Drugs of the Future 1998, 23(3): 319-356

CCC: 0377-8282/98

Information Update

Volume 1-22, Number 3

Estimated developmental phase for this month's updated products:

Preclinical

Liposome-encapsulated hemoglobin (blood substitute; NeXtar)
ONO-3404 (protease inhibitor, treatment of pancreas disorders; Ono)

Phase I

CMDA (antineoplastic; Inst. Cancer Res.)
Englitazone sodium (antidiabetic; Pfizer)
Sinitrodil (antianginal, vasodilator; Italfarmaco)

Phase II

Amphotericin B-intralipid (antifungal; SmithKline Beckman)
Carzelesin (antineoplastic, alkylating agent; Pharmacia & Upjohn)
MKC-242 (anxiolytic, antidepressant, 5-HT_{1A} agonist; Mitsubishi Chem., Astra, Hoechst Marion Roussel)
Piroxantrone (antineoplastic; Parke-Davis, DuPont Merck)
TAK-147 (cognition enhancer, acetylcholinesterase inhibitor; Takeda)
YM-90K (neuroprotectant, AMPA receptor antagonist; Yamanouchi)

Phase III

Apafant (antiallergic/antiasthmatic, PAF antagonist; Boehringer Ingelheim, Discovery Labs.)
Cetrorelix (antineoplastic, LHRH antagonist, treatment of BPH; Asta Medica, Nippon Kayaku, Shionogi)
Cristanol mesilate (antineoplastic, DNA topoisomerase II inhibitor; Glaxo Wellcome, Ilex Oncology, Janssen, Sanofi Winthrop)
Droloxifene (antineoplastic, antiestrogen, treatment of osteoporosis; Klinge Pharma, Fujisawa, Pfizer)
Eletriptan (antimigraine, 5-HT_{1D} agonist; Pfizer)
Fenretinide (antineoplastic; Johnson & Johnson, Natl. Cancer Inst.)
Gatifloxacin (fluoroquinolone antibacterial; Kyorin, Bristol-Myers Squibb, Grünenthal, Handok)
Miproxifene phosphate (antineoplastic; Taiho, Synphar)
Mitoguazone (antineoplastic; Natl. Cancer Inst., Ilex Oncology, Sanofi Winthrop)
MTP-PE (immunostimulant; Novartis, Chiron, Jenner Technologies, NABI)
Nifekalant hydrochloride (antiarrhythmic, potassium channel blocker; Mitsui Toatsu)
S-1090 (cephalosporin; Shionogi)
Sematilide hydrochloride (antiarrhythmic, Berlex, Schering AG, Roussel Morishita)
Silipide (hepatoprotectant; Inverni Della Beffa)
Sparfosic acid (antineoplastic, antiviral; Parke-Davis, US Bioscience)
Tirapazamine (radiosensitizer, chemosensitizer; Sanofi Winthrop, SRI Intl.)
Voriconazole (antifungal; Pfizer)

Launched/Year

Anagrelide hydrochloride (treatment of thrombocythemia, phosphodiesterase III inhibitor; Bristol-Myers Squibb, Roberts, Inverni Della Beffa)/1997
Dalargin (antiulcerative, antianginal; Acad. Med. Sci., All Union Cardiol. Res. Center)/1988
Delavirdine mesilate (antiviral for AIDS, reverse transcriptase inhibitor; Pharmacia & Upjohn)/1997
Eflornithine hydrochloride (antineoplastic, ornithine decarboxylase inhibitor; Natl. Cancer Inst., Ilex Oncology)/1991
Flurithromycin (macrolide antibiotic; Pharmacia & Upjohn, Fournier Pierrel Farma, Mediolanum, Poli Ind. Chimica)/1997
Follitropin beta (treatment of female intertility; Organon)/1996
Irinotecan (antineoplastic; Yakult Honsha, Daiichi Pharm., Pharmacia & Upjohn, Prodesfarma, Rhône-Poulenc Rorer)/1994
Saquinavir mesilate (antiviral for AIDS, HIV-1 protease inhibitor; Roche)/1995
Tazarotene (antipsoriatic, antiacne; Allergan)/1996
Zafirlukast (antiallergic/antiasthmatic, leukotriene D_4 antagonist; Zeneca)/1996
Zolmitriptan (antimigraine, 5-HT_{1A} agonist; Zeneca)/1997

