects were randomly administered placebo or eprosartan (25, 100, 200, 300 or 400 mg b.i.d.) Higher doses of eprosartan (200-400 mg b.i.d.) significantly lowered diastolic and systolic blood pressure, without affecting heart rate. The drug was well-tolerated and had a low incidence of adverse effects (5).

Eprosartan was analyzed for possible drug interactions. *In vitro* results indicate that eprosartan did not affect plasma protein binding of phenytoin or racemic warfarin. Human cytochrome P450 enzymes are not inhibited by eprosartan at concentrations up to 100 μM. In double-blind, randomized, placebo-controlled studies, eprosartan (300 mg b.i.d.) did not affect the anticoagulant activity of a titrated dose of warfarin. Eprosartan (200 mg b.i.d.) did not alter mean 24-h plasma glucose concentrations in type II diabetes patients on glyburide therapy. In open-label studies with healthy subjects, the pharmacokinetics of eprosartan (400 mg) was not altered by ranitidine (150 mg b.i.d. for 3 days). Furthermore, eprosartan (200 mg b.i.d.) did not alter the pharmacokinetics of oral digoxin (0.6 mg) and the steady-state pharmacokinetics of eprosartan (300 mg b.i.d.) was not affected by fluconazole or ketoconazole (6).

Patients with varying degrees of renal impairment (normal, mild, moderate, or severe) participated in an open-label, parallel-group study to compare the pharmacokinetics of multiple oral doses of eprosartan. Overall, eprosartan was safe and well-tolerated in all study groups and, based on its moderate renal clearance and safety profile, no dose adjustment is required in patients with renal insufficiency (7).

Results of a double-blind, randomized, placebo-controlled, crossover study in 57 male patients with mild to moderate essential hypertension have shown that single and repeated doses of eprosartan (50-1200 mg/day) were well tolerated and had no effect on serum uric acid excretion (8).

Eprosartan and enalapril were compared in a 6-week, double-blind, placebo-controlled, multicenter study. Patients with a history of ACE inhibitor-induced cough and essential hypertension were administered placebo (45 patients), eprosartan 300 mg b.i.d. (46 patients) or enalapril 20 mg o.d. (44 patients). Patients treated with eprosartan showed a lower incidence of persistent, non-productive cough than those with enalapril (9).

The safety of eprosartan in 364 elderly patients, including 56 subjects over 65 years of age, was tested in an 8-week, parallel-group, randomized, placebo-controlled study. Subjects received eprosartan 600, 800 or 1200 mg once daily. Drug-related adverse events were similar in younger, older and placebo groups. A once-daily dose of 600 mg of eprosartan was extremely well-tolerated in elderly hypertensive patients (10).

A 26-week, multicenter, double-blind, parallel-group, randomized study assessed the efficacy of eprosartan *versus* enalapril in 528 patients with mild to moderate essential hypertension. Patients received titrated doses of eprosartan (200-300 mg b.i.d.) or enalapril (5-20 mg/day). Hydrochlorothiazide was given for additional blood pressure control as needed. Overall, eprosartan showed higher response rates and patients experienced a lower incidence of cough (11).

Eprosartan and enalapril were compared in a 26-week, double-blind, parallel-group, randomized study in patients with mild to moderate hypertension. Efficacy and tolerability were assessed in a subgroup analysis of elderly patients. During an 18-week titration period, subjects were randomized to eprosartan 400-600 mg daily (200 young patients and 63 elderly patients) administered as two divided doses or enalapril 5-20 mg daily (201 young patients and 62 elderly patients). Hydrochlorothiazide achieved additional blood pressure control as necessary. As compared with enalapril, eprosartan produced higher response rates, lower incidences of dizziness and was better-tolerated, thus making it an effective treatment for elderly patients (12).

Evaluation of eprosartan in 23 healthy young men receiving doses of 100, 200, 400 or 800 mg showed that the drug was safe and well tolerated. Two-fold increments in dosing produced 1.6- to 1.8-fold increases in AUCs and C_{max}. Both the 200- and 400-mg doses were associated with an acceptance region of 30% for the AUC, and C_{max} for the 200-mg dose, suggesting slight saturation of drug absorption over the dose range of 100-800 mg. The changes observed were attributed to the pH-dependent aqueous solubility and lipophilicity of the drug (13).

The pharmacokinetics of eprosartan following administration of a single oral 100 mg-dose was evaluated in 8 healthy subjects and 8 patients with hepatic disease. Unbound maximum plasma concentrations and the degree of plasma protein binding were similar in both groups, while total and unbound AUC values were 40 and 50% higher in patients with hepatic disease (14).

SmithKline Beecham and Hoechst Marion Roussel have established an agreement for the copromotion of SmithKline Beecham's eprosartan (Teveten™) in Germany, effective as of October 1, 1997 (15).

Eprosartan mesilate (Teveten™) has been cleared by the FDA for use either alone or in combination with other antihypertensives such as diuretics and calcium channel blockers in the treatment of hypertension (16).

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Original monograph - Drugs Fut 1997, 22: 1079.

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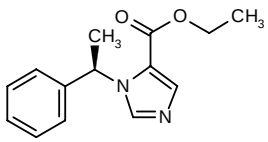
Angiotensin II antagonist effective for progression of diabetic nephropathy. Daily Essentials April 29, 1997.

Etomidate

Anesthetic

EN: 091309



$C_{14}H_{16}N_2O_2$ **Abbott; Janssen**

Oral transmucosal etomidate was evaluated in 10 healthy volunteers receiving doses of 12.5, 25, 50 and 100 mg. The drug was detectable in the blood system 5 min postadministration, reaching peak concentrations of 61-174 ng/ml after 20-30 min. Induction of light sleep and drowsiness was dose-related and occurred without any episodes of $Sp(O_2)$ < 90%, hypotension or emesis. Reports of nausea were rare, and a brief episode of involuntary tremor was reported by 2 subjects. Thus, oral transmucosal etomidate may be a useful drug for the induction of mild to moderate sedation with rapid recovery (1).

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Fexofenadine Hydrochloride

Antihistamine

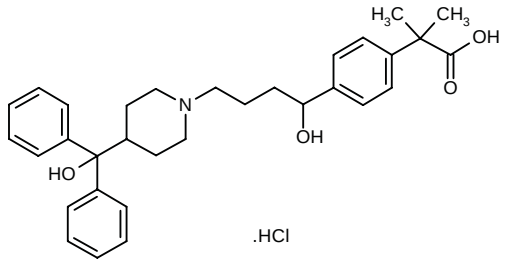
Allegra®

Treatment of Allergic Rhinitis

Telfast®

Allegra-D™

EN: 231566



$C_{32}H_{39}NO_4$.HCl

Sepracor; Andrx; Hoechst Marion Roussel

A placebo-controlled, double-blind trial of fexofenadine hydrochloride was conducted in 570 patients to determine clinical efficacy in treating ragweed seasonal allergic rhinitis. Subjects randomly received 60, 120 or 240 mg b.i.d. at 12-h intervals. Optimal dosage was shown to be 60 mg b.i.d. with no detectable side effects (1).

Hoechst Marion Roussel has launched Allegra-D™ Extended-Release Tablets, a combination product incorporating fexofenadine hydrochloride 60 mg and pseudoephedrine hydrochloride 120 mg, in the U.S. for the treatment of allergy sufferers with nasal congestion (2).

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Fexofenadine introduced in the U.K. Daily Essentials April 1, 1997.

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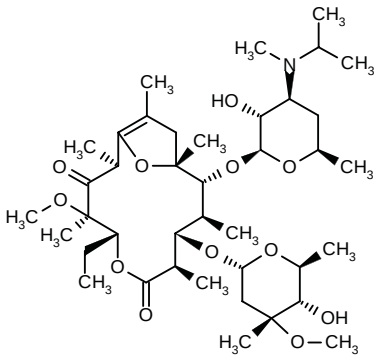
GM-611

Gastrointestinal Motility Stimulant

EN: 205573



$C_{40}H_{69}NO_{12}$ **Chugai**

GM-611 has been reported to be in phase I clinical testing in the U.S (1).

1. *Chugai begins clinical testing of prokinetic agent*. Daily Essentials July 2, 1998.

Original monograph - Drugs Fut 1994, 19: 910.

Interferon-α B/D Hybrid

Antiviral
Antineoplastic

EN: 173413

Novartis

Results of studies in BALB/c mice have shown that daily doses of recombinant interferon-α B/D hybrid (5 x 10^7, 5 x 10^6 and 5 x 10^5 U/kg), administered on the day of infection or on days 1 and 2 postinfection, protected mice against Ebola virus infection, whereas the drug was ineffective when started on day 3 postinfection (1).

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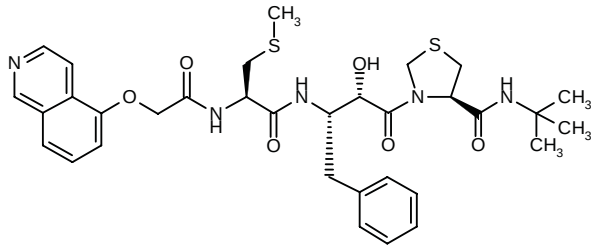
KNI-272

Anti-HIV
HIV-1 Protease Inhibitor

EN: 188524



$C_{33}H_{41}N_5O_6S_2$ **Japan Energy; Natl. Cancer Inst. (US)**

The *in vitro* antiviral activity and pharmacokinetics of KNI-272 in combination with other protease inhibitors were evaluated in various drug resistant HIV-1 strains. Cross-resistance studies showed that KNI-272-resistant virus was sensitive to saquinavir, indinavir and nelfinavir but resistant to ritonavir. KNI-272 remained active against indinavir-resistant clinical isolates. Synergism was noted when KNI-272 was combined with saquinavir, indinavir, nelfinavir or 141W94. In combination with ritonavir and indinavir, pharmacokinetic profiles were greatly improved. Coadministration of KNI-272 with nelfinavir or delavirdine also improved the pharmacokinetics (1).

The pharmacokinetics of KNI-272 were evaluated in the plasma and cerebrospinal fluid in monkeys receiving 50 mg/kg i.v., and after intravenous and oral administration of 100, 200, 330 and 500 mg/m^2 q.i.d. in pediatric patients with HIV infection. In monkeys, the plasma concentration-time profile was characterized by a high interanimal variability and rapid elimination, with the concentration achieved in cerebrospinal fluid being 1% of the concentration in plasma. In children, the drug was rapidly eliminated with saturable bioavailability and limited distribution. No significant increases in CD4 cell count, or decrease in p24 antigen or HIV RNA levels were observed. It appears that the pharmacokinetic profile of KNI-272 may limit its efficacy in the treatment of HIV infected pediatric patients (2).

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Original monograph - Drugs Fut 1996, 21: 1022.

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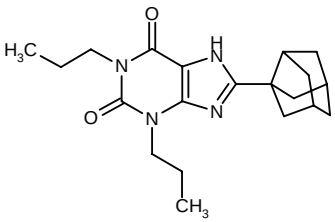
KW-3902

Diuretic
Kidney Function Improver
Adenosine A_1 Antagonist

EN: 170942



$C_{20}H_{28}N_4O_2$ **Kyowa Hakko**

The effects of intravenous infusion of HMR-4902 were investigated in ischemia-induced acute renal failure in rats. Results indicate that HMR-4902 acutely ameliorated renal hemodynamics, decreased sodium loss and increased the survival rate in rats with acute renal failure. Inhibition of renal adenosine effects, including modulation of the Na^+/H^+ exchanger, is the suggested mechanism of protection (1).

The effects of KW-3902 on the role of adenosine in controlling renal hemodynamincs and urine formation were evaluated in anesthetized dogs. KW-3902 (10 μg/kg/min) almost completely inhibited adenosine-induced renal vasoconstriction by A_1 receptors, indicating that whole kidney renal hemodynamics are not significantly affected by endogenous adenosine (2).

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Lidakol™

Antiviral

EN: 183153

$CH_3(CH_2)_{21}OH$

$C_{22}H_{46}O$ **Lidak; Yamanouchi; Grelan**

Lidak has filed an NDA for Lidakol® (*n*-docosanol 10% cream) with the FDA. The company is seeking approval to market the drug as a topical treatment for recurrent oral herpes (1).

Lidak has received notification from the FDA that its NDA for Lidakol® topical cream (*n*-docosanol) has been accepted for review. The company is seeking approval for this drug as a treatment for oral herpes (2).

1. *Lidak submits NDA for Lidakol®*. Daily Essentials Dec 29, 1997.

2. *Lidakol NDA accepted for review*. Daily Essentials March 17, 1998.

Original monograph - Drugs Fut 1992, 17: 879.

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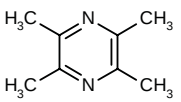
Lidak Pharmaceuticals reports cancellation of Bristol-Myers Squibb North American license. Lidak Pharmaceuticals Press Release Dec 31, 1997.

Positive phase III results for Lidakol in oral herpes. Daily Essentials Aug 19, 1997.

Ligustrazine

Neuroprotectant

EN: 149375



$C_8H_{12}N_2$ **Chinese Univ. Hong Kong; Beijing Med. Univ.**

The endothelin-antagonist effects of tetramethylpyrazine have been investigated in various animal models. Coronary vasoconstriction induced in anesthetized closed-chest dogs by infusion of ET-1 directly into the left coronary artery was attenuated significantly by pretreatment with tetramethylpyrazine, as seen by inhibition of the ET-1-induced decrease in coronary artery

diameter and resulting vasoconstriction in pretreated animals. ET-1-induced myocardial tissue damage was prevented completely by tetramethylpyrazine. In another model, plasma ET-1 levels decreased and 6-keto-PGF_1 levels increased in rabbits treated with the compound, as determined by RIA 90 min after injection of the compound. (1).

The effects of tetramethylpyrazine on plasma levels of endothelin-1 (ET-1) have been studied in dogs. The compound was administered by i.v. injection at the dose of 80 mg/kg prior to exposure to hypoxia. Mean pulmonary arterial pressure, pulmonary vascular resistance and plasma ET-1 levels in the abdominal aorta all increased significantly in animals subjected to acute hypoxia, but pretreatment with tetramethylpyrazine was able to significantly attenuate these changes. These results indicate that tetramethylpyrazine, in addition to its calcium channel-blocking effects, also decreases plasma levels of ET-1, making it a potentially useful agent for the treatment of pulmonary hypertension (2).

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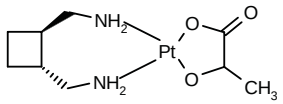
Lobaplatin

Antineoplastic
Platinum Complex

EN: 149864



$C_9H_{18}N_2O_3Pt$ **Asta Medica**

Sixty cases of chronic myeloid leukemia were treated with lobaplatin in a pilot study. Every 3 weeks for 1-4 injections (cycles), patients received 50 mg lobaplatin. Patients in chronic phase showed 62.5% complete response, 30% partial response, and 7.5% were nonresponders. There were 2 complete and 3 partial responses in 8 patients in accelerated phase and 2 partial responses in patients in blastic phase. Of 15 patients who were refractory to conventional treatment, there were 4 and 5 cases of complete and partial response, respectively (1).

1. Lu, D.-P., Xu, L.-P., Chen, S.-S., Hong, W.-D., Zhnag, G.-C. *Lobaplatin for treatment of chronic myeloid leukemia (CML) - A pilot study*. Blood 1997, 90(10, Suppl. 1, Part 2): Abst 3987.

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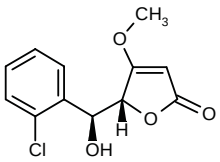
Losigamone

Anticonvulsant

EN: 138456



$C_{12}H_{11}ClO_4$ **Schwabe**

The pharmacokinetics of losigamone were determined in a crossover study in 5 healthy volunteers administered an oral suspension of 200 mg [^{14}C]-labelled losigamone and 100 mg of each of the unlabelled enantiomers. The absorption of losigamone was rapid. The plasma concentration of the parent compound vs. total radioactivity was 40%, with an overall recovery of total radioactivity of 97%. Protein binding was 50%, with only traces of unchanged drug found in urine. Values for mean oral clearance were 1863 ml/min and 171 ml/min for the (–)- and (+)-enantiomers, respectively. No chiral inversion after administration was reported (1).

A review of the medicinal chemistry, pharmacology, safety and toxicology, pharmacokinetics and clinical studies of losigamone, the first experimental antiepileptic drug to be identified using a medicinal plant-based discovery program, has recently been published (2).

1. Peeters, P.A.M., Van Lier, J.J., Van De Merbel, N., Oosterhuis, B., Wieling, J., Jonkman, J.H.G., Klessing, K., Biber, A. *Pharmacokinetics of [C-14]-labelled losigamone and enantiomers after oral administration to healthy subjects*. Eur J Drug Metab Pharmacokinet 1998, 23(1): 45.

2. Chatterjee, S.S., Nöldner, M. *Losigamone: From plant extract to antiepileptic drug*. CNS Drug Rev 1997, 3(3): 225.

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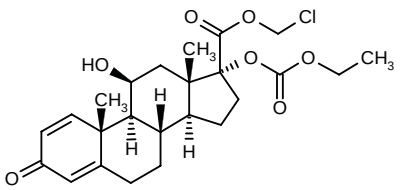
Loteprednol Etabonate *Ocular Antiinflammatory*
P-5604 *Topical Corticosteroid*
HGP-1
CDDD-5604
Lotemax™
Alrex™

EN: 170014



$C_{24}H_{31}ClO_7$ **Pharmos; Bausch & Lomb**

A randomized, double-masked, placebo-controlled trial was performed in 14 healthy volunteers to assess systemic exposure to loteprednol etabonate after chronic ocular instillation. On days 0 and 1, subjects instilled one drop in each eye 8 times daily. On days 2-42, the dose was reduced to 4 times daily. Plasma levels of loteprednol and its major metabolite, PJ-91, were below the level of quantitation for all participants, while plasma cortisol levels were within normal range. No systemic levels or hypothalamic pituitary axis suppression was detected (1).

Bausch & Lomb and Pharmos have received an approvable letter from the FDA relating to their NDA filed for loteprednol etabonate ophthalmic suspension 0.5% (Lotemax™) (2).

Lotemax™ and Alrex™, sterile opththalmic suspensions of loteprednol etabonate, have been introduced in the U.S. for the treatment of steroid-responsive ocular inflammatory and allergic conditions such as allergic conjunctivitis, herpes zoster keratitis and iritis, as well as postoperative inflammation following ocular surgery (Lotemax™) and the temporary relief of the signs and symptoms of seasonal allergic conjunctivitis (Alrex™). Both products are marketed by Bausch & Lomb and were codeveloped by Pharmos and Bausch & Lomb. Lotemax™ is available as bottles containing 5 mg/ml (0.5%) loteprednol etabonate and Alrex™ contains 2 mg/ml (0.2%) active ingredient (3).

1. Howes, J., Novack, G.D. *Failure to detect systemic levels, and effects of loteprednol etabonate and its metabolite, PJ-91, following chronic ocular administration*. J Ocular Pharmacol Ther 1998, 14(2): 153.

2. *Lotemax deemed approvable by FDA*. Daily Essentials Sept 26, 1997.

3. *New topical corticosteroid available in U.S. for ophthalmic use*. Daily Essentials June 1, 1998.

Original monograph - Drugs Fut 1997, 22: 1086.

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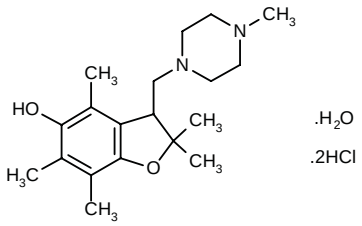
FDA approves ocular antiinflammatory agent. Daily Essentials March 11, 1998.

MDL-74180 *Neuroprotectant*
MDL-74722 [as (+)-enantiomer] *Antioxidant*
MDL-75204 [as (–)-enantiomer]

EN: 218838



$C_{19}H_{30}N_2O_2.2HCl.H_2O$ **Hoechst Marion Roussel**

In a rat model of focal cerebral ischemia, treatment with MDL-74,722 (2 mg/kg/h i.v. for 3 h) started 105 min after left middle cerebral artery occlusion resulted in a significant reduction (49%) in infarct volume (1).

1. van der Worp, H.B., Kappelle, L.J., de Wildt, D.J., Bär, P.R. *The vitamin E analog MDL 74,722 reduces infarct volume after transient focal cerebral ischemia in rats*. Stroke 1998, 29(1): Abst P169.

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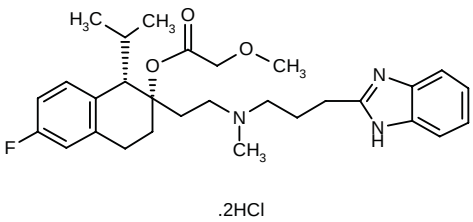
Mibefradil Hydrochloride *Antihypertensive*
Ro-40-5967 *Calcium Antagonist*
Posicor®
Cerate 50®

EN: 150839



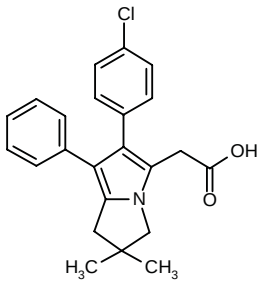
$C_{29}H_{38}FN_3O_3.2HCl$ **Roche; Asta Medica**

Roche announced in June, 1998 the voluntary withdrawal of mibefradil hydrochloride (Posicor®), first introduced in mid-1997 and now available in 38 countries, and advises physicians to offer alternative therapies to their patients. Posicor® has proven consistently effective and well tolerated when used appropriately for the treatment of both hypertension and chronic angina pectoris. However, the combination of Posicor® with some other commonly used drugs, including other cardiovascular agents, may increase the frequency of side effects of the other medications (1).