Amphotericin B-Intralipid

Antifungal

EN: 197215

SmithKline Beckman

In a nonrandomized study in 27 neutropenic patients with suspected fungal infection undergoing intensive chemotherapy, treatment with amphotericin B dissolved in Intralipid (mean daily dose of 0.8 mg/kg i.v. over 1 h) resulted in resolution of fever in 27 of 34 episodes within a mean period of treatment of 5.6 days (1).

A randomized phase II trial in 51 neutropenic patients with antibiotic-refractory fever of unknown origin or pneumonia confirmed that there are no significant differences in the toxicity of amphotericin B (75 mg/kg/day i.v. as a 1-h infusion) in Intralipid 20% compared to the conventional formulation in dextrose 5%. Patients receiving the Intralipid formulation reported severe but reversible pulmonary side effects, possibly due to the instability of the formulation (2).

Intralipid-based amphotericin B therapy (total dosage 19.8 ± 3.3 mg/kg) for 10 days in 52 low-birth-weight neonates with fungal infections was found to be effective and nonnephrotoxic (3).

1. Chitnavis, D., Maddon, J., Litlewood, T.J. *The treatment of suspected fungal infection with amphotericin in intralipid.* Brit J Haematol 1996, 93(Suppl. 2): Abst 995.

2. Schöffski, P., Freund, M., Wunder, R., Petersen, D., Ganser, A. *No evidence of improved toxicity of amphotericin B in intralipid: Results of a confirmatory randomized phase II-trial.* Clin Microbiol Infect 1997, 3(Suppl. 2): Abst P1237.

3. Friedlich, P.S., Steinberg, I., Fujitani, A., deLemos, R.A. *Renal tolerance with the use of intralipid-amphotericin B in low-birth-weight neonates.* Amer J Perinatol 1997, 14(7): 377.

Original monograph - Drugs Fut 1994, 19: 225.

Additional Reference

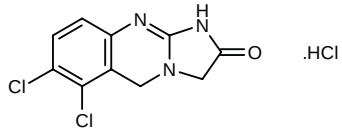
Friedlich, P. et al. *Renal tolerance with the use of intralipid-amphotericin B in low birthweight neonates.* J Invest Med 1997, 45(1): 176A.

Anagrelide Hydrochloride

Agrelin® *Treatment of Thrombocythemia*

Agrylin® *Phosphodiesterase III Inhibitor*

EN: 090016



.HCl

$C_{10}H_7Cl_2N_3O.HCl$

Bristol-Myers Squibb; Roberts; Inverni Della Beffa

In a study in 33 patients with essential thrombocythemia or chronic myelogenous leukemia, treatment with anagrelide (2-3 mg/day) reduced platelet count by 50% in 84% of the patients. Tolerance to the drug was good, and dose-dependent side effects such as headache, tachycardia, diarrhea and stomach pain were mild and disappeared within days (1).

In a study in 60 patients with essential thrombocythemia, chronic myelogenous leukemia or polycythemia vera, treatment with anagrelide hydrochloride (2-3 mg/day) resulted in hematological responses in 84% of patients and clinical responses in 80% of patients. Mild side effects, including headache, tachycardia, diarrhea and stomach pain, were dose-dependent and disappeared within several days (2).

In a study in 12 patients with chronic myelogenous leukemia and high platelet counts who were being treated with hydroxyurea alone or in combination with interferon-α, the addition of anagrelide (mean dose of 2 mg/day) resulted in a decrease in platelet counts in all 12 patients which lasted for at least 4 weeks. Mild and transient adverse events were reported in 3 patients and consisted of headache, tachycardia, palpitation and fluid retention (3).

Anagrelide hydrochloride (Agrylin™) has