1. *Posicor voluntarily withdrawn from the market*. Daily Essentials June 8, 1998.

ML-3000 *Antiinflammatory*
Cyclooxygenase /Lipoxygenase Inhibitor

EN: 210861

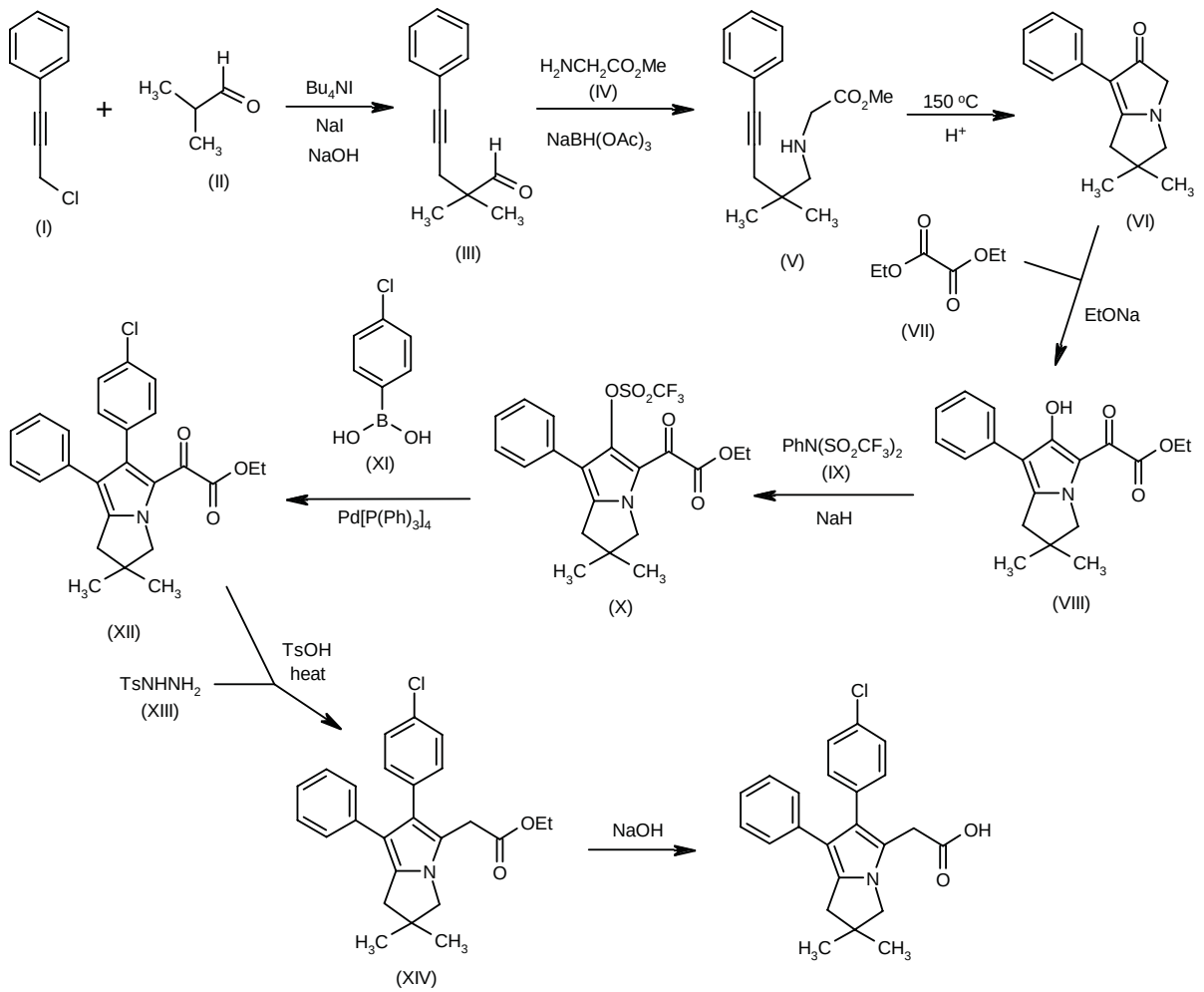


$C_{23}H_{22}ClNO_2$ **Merckle; Alfa Wassermann; Lacer**

A new synthesis of ML-3000 has been published: The reaction of 3-phenyl-2-propynyl chloride (I) with isobutyraldehyde (II) by means of tetrabutylammonium iodide/NaI/NaOH in toluene/water gives 2,2-dimethyl-5-phenyl-4-pentynal (III), which is condensed with glycine methyl ester by means of $NaBH(OAc)_3$ and triethylamine in dichloromethane yielding the *N*-alkyl-glycine (V). The cyclization of (V) by means of pivalic acid at 150 °C affords the bicyclic ketone (VI), which is condensed with diethyl oxalate (VII) by means of sodium ethoxide in ethanol giving the ethoxalyl derivative (VIII). The esterification of (VIII) with the triflic amide (IX) yields the triflate (X), which is condensed with 4-chlorophenylboronic acid (XI) by means of palladium tetrakis(triphenylphosphine) as catalyst in refluxing THF affording the compound (XII). The reduction of the oxoacetic group with tosyl hydrazide (XIII) in refluxing ethanol gives the expected acetate derivative (XIV), which is finally hydrolyzed with NaOH in hot ethanol/water (1). Scheme 1.

The synthesis of the acyl glucuronide of ML-3000 has been described: The cleavage of the lactone ring of D-glucuronic acid γ-lactone (I) gives the bromide derivative (II), which is treated with silver oxide and benzyl alcohol to yield compound (III). The methanolysis of (III) with sodium methoxide in methanol, followed by treatment with *tert*-butyldimethylsilyl chloride (TBDMS-Cl) and imidazole affords silylated compound (IV). The hydrolysis of the ester group of (IV) with NaOH in THF/water, followed by reesterification with diethyl chlorophosphate, 2,2,2-

Scheme 1: Synthesis of ML-3000



trichloroehanol and DMAP gives the silylated trichloroethyl ester (V), which is debenzylated by hidrogenation with H_2 over Pd/C in ethyl acetate yielding D-glucuronate (VI). The esterification of the acid group of ML-3000 (VII) with (VI) by means of triphenylphosphine and DIAD in THF affords the corresponding ester (VIII), which is finally deprotected first with Zn and KH_2PO_4 to eliminate the trichloroethyl group, and then with THF in acetonitrile to eliminate the silyl groups. The product wasisolated as a 1:2 mixture of the α- and β-anomers (2). Scheme 2.

The first results from a placebo-controlled, double-blind, dose-finding phase II study of ML-3000 in patients with osteoarthritis, who were administere the compound at doses of 100, 200 or 400 mg b.i.d., confirm the activity and excellent tolerability of ML-3000. The doses of 200 and 400 mg b.i.d. had significantly greater antiinflammatory and analgesic efficacy than placebo, while the lowest dose did not. No serious adverse effects were seen with the compound, and gastrointestinal tolerability was reported to be optimal (3).

1. Cossy, J., Belotti, D. *Synthesis of ML-3000, an inhibitor of cyclooxygenase and 5-lipoxygenase*. J Org Chem 1997, 62(23): 7900.

2. Kirschning, A., Ries, M., Domann, S., Martin, W., Albrecht, W., Arnold, P., Laufer, S. *Synthesis and biological identification of the acyl glucuronide of the antiinflammatory drug ML-3000*. Bioorg Med Chem Lett 1997, 7(7): 903.

3. *First phase II results reported for EuroAlliance's DAAID*. Daily Essentials Feb 23, 1998.

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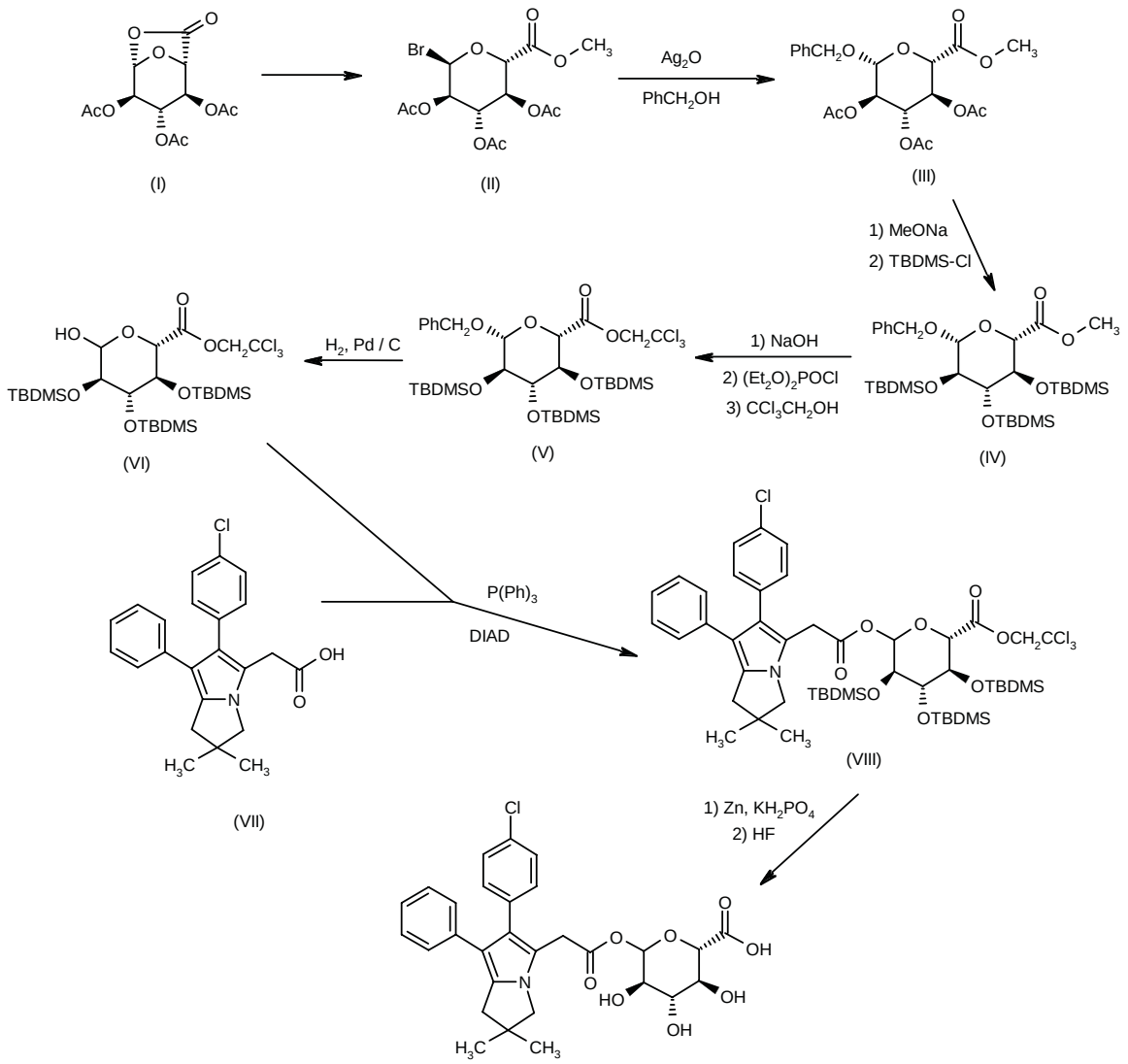
Scheme 2: Synthesis of the Acyl Glucuronide of ML-3000

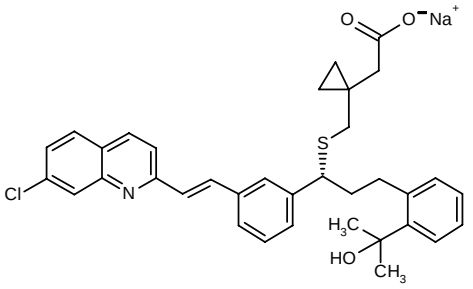


Montelukast Sodium

MK-476
MK-0476
L-706631
Singulair™

Antiallergic/Antiasthmatic
Leukotriene CysLT$_1$ Antagonist

EN: 205402



$C_{35}H_{35}ClNNaO_3S$

Merck & Co.; Merck Frosst

Results of studies in rats have shown that ET-1 production was significantly reduced by montelukast during eosinophilic airway inflammation, indicating that montelukast has antiinflammatory properties (1).

The protective effects of montelukast were evaluated following administration of 0.4, 2, 10 and 50 mg in 27 healthy nonsmoking subjects with asthma. Dose-related protection against bronchoconstriction was observed, as well as protection against exercise-induced bronchoconstriction with the two higher doses. Important clinical effects were not observed and the drug was well tolerated at all dose levels (2).

Oral administration of montelukast in 343 asthmatic patients at doses of 10, 100 or 200 mg once daily in the evening, or 10 or 50 mg twice daily for 6 weeks, produced significant improvements in asthma control even at doses as low as 10 mg administered in the evening (3).

Administration of montelukast 10 mg once daily or beclomethasone 200 μg twice daily in 895 patients with

chronic asthma improved all endpoints evaluated as compared to treatment with placebo. However, montelukast had a more rapid onset of action, while beclomethasone had a larger average treatment response (4).

The safety of montelukast was evaluated in 1955 adult and 201 pediatric patients. The frequency of adverse experiences was comparable in both adult and pediatric study groups and similar to the frequency reported in the placebo-treated group, with headache, asthma and upper respiratory infections being the most commonly reported side effects. More importantly, both pediatric and adult groups demonstrated frequencies of cases with elevated transaminase levels comparable to placebo-treated groups (5).

The efficacy of mono- and combination therapy with montelukast and loratadine in the treatment of seasonal allergic rhinitis was evaluated in 460 males and females. Administration of montelukast with loratadine at doses of 10 mg each, improved nasal and eye symptoms, as well as night-time symptoms, as compared to treatment with placebo. The combination therapy demonstrated rapid onset and synergistic effects as compared to monotherapy and treatment with placebo (6).

The protective effects of montelukast 10 mg q.i.d. and salmeterol 42 μg b.i.d. against exercise-induced asthma were compared in 197 adults. Both therapies were equally protective when evaluated on day three of treatment, although montelukast was numerically better. At week 8, montelukast showed significantly better protective activity than salmeterol, and its effects were more persistent than the effects of salmeterol. Both therapies were well tolerated and few patients withdrew from the study due to adverse effects (7).

Combination therapy consisting of montelukast 10 mg and loratadine 20 mg was compared to montelukast monotherapy (10 mg) in 136 adult patients with chronic asthma. Evaluation of FEV_1, daily β-agonist use, daytime symptoms and morning/afternoon PEFR indicated that combination therapy produced significant improvements in all endpoints compared to montelukast monotherapy (8).

Chronic administration of montelukast (10 mg/day) and salmeterol (42 μg b.i.d.) were compared for their ability to prevent exercise-induced bronchoconstriction in 191 adult asthmatics. Evaluation of mean change in maximum % fall FEV_1 and $AUC_{(0\text{-}60\ min)}$ indicated that montelukast maintained its bronchoprotective effects throughout the study, while the protective effects of salmeterol decreased following weeks 4 and 8 (9).

In 681 patients with chronic stable asthma aged 15 or older, montelukast 10 mg improved airway obstruction and patient-reported end points within the first day of treatment. The incidence of adverse events were similar in montelukast- and placebo-treated groups. Montelukast was generally well tolerated with an adverse profile comparable with that of placebo (10).

The therapeutic effects of montelukast were evaluated in patients with chronic asthma randomized to receive doses of 2, 10 or 50 mg once daily. All doses improved forced expiratory volume in one second (FEV_1), and morning and evening peak expiratory how rate. It was thus concluded that administration of montelukast 2-50 mg benefits chronic asthma patients by improving asthma control end points (11).

A large clinical trial has compared the efficacy of oral montelukast sodium, loratadine or their combination in 460 patients with seasonal allergic rhinitis and conjunctivitis. Following a week-long, single-blind, placebo run-in period, patients were randomized to treatment with montelukast (10 or 20 mg), loratadine (10 mg), montelukast + loratadine (10 mg + 10 mg) or placebo for 2 weeks. The treatments were compared in terms of daytime nasal (stuffy, runny, itchy nose and sneezing) and eye (puffy, teary, itchy and red eyes) symptoms, nighttime symptoms and rhinoconjunctivitis. Concomitant montelukast + loratadine therapy provided the best improvement in combined symptoms, as well as individual nasal and eye symptoms. The incidence of adverse clinical and laboratory events was similar in all treatment groups (12).

Results of an open, 1-period, multicenter study in 2- to 5-year-old asthmatic patients (n = 15) indicated that a single 4-mg chewable tablet dose of montelukast was the optimum dose for this age group (13).

Oral montelukast sodium (5-mg chewable tablet before bedtime) was evaluated in 336 pediatric outpatients aged 6-14 years at 47 centers across the U.S. Treatment with montelukast significantly improved FEV_1 and several secondary outcomes as compared to placebo in children with a history of intermittent or persistent asthma symptoms. Therapy-related effects were observed one day following the first dose and were maintained consistently over time, indicating that the compound may be an effective long-term antiasthma therapy in pediatric patients. Adverse experiences included headache, asthma and upper respiratory tract infection (14).

The pharmacokinetics and bioavailability of montelukast sodium were evaluated in 24 young and elderly healthy subjects. Plasma concentrations of the drug following oral administration of a 10 mg-dose differed very little on days 1 and 7 in young subjects, with constant trough concentrations of 18-24 ng/ml and a 14% accumulation of the drug. In elderly subjects, administration of 7 mg i.v. infusion produced a mean plasma clearance of 30.8 ml/min, a steady-state volume of distribution of 9.7 l, plasma terminal half-life of 6.7 h and a mean residence time of 5.4 h. A 10-mg oral dose produced bioavailabilities of 61% and 62% in elderly and young subjects, respectively, and similar values for AUC, C_{max}, t_{max}, $t_{1/2}$ and plasma concentrations in young and elderly subjects. Overall, the results indicate that pharmacokinetics of montelukast sodium are not age-dependent (15).

Montelukast sodium (Singulair™) has been introduced in Mexico for the management of chronic asthma in adults and children aged 6 years and over. It is supplied as 10-mg tablets for adults and 5-mg chewable tablets for children (16).

Merck Sharp & Dohme has introduced montelukast sodium (Singulair™) in the U.K. as once-daily add-on therapy in adults and children 6 years and older with mild

to moderate asthma inadequately controlled by inhaled corticosteroids and short-acting β_2-agonists, and for exercise-induced bronchoconstriction. It is available as 5-mg chewable tablets for children and 10-mg tablets for adults (17).

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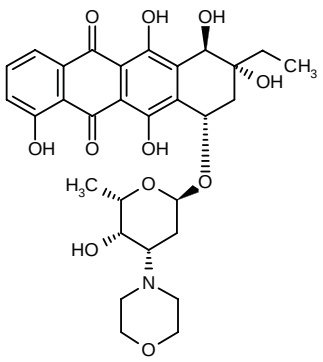
New treatment for chronic asthma receives first European approval in Finland. Merck & Co., Inc. Press Release Sept 2, 1997.

MX2 *Antineoplastic*
KRN-8602 (as diHCl)

EN: 127759



$C_{30}H_{35}NO_{11}$ **Kirin Brewery**

A comparative study of MX2 and daunorubicin was carried out in 58 adult patients with acute myelogenous leukemia. Patients were randomized to receive either MX2 15 mg/m^2 i.v. on days 1-5 together with cytarabine 100 mg/m^2 i.v. on days 1-7, or daunorubicin 40 mg/m^2 i.v. on days 1-3 together with cytarabine 100 mg/m^2 i.v. on days 1-7. No statistical differences were observed between the two regimens apart from PS. Complete remission rates of 78.6 and 73.1% were observed in patients receiving MX2 and daunorubicin, respectively. Nausea, vomiting and anorexia were reported more frequently in the group treated with MX2 than in the daunorubicin-treated group (1).

Fifty-three patients with recurrent cerebral glioma (18, anaplastic astrocytoma; 35, glioblastoma multiforme) and at least one prior resection participated in an open-label, non-randomized, phase II study of MX2. Patients had histologically proven high grade malignant glioma and had not undergone chemotherapy within the preceding 12 weeks or radiotherapy within the previous 4 months. MX2 at 40 mg/m^2 i.v. (q28d) was administered for up to 6 cycles. MX2 was well-tolerated and showed an overall response rate of 42%, indicating its promise as a new palliative treatment of recurrent high grade glioma (2).

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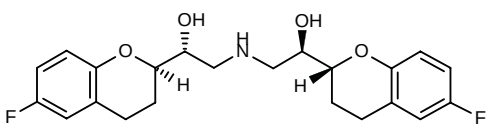

$C_{22}H_{25}F_2NO_4$ **Janssen; Meiji Seika; Menarini**

Results of a multicenter, randomized, double-blind study in patients with essential hypertension showed that nebivolol (5 mg/day) was more effective than enalapril (10 mg/day) in reducing sitting diastolic blood pressure and produced a higher response rate (70% *vs.* 55%). Both drugs were well tolerated but only nebivolol produced slight but significant reductions in heart rate (1).

Hemodynamics and pharmacokinetics of nebivolol (5 mg/day p.o.) were evaluated in 15 patients with essential hypertension. Blood pressure and heart rate decreased during steady state as compared to placebo, while venous volume was reduced during acute, but not steady-state, dosing. Peripheral resistance in patients receiving nebivolol did not differ following administration of the first dose as compared to placebo-treated subjects, but was reduced significantly after 4 weeks of treatment (2).

Results of a double-blind, randomized, parallel-group trial in patients with essential hypertension showed that treatment with nebivolol (5 mg/day) and atenolol (50 mg/day) produced significant and similar reductions in systolic and diastolic blood pressure, and small but significant reductions in heart rate (3).

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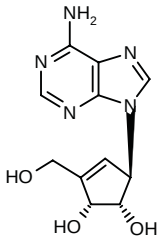
Neplanocin A

Antineoplastic

EN: 090983



$C_{11}H_{13}N_5O_3$ **Toyo Jozo**

A new synthesis of neplanocin A has been reported: The ring opening of 2',3'-*O*-isopropylideneadenine (I) with diisobutylaluminium hydride (DIBAL) in THF gives (2*S*,3*R*,4*R*)-9-[4,5-dihydroxy-2,3-(isopropylidenedioxy)-pentyl]adenosine (II), which is partially protected with *tert*-butyldimethylsilyl chloride (TBDMS-Cl) and imidazole in DMF yielding the monosilylated compound (III). The Dess-Martin oxidation of (III) in dichloromethane affords the correponding ketone (IV), which is cyclized with the lithium derivative of the trimethylsilyl diazomethane in THF/hexane to give the proteced compound 2,3-*O*-isopropylidene-4'-*O*-(*tert*-butyldimethylsilyl)neplanocin A (V). Finally, this compound is deprotected by the usual deprotection methods (1). Scheme 3.

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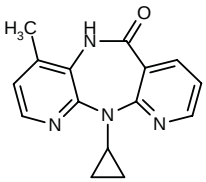
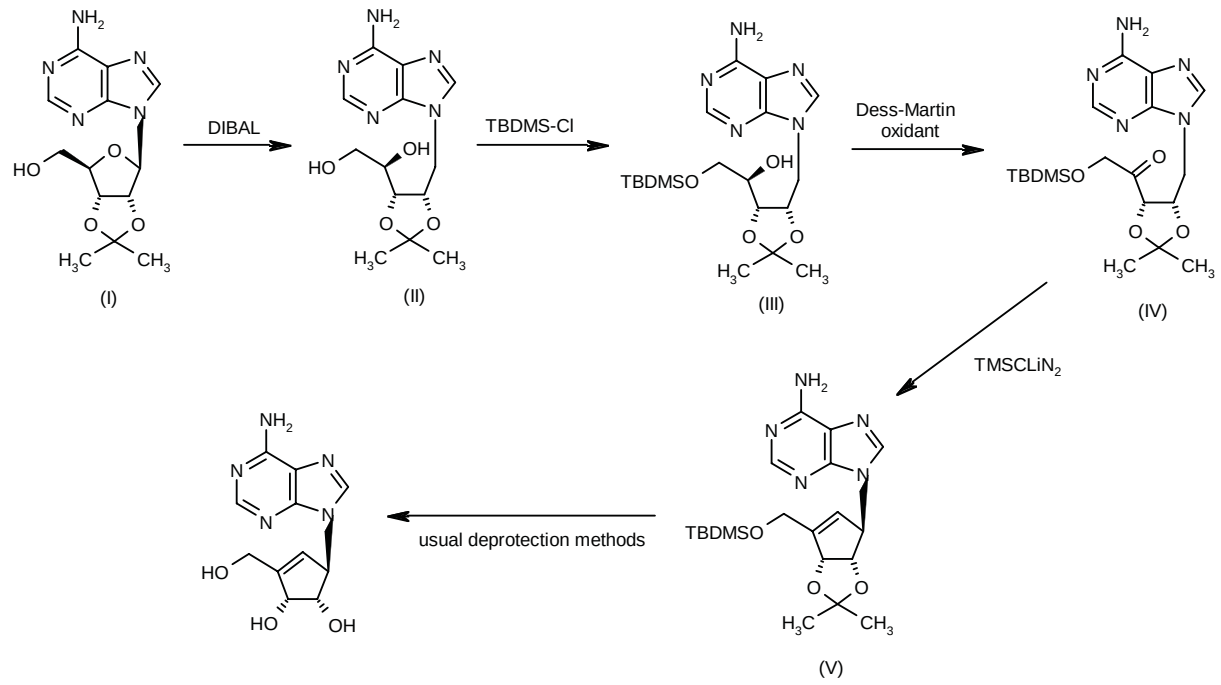


$C_{15}H_{14}N_4O$ **Boehringer Ingelheim; Roxane Lab.; Glaxo Wellcome**

Boehringer Ingelheim has launched nevirapine (Viramune®) in the U.K., where it is indicated for use in combination with at least two other antiretroviral compounds in the treatment of HIV-1-infected adult patients with advanced or progressive immunodeficiency (1).

Scheme 3: Synthesis of Neplanocin A



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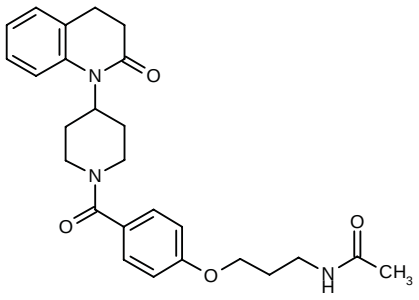
OPC-21268

Vasopressin V_{1A} Antagonist
Antihypertensive
EN: 176607 *Treatment of Congestive Heart Failure*



$C_{26}H_{31}N_3O_4$ **Otsuka**

The effects of single oral administration of OPC-21268 (100 mg) on plasma vasopressin levels and blood pressure were evaluated in 12 normotensive subjects, 12 patients with mild essential hypertension on a regular sodium diet and 8 hypertensive patients on high and low sodium diets. Dietary sodium intake appeared to have no significant effects on plasma vasopressin levels, blood pressure or heart rate in any of the study groups (1).

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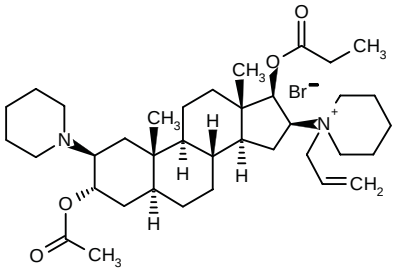
Org-9487 *Nondepolarizing Neuromuscular Blocker*
Rapacuronium Bromide

EN: 203872



$C_{37}H_{61}BrN_2O_4$ **Akzo Nobel**

The effects of Org-9487 (1.5 and 2.5 mg/kg i.v.) were compared to succinylcholine and mivacurium in 125 ASA I-III status patients undergoing anesthesia with fentanyl and propofol, with N_2O:O_2 (60:40) maintenance. Org-9487-treated patients had a higher heart rate than mivacurium-treated patients and the higher dose of Org-9487 also resulted in higher heart rates than in succinylcholine-treated patients. Any blood pressure changes were mild (1).

In a randomized, comparative trial in 30 healthy patients undergoing elective ophthalmic surgery, neither Org-9487 (1.5 mg/kg i.v.) nor vecuronium (0.1 mg/kg i.v.) had any significant effect on intraocular pressure, whereas succinylcholine (1 mg/kg i.v.) caused a marked rise in intraocular pressure (2).

In a randomized, double-blind study in 55 patients, the onset of vecuronium-induced neuromuscular blockade following intubation with Org-9487 (1.5 mg/kg) was similar to that of succinylcholine (1 mg/kg), although the duration of blockade tended to be prolonged for a longer period of time with Org-9487 (3).

Results from a pharmacodynamics study in 6 patients with cirrhosis and 7 patients with normal liver and kidney function have shown that the intensity and duration of a single bolus of Org-9487 (1.5 mg/kg) are not altered by liver cirrhosis (4).

In a randomized, single-blind study in 30 healthy adult patients, administration of Org-9487 (1.5 and 2.5 mg/kg) under stable anesthetic conditions caused a statistically significant and dose-dependent increase in heart rate but had no significant effects on blood pressure. These effects were not observed with succinylcholine (1 mg/kg) or mivacurium (0.25 mg/kg) and did not appear to be related to histamine release (5).

A study was conducted to compare recovery after three maintenance doses of Org-9487, with or without neostigmine. Thirty patients received propofol plus alfentanil anesthesia, followed by propofol and alfentanil infusion and 60% nitrous oxide in oxygen. All patients also received an intubating dose of Org-9487 (1.5 mg/kg), with three maintenance doses of the compound (0.5 mg/kg) administered each time ulnar nerve stimulation response recovered to 25%. At this point patients were randomized to receive neostigmine (0.05 mg/kg) reversal or no rever-

sal, and time to recovery was compared. Repeat doses of Org-9487 resulted in an increased duration of effect and slower spontaneous recovery as compared to that achieved after a single administration of the compound. Neostigmine administration led to rapid reversal of Org-9487-induced muscle relaxation (6).

An open-label, multicenter, double-blind, randomized, phase II study was performed in 66 adults to evaluate early reversal of intubating doses of Org-9487 and to specify optimal neostigmine administration. Anesthesia was induced by fentanyl and thiopental and maintained by fentanyl and propofol. Once stabilized, Org-9487 (1.5 or 2.5 mg/kg) was administered, followed 2-5 min later by neostigmine (0, 50 or 70 μg/kg). Neostigmine accelerated recovery of both doses of Org-9487 without any time or dose differences being observed (7).

Anesthesia was induced in 20 adults with propofol, fentanyl and Org-9487 and maintained with nitrous oxide 60% in oxygen with isoflurane, sevoflurane, desflurane or propofol. An infusion of Org-9487 was initiated and then adjusted to maintain T1 at 10% of baseline for 1 h after which it was stopped. Patients with TOF ratio (T4/T1) < 0.7 were administered 0.05 mg/kg neostigmine and 0.01 mg/kg glycopyrrolate. Results indicated that residual neuromuscular blockade after Org-9487 infusion can be reversed using neostigmine within 3 min (8).

Onset of action of Org-9487 was evaluated in 20 adult patients undergoing general surgery expected to last longer than 2 h. Anesthesia was induced with propofol (2.5 mg/kg) and fentanyl (2 μg/kg) and neuromuscular blockade was evaluated. The T1 twitch height was calibrated to 100%, followed by administration of Org-9487 (1.5 mg/kg i.v.). T1 reached maximal neuromuscular blockade at 74 sec (9).

The neuromuscular effects of Org-9487, mivacurium and succinylcholine were compared in 125 ASA 1-3 patients. Anesthesia was induced with fentanyl (1-5 μg/kg i.v.), propofol (1.5-2 mg/kg i.v.) and maintained by a 60:40 mixture of nitrous oxide and oxygen. Org-9487 (1.5 or 2.5 mg/kg), succinylcholine (1 mg/kg) or mivacurium (0.15 mg/kg followed by 0.1 mg/kg) were then randomly administered. Final results indicated that either dose of Org-9487 would be an adequate substitute for succinylcholine (10).

Results from a randomized, assessor-blinded, placebo-controlled study in 13 evaluable patients with coronary artery disease indicated that the hemodynamic effects of Org-9487 (1.5 mg/kg) were similar to those of rocuronium (0.6 mg/kg) and appeared to be clinically insignificant (11).

Findings from a randomized study in 24 healthy adults undergoing elective surgery demonstrated that a 2.5-mg/kg dose of Org-9487 had a rapid onset of effect similar to that of succinylcholine (1 mg/kg) and a longer duration of effect than succinylcholine and mivacurium (0.25 mg/kg). A 1.5-mg/kg dose of Org-9487 had a slower onset and longer duration of effect than succinylcholine and a duration of effect similar to that of mivacurium (12).

Results from a randomized, assesor-blinded study in 38 patients undergoing elective cesarean section showed that Org-9487 (2.5 mg/kg) was a good substitute for succinylcholine (1.5 mg/kg) in rapid sequence induction, provided good intubating conditions and was associated with good neonatal outcome (13).

A randomized study in 102 pediatric patients anesthetized with halothane showed that there was a higher incidence of deep neuromuscular block 1 min after intubation with Org-9487 (1,2 or 3 mg/kg) than with mivacurium (0.2 mg/kg). The time to early recovery was similar for both drugs, although pharmacological reversal may be necessary with the higher doses of Org-9487 due to a fade in the TOF ratio (14).

Rapacuronium bromide is the new proposed international nonproprietary name for Org-9487 (15).

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Peldesine
BCX-34

Immunosuppressant
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Purine Nucleoside Phosphorylase Inhibitor
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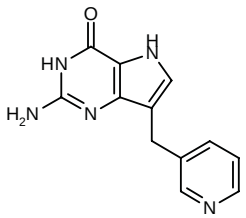

$C_{12}H_{11}N_5O$ **BioCryst; Torii**

Results of *in vivo* studies showed that the optimal concentration of BCX-34 in cream for skin absorption is 3% dose level. The amounts of BCX-34 in the upper layers of the stratum corneum were significantly increased when exposure time was increased from 6 to 24 h (1).

Multiple oral doses of BCX-34 (18, 36, 60, 90 or 126 mg/m^2 b.i.d.) in 23 patients with cutaneous T-cell lymphoma resulted in elevated plasma inosine levels at all dosing regimens (2).

Based on the results of preliminary data from two phase III trials of a topical cream formulation of BCX-34 for the treatment of psoriasis and cutaneous T-cell lymphoma (CTCL), showing no statistically significant differences between active drug and placebo, BioCryst does not plan to continue development of the topical cream formulation of the drug (3).

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Topical BCX-34 not effective in phase II. Daily Essentials May 4, 1998.

Riluzole
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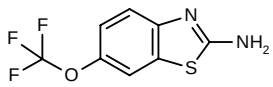
EN: 111447



$C_8H_5F_3N_2OS$ **Rhône-Poulenc Rorer**

The effects of riluzole alone and in combination with NMDA, D-cycloserine or GYKI 52466 were assessed by behavioral paradigms to evaluate sniffing, locomotion, ataxia and rigidity. Riluzole modulated neither sniffing nor locomotion, although it impaired motor coordination and lessened rigidity caused by blockade of dopamine D_1 and D_2 receptor antagonists. Spontaneous behavior decreased and motor coordination was hindered at higher doses. Coadministration with NMDA, but not GYKI 52466, enhanced the effects of riluzole, while D-cycloserine augmented the anticataleptic properties of riluzole. These findings indicate that riluzole affects glutamatergic transmission by a more indirect mechanism (1).

Administration of single oral doses of riluzole (50 mg) in 12 patients with chronic liver disease produced 1.7- and 3-fold increments in AUC in patients with mild and moderate liver disease, respectively, while C_{max} in the respective patient populations decreased by a factor of 1.4 and 4. These results indicate that riluzole should be used cautiously in patients with mild to moderate liver disease (2).

Riluzole (50 mg p.o. b.i.d.) was evaluated in a 6-week, open-label trial in 8 patients with Huntington's disease. The chorea rating score improved from a baseline value of 8.5 to 5.5 during treatment, but returned to 7.8 following discontinuation of therapy. There were no significant treatment-related effects on dystonia and total functional capacity scores (3).

Evaluation of riluzole in 100 patients with amyotrophic lateral sclerosis indicated an inter- and intraindividual variability of 51.4 and 28.0%, respectively, in a one-compartment pharmacokinetic model. Clearance of the drug was independent of dosage (25-100 mg b.i.d.), treatment duration, age and renal function, with most important covariates being gender and smoking. Clearance was estimated at 51.4 l/h in nonsmoking male patients, but was lower in women and nonsmokers. The recommend-

ed dosage of 50 mg b.i.d. produced gender- and smoking-related variations within the range of exposures achieved during this study (4).

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Original monograph - Drugs Fut 1994, 19: 920.

RSHZ19
SB-209763
Felvizumab

Antiviral

EN: 211558

SmithKline Beecham

Felvizumab has been proposed as the international nonproprietary name for RSHZ19 (1).

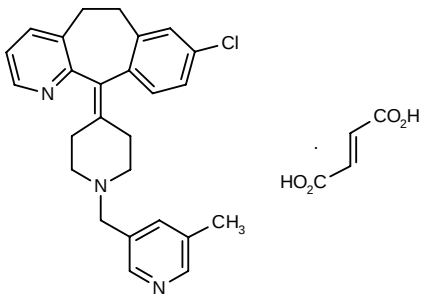
1. *Proposed international nonproprietary names (Prop. INN): List 77*. WHO Drug Inf 1997, 11(2): 91.

Original monograph - Drugs Fut 1996, 21: 1047.

Rupatadine Fumarate

Antihistamine
PAF Antagonist
Treatment of Allergic Rhinitis

EN: 204914



$C_{26}H_{26}ClN_3.C_4H_4O_4$ **Uriach**

In a guinea pig model of allergic asthma, previously sensitized animals were challenged with 0.5% ovalbumin aerosol for 5 min, resulting in adverse reactions such as dyspnea, cyanosis and bronchospasm. Treatment with rupatadine (10 mg/kg p.o.) 1 h before challenge inhibited early symptoms and bronchoalveolar lavage eosinophil recruitment (1).

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Original monograph - Drugs Fut 1996, 21: 1032.

Saruplase
Rescupase®

Thrombolytic
Treatment of Myocardial Infarction

EN: 122882

$C_{2031}H_{3121}N_{585}O_{601}S_{31}$ **Grünenthal**

Saruplase was administered to a total of 2509 patients suffering acute myocardial infarction (AMI) in 5 separate clinical trials conducted at more than 100 European centers. Saruplase was administered by infusion (dose titrated against APTT) within 6 h of onset of symptoms, preceded by administration of 5000 IU heparin by i.v. bolus. Meta-analysis of the patients in these trials showed that saruplase is a safe and effective thrombolytic agent in AMI patients. Total mortality upon discharge was 4.7% (4.1% in males and 7.4% in females) and global incidence of stroke was 1.3% (1.0% in males and 2.4% in females). Mortality was higher than the average in patients with anterior infarction, previous angina pectoris or previous myocardial infarction (5.7%, 10.2% and 9.8%, respectively), as well as in those with diabetes or previously known hypertension (both 5.9%). One of the studies established greater efficacy for saruplase as compared to streptokinase with respect to mortality, and in another study stroke rate was lower in patients on saruplase than in those given alteplase (1).

Saruplase 20 mg bolus followed by 60 mg infusion, and streptokinase 1.5 MU infusion were evaluated in 3089 patients with acute myocardial infarction. All patients were given heparin infusions prior to treatments. Mortality due to any cause occurred in 5.7% of saruplase-treated patients and in 6.7% of patients treated with streptokinase. Hemorrhagic strokes were more frequently reported in the saruplase-treated group, while the incidence of thromboembolic strokes was higher in the streptokinase-treated group. Bleeding and reinfarction rates were similar in both groups (2).

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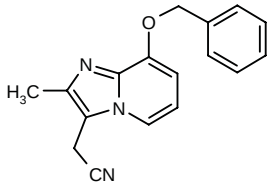
Original monograph - Drugs Fut 1986, 11: 851.

Sch-28080

Antiulcerative
H^+/K^+-ATPase Inhibitor

EN: 090784



$C_{17}H_{15}N_3O$ **Schering-Plough**

Results from studies using site-directed mutagenesis and chimera construction indicate that the sixth transmembrane segment, rather than the first intracellular loop as previously reported, is the binding site of the proton pump inhibitor, SCH-28080 (1).

1. Asano, S., et al. *Mutational study on binding site of proton pump inhibitor, SCH 28080*. Digestion 1998, 59(Suppl. 3): Abst ExhB1135.

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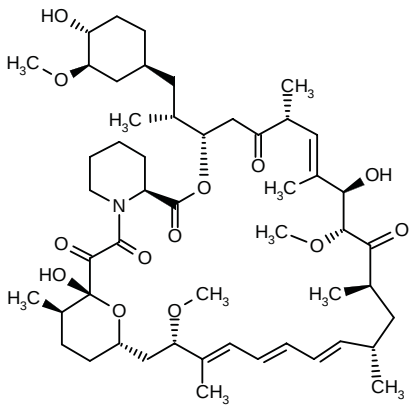
Sirolimus
Rapamune®

Immunosuppressant
Antifungal

EN: 175652



$C_{51}H_{79}NO_{13}$ **Wyeth-Ayerst; NanoSystems**

Differential hybridization studies have identified seven rapamycin-sensitive genes, one of which encoded a protein highly homologous to the ct subunit of the proteasome activator (PA28 β). Data imply that the proteasome activator is a significant downstream target of rapamycin and that an immune response could be modulated via the proteasome's activity (1).

In a primate model of kidney transplantation, monotherapy and combination therapy with FK506 (4.0 and 8.0 mg/kg) and rapamycin (0.5 and 1.0 mg/kg) for 60 days failed to have an effect on allograft survival. There were no observed rejections, and infection was the major cause of death in high-dose combination groups (2).

In a study of refractory renal allograft rejection under ciclosporin-based therapy, 13 adult patients received donor kidneys 6-24 months before treatment with rapaymcin. Rapamycin therapy (7 mg/m^2 for 5 days, then continued at 5 mg/m^2) was successful in reversing rejection episodes in 9 of the 13 recipients, 5 of whom were also weaned from steroids (3).

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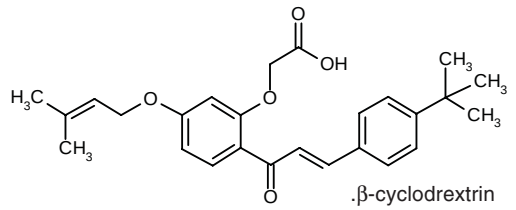
SU-840

Antiulcerative

EN: 207877



$C_{26}H_{30}O_5.C_{42}H_{70}O_{35}$ **Taisho**

SU-840 has shown gastroprotective and hyperemic activity against acid-independent (100% ethanol) and acid-dependent irritants (aspirin) and stress involving prostaglandins, sulfhydryls and NO-mediated hyperemia. SU-840 apparently requires NO-enhanced gastric blood flow to hasten ulcer healing. SU-840 (6.25-100 mg/kg i.g.) dose-dependently reduced gastric acid secretion, pepsin secretion and gastric lesions, with ID_{50}s of 28, 17 and 95 mg/kg, respectively (1).

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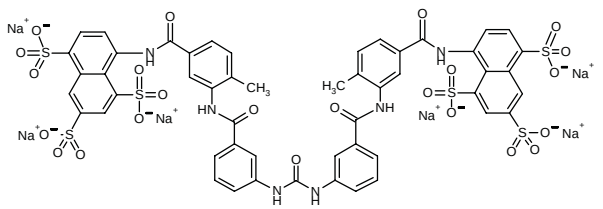
Suramin Sodium
Metaret®

Antineoplastic

EN: 116051



$C_{51}H_{34}N_6Na_6O_{23}S_6$ **Warner-Lambert; Natl. Cancer Inst. (US)**

In a phase I study in 32 patients with hormone refractory prostate cancer treated with suramin (300, 350 or 450 μg/ml i.v. 5 times/day), results demonstrated that 300 μg/ml was effective and well tolerated. Two of 12 patients with measurable disease had partial responses, 11/32 displayed a greater than 50% decrease in PSA after more than 4 weeks and 12/19 patients with pain showed improvement. Median time to progression and survival time were 5 and 17.6 months, respectively (1).

In a phase I, multicenter, open-label trial, 27 patients with advanced cancer were assigned to 1 of 3 renal function cohorts and administered suramin for a 12-week course. Results demonstrated that renal dysfunction did not influence the pharmacokinetics of suramin, including clearance. Total clearance of suramin was found to be primarily nonrenal with a free plasma clearance of 81% at week 1 and 64% at week 9. Side effects were mild to moderate and were similar in all treatment groups (2).

A phase I study of suramin in combination with doxorubicin was performed in 24 patients with androgen-independent prostate cancer. Fifty percent of the patients had a 50% decrease in prostate-specific antigen, while 60% of the subjects demonstrated a more than 50% decrease in measurable lesions. Maximum tolerated plasma levels of suramin were 151-200 μg/ml when administered in combination with doxorubicin. Side effects following combination therapy were similar to those observed after monotherapy of either compound (3).

In an ongoing phase II study, 248 patients with hormone refractory prostate cancer were administered suramin (3.19, 5.32 or 7.66 g/m^2) on days 1, 2, 8, and 9 of a 28-day cycle for 3 cycles. Suramin treatment was concluded to be safe with only moderate toxicity; grade 1-2 and grade 3-4 adverse events were observed in 95 and 76% of the patients, respectively (4).

The antitumor efficacy of cisplatin, paclitaxel and suramin as single agents and in combination was tested in vivo against 4 cell lines (1 epithelial, 3 fibrosarcomatous) of human pleural malignant mesothelioma xenografts in athymic nude mice. At day 54 or 55, mice were randomized to receive cisplatin (4 mg/kg i.p. weekly x 5), paclitaxel (12.5 mg/kg s.c. daily 5 days/week for 3 consecutive weeks) or suramin (60 mg/kg i.p. daily x 4). When administered alone, cisplatin and paclitaxel showed similar antitumor effects against 2 lines, whereas suramin was inactive in all 4 lines (5).

Warner-Lambert has submitted an NDA with the FDA seeking approval for suramin sodium (Metaret®) for the treatment of advanced hormone-refractory prostate cancer (6).

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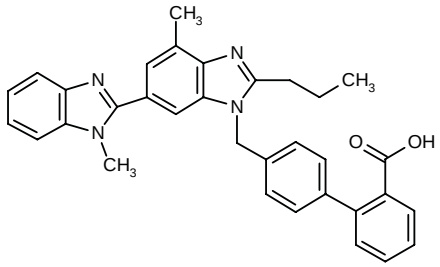
Telmisartan
BIBR-277

Antihypertensive
Angiotensin AT_1 Antagonist

EN: 195173



$C_{33}H_{30}N_4O_2$

Boehringer Ingelheim; Glaxo Wellcome

The effects of angiotensin II and telmisartan on gastric mucosal hemodynamics and the hyperemic response to acid back-diffusion were evaluated in normal rats and in animals subjected to hemorrhage to examine possible angiotensin II contributions to shock-induced dysfunction of gastric circulation. Findings disprove any contribution of angiotensin II to gastric vascular disorders in hemorrhagic shock (1).

Telmisartan (80-160 mg/day) reduced supine diastolic blood pressure to below 90 mmHg in 55% of patients in a study group of 85, while enalapril (20-40 mg) achieved this effect in only 35% of the patients. Reductions in systolic and diastolic blood pressure were 14.6 and 13.2 mmHg, respectively, in patients treated with telmisartan, compared to 13.0 and 12.9 mmHg, respectively, in enalapril-treated patients. Addition of diuretics produced a greater effect in telmisartan-treated patients than in the enalapril group (2).

The safety and efficacy of telmisartan (40, 80 and 160 mg) and lisinopril (10, 20 and 40 mg) were evaluated in 578 patients with mild to moderate hypertension. Control of supine diastolic blood pressure was achieved in 82.8% of subjects treated with telmisartan, as compared to 87% of lisinopril-treated subjects. Systolic and diastolic blood pressure reductions of 19.9 and 16.0 mmHg, respectively, were observed in telmisartan-treated patients, with corresponding reductions in the lisinopril group of 18.0 and 14.7 mmHg, respectively. Cough was reported more frequently with lisinopril (3).

In a multicenter, randomized, double-blind, parallel study, 92 patients with a confirmed history of ACE inhibitor cough were administered telmisartan (80 mg), lisinopril (20 mg) or a placebo daily for up to 8 weeks. Telmisartan-treated patients had a significantly lower incidence of cough (16% *vs.* 60% with lisinopril), although a higher rate of upper respiratory tract infection was observed as compared to the placebo group (15.6% *vs.* 0%). No statistical differences were noted in side effects or efficacy of blood pressure reduction between telmisartan- and lisinopril-treated groups (4).

In a multicenter, randomized, double-blind, placebo-controlled study, patients with mild to moderate hypertension were administered once-daily telmisartan (40-120 mg), atenolol (50-100 mg) or placebo. An 80-mg regimen of telmisartan was shown to be comparable to atenolol in reducing blood pressure. The incidence of adverse effects was similar for both drugs (5).

Telmisartan (40, 80, 120 and 160 mg/day) and enalapril (20 mg/day) were randomly administered to 433 hypertensive patients in a multicenter, double-blind, placebo-controlled trial. At 12 weeks, baseline trough BPs were evaluated and compared. Both drugs produced sustained and effective reductions in blood pressure as compared to placebo. Adverse events, with the exception of cough in the enalapril group, were comparable for all regimens (6).

The antihypertensive effects of telmisartan (40, 80, 120 and 160 mg) were compared to those of enalapril (20 mg) in a multicenter, double-blind, pacebo-controlled study in 433 patients. Both drugs significantly reduced trough blood pressure, although reductions in telmisartan-treated patients at all dose levels were greater than those in enalapril-treated patients. The side effect profiles were similar in all treatment groups, except for cough which was more frequent in the enalapril group (7).

A dose-response study of telmisartan (20, 40, 80, or 160 mg/day x 4 weeks) was performed in 277 patients with mild to moderate hypertension. A significant reduction in mean trough blood pressure was observed following administration of all doses, and a linear dose-response relationship was observed for systolic, but not diastolic, blood pressure. Diastolic blood pressure was reduced by 6.5-10.1 mmHg, while systolic blood pressure decreased by 6.5-14.9 mmHg (8).

Dose response and safety of telmisartan were evaluated in 277 patients with mild to moderate hypertension. Subjects were randomized to receive either placebo or telmisartan (20, 40, 80, 120 or 160 mg/day for 4 weeks) after a 4-week placebo washout period. Blood pressure was significantly reduced and maintained throughout the 24-h dosing period with all doses of telmisartan, and side effects were similar for telmisartan- and placebo-treated patients (9).

A 26-week, randomized, double-blind, parallel-group study compared the long-term safety and efficacy of telmisartan (40, 80 or 120 mg/day) and atenolol (50 or 100 mg/day) in 553 patients with mild to moderate hypertension. Drug-related adverse events were slightly less frequent in patients receiving telmisartan, with male impotence and fatigue being reported in atenolol-treated patients. Telmisartan was determined to be at least as effective as atenolol and had a better side effect profile (10).

The efficacy and safety of telmisartan (40, 80 and 120 mg/day) and atenolol (50 and 100 mg/day) were evaluated in an 8-week, multicenter, randomized, double-blind, placebo-controlled trial in 229 patients with mild to moderate hypertension. The incidence and severity of adverse events were similar in all treatment regimens, with headache and dizziness most commonly reported, and telmisartan 80 mg was as effective as atenolol in reducing blood pressure (11).

Telmisartan (80 and 160 mg/day) was compared to enalapril (20 and 40 mg/day) in 85 subjects with severe hypertension in a multicenter, open-label trial lasting 8 weeks, in which hydrochlorothiazide (25 mg) and amlodipine (5 mg) were added to control supine diastolic blood pressure if needed. Supine diastolic blood pressure of <90 mmHg was achieved in 55% and 35% of patients on telmisartan and enalapril, respectively. Telmisartan significantly reduced blood pressure and was considered to be safe and effective when administered alone or in combination with other agents (12).

Glaxo Wellcome and Boehringer Ingelheim have signed an agreement under which they will collaborate to complete the clinical development and launch of Boehringer's telmisartan. The two companies will jointly perform further clinical research to establish the profile of telmisartan in various patient populations. In return, Glaxo Wellcome will receive rights to market telmisartan as well as a combination product incorporating telmisartan and hydrochlorothiazide. The agreement covers most markets worldwide except for the U.S., Japan and certain other countries (13).

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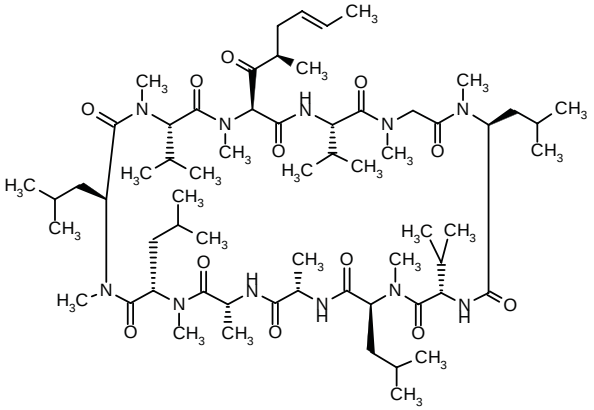
Valspodar
PSC-833
SDZ-PSC-833

Multidrug Resistance Modulator

EN: 182411



$C_{63}H_{111}N_{11}O_{12}$ **Novartis**

When PSC-833 (1-10 μM) was added to a MCF-7 cell culture with [^{3}H]-serine or [^{3}H]-palmitic acid, the levels of [^{3}H]-ceramide rose significantly in a dose-responsive fashion. PSC-833 did not affect ceramide formation through a sphingomyelinase pathway, since no increase in cellular sphingomyelin radioactivity was observed. Cell proliferation assays showed that elicitation of ceramide formation by PSC-833 and increased cytotoxicity were clearly related. At 2.5 μM, ciclosporin and PSC-833 treatment increased ceramide formation by 20% and 7.5-fold, respectively. These results demonstrate a new action of PSC-833 which may contribute to its potency as a multidrug resistance modulator (1).

The modulating effects of PSC-833, ciclosporin, verapamil and genistein on daunorubicin cytotoxicity were studied in childhood acute lymphoblastic leukemia cells. Findings indicated that PSC-833, ciclosporin and verapamil may be used to sensitize cells to daunorubicin but patients should undergo prior *in vitro* screening to determine therapeutic benefit from the modulators (2).

PSC-833 (1 μM) restored the apoptotic potential of TNFα (10 ng/ml) in inherently TNFα-resistant human leukemia KG1a cells. In addition, a 3-fold increase in the sphingomyelin content of inner plasma membranes and basal neutral sphingomyelinase activity was observed (3).

The modulating activity of PSC-833 was evaluated in MDR P388/ADR and MCF7/ADR cell lines. Flow cytome-

try and fluorescence microscopy assessed cellular uptake levels and intracellular doxorubicin distribution. Where chemosensitization was complicated at the tumor site, PSC-833 (1 μM) provided almost complete MDR reversal and demonstrated significant latent MDR modulating activity (4).

PSC-833 and estramustine demonstrated synergistic inhibitory effects on androgen receptor phosphorylation and dephosphorylation in LNCaP cells. The IC_{50} for androgen receptor phosphorylation was 5 μM in the presence of PSC-833, compared to 20 μM observed with estramustine alone. This result coincided with the observed downregulation of PSA expression. The presence of the two compounds also reduced the $t_{1/2}$ of the androgen receptor protein from 2.5 to 1.5 h in LNCaP cells (5).

The multidrug resistance-reversing ability of SDZ PSC-833 was evaluated in a study in which mdr1a (–/–) and wildtype mdr1a (+/+) mice were administered a constant i.v. infusion of [^{14}C]-SDZ PSC-833 (2 μg/min) for 4-h. The mdr1a(–/–)/(+/+) ratio of accumulated brain SDZ PSC-833 decreased and increased in response to high and low plasma SDZ PSC-833 concentration, respectively. These results together with the observation that SDZ PSC-833 mediates brain penetration by inhibition of the P-glycoprotein (P-gp) pump in mdr1a (+/+) mice, illustrates an interaction of SDZ PSC-833 with the blood-brain barrier. Mdr1a P-gp was concluded not to be involved in the disposition of this drug since accumulation in other mdr1a P-gp-expressed tissues and metabolism and elimination were not affected by mdr1a gene disruption (6).

The possibility of measuring serum PSC-833 concentrations using the rhodamine (Rh) 123 retention bioassay was evaluated in 8 healthy volunteers given one oral dose of 400 mg and 5 doses of 200 mg. A good correlation in serum PSC-833 concentrations was observed between measurements using the Rh 123 bioassay and those using radioimmunoassay. In addition, the Rh 123 bioassay results correlated well with doxorubicin resistance reversal *ex vivo* (7).

In a phase I dose-finding study, 22 patients with relapsed or refractory acute leukemia were initially administered ara-C 1 g/m^2/day for 6 days in combination with continuous intravenous infusion of PSC-833 and 6-day courses of escalating doses of mitoxantrone and etoposide. The regimen was generally well tolerated, with an observed complete response rate of 27% (8).

Phase I and II trials have shown that PSC-833 inhibited P-glycoprotein (P-gp) expression, cytochrome P-450 3A4, and multiple organic anion transporters in normal kidney and liver. Inhibition of P-gp prevented MDR in preclinical models and results using mdr gene knockout mice demonstrated the role of this gene in the action of cytotoxic drugs. Phase III trials continue to examine the efficacy of PSC-833 therapy on multidrug resistance in acute myeloid leukemias, multiple myeloma and ovarian cancer (9).

Pharmacokinetic interactions between PSC-833 and doxorubicin and paclitaxel were evaluated in a phase I trial in 28 patients with refractory solid tumors. Significant interactions were detected between PSC-833 and both drugs, with prolonged plasma half-lives of 77 and 99% for doxorubicin and paclitaxel, respectively. Increments of 84% for doxorubicin and 165% for paclitaxel in mean plasma residence time were also observed. There were 3 partial remissions and 2 minor responses, with neutropenia and thrombocytopenia as hematological toxicities. The changes in pharmacokinetic constants indicate that dose modifications should be considered when PSC-833 is coadministered with doxorubicin and paclitaxel (10).

A dose-finding, pharmacokinetic study evaluated the combination of doxorubicin with PSC-833 in 38 patients with advanced solid tumors. PSC-833 was administered at escalating doses of 2.5-25 mg/kg/day for 5 days every 12 h; 4 h after PSC-833 on day 3, doxorubicin was administered by i.v. push. Substantial hematological and central nervous system toxicities were observed with the combination, thus requiring a marked reduction in the doxorubicin dose (from 50 to 20 mg/m^2) (11).

The multidrug resistance modulating effects of PSC-833 (5 mg/kg q.i.d.) were evaluated in a phase I/II trial in 22 patients with relapsed or refractory non-Hodgkin's lymphoma treated for 51 cycles with a combination of vincristine, mitoxantrone, cyclophosphamide, etoposide and prednisone. Complete response/minimal disease was observed in 6 patients and partial response in 3 patients. Treatment cycles were associated with neutropenia, thrombocytopenia, unsteady gait and the inability to walk without assistance. The combination treatment was well tolerated and appeared to have significant activity (12).

A combination treatment consisting of PSC-833 with cyclophosphamide, doxorubicin, vincristine and prednisone was evaluated in a phase II trial in 20 patients with relapsed or refractory non-Hodgkin's lymphoma. The response rate was 22%, while the median plasma trough concentration of PSC-388 at steady state was 2505 ng/ml. Treatment-related deaths were not observed, although 3 patients died from progressive disease. Hematologic toxicities included neutropenia, anemia and thrombocytopenia, while nonhematologic effects included constipation, abdominal pain, musculoskeletal pain, fever and ataxia. Multidrug resistance modulation with PSC-833 proved ineffective in this particular study group (13).

The absorption and pharmacokinetics of valspodar (200 mg i.v. and 600 mg p.o.) were evaluated in 20 volunteers receiving the drug either as a conventional oral solution, a microemulsion oral solution or a microemulsion soft gelatin capsule. The two microemulsion dosage forms of administration resulted in significantly faster and less variable rates of absorption as compared to the conventional oral solution, and were bioequivalent with approximately a 2-fold higher absolute bioavailabilty than the conventional oral solution. Single administration of microemulsion capsules (200, 400 and 600 mg) under fasting conditions and a 400-mg dose following the intake of a fat-rich meal in 24 volunteers produced dose-proportional AUC values over the entire dose range. Intake of a fat-rich meal delayed absorption, increased t_{max} and

increased the AUC by 24%. Hyperbilirubinemia was observed following administrations of all doses (14).

The pharmacokinetics of valspodar were evaluated following oral and intravenous administration. Subjects receiving valspodar 200 mg i.v. infusion and 400 mg oral microemulsion gelatin capsules demonstrated low to moderate inter- and intrasubject variability with coefficients of variation ranging from 9-19%, and an absolute bioavailabilty of 60% following administration of the microemulsion formulation. Absorption of valspodar following oral administration was uniform and reproducible, with equivalent C_{max}, t_{max} and AUC values. Low to moderate pharmacokinetic variability was observed between the two routes of administration (15).

Novartis has initiated two international phase III trials to evaluate PSC-833 for the treatment of multidrug-resistant cancer, in combination with standard chemotherapy. The first trial expects to evaluate PSC-833 in approximately 650 patients with acute myelogenous leukemia at 100 sites, including the U.S. and worldwide. Another trial will evaluate the combination treatment in 698 women with advanced (stage III or IV) ovarian cancer in the U.S., Canada, Europe, the Middle East, Russia and Australia (16).

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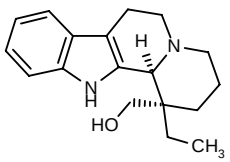
Vintoperol

Peripheral Vasodilator

EN: 122375



$C_{18}H_{24}N_2O$ **Gedeon Richter; Takata Seiyaku**

The inhibitory effects on lipid peroxidation and free radical scavenging by vintoperol were tested *in vitro*. Vintoperol moderately and weakly inhibited lipid peroxidation (LPO) induced by Fe^2 in brain homogenate (IC_{50} = 58.2 μM) and synaptosomes (IC_{50} = 97.2 μM), respectively, and was inactive in synaptosomal Fe^3-evoked LPO. It also showed moderate efficacy on microsomal NADPH- or NADH-stimulated LPO (IC_{50} =100.2 and 83.9 μM, respectively) and was active against LPO induced by ascorbic acid in brain microsomes (IC_{50} = 30.7 μM). In addition, vintoperol demonstrated antioxidant activity that was similar to ellagic acid but weaker than that of idebenone. This moderate antioxidant activity may constitute part of its vascular mechanism of action (1).

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Original monograph - Drugs Fut 1986, 11: 853.

VIP Aviptadil

Gastrointestinal Motility Inhibitor

EN: 125580

H-His-Ser-Asp-Ala-Val-Phe-Thr-Asp-Asn-Tyr-Thr-Arg-Leu-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Asn-Ser-Ile-Leu-Asn-NH_2

$C_{147}H_{238}N_{44}O_{42}S$ **RTP Pharma**

Aviptadil is the proposed international nonproprietary name for VIP (1).

1. *Proposed international nonproprietary names (Prop. INN): List 78.* WHO Drug Inform 1997, 11(4): 267.

Original monograph - Drugs Fut 1987, 12: 977.

Latebreaking News

- Amtolmetin guacil was recently launched by Sigma-Tau in Italy as Eufans®.
- The FDA's Oncologic Drugs Advisory Committee has not approved the NDA submitted by Warner-Lambert for suramin sodium (Metaret™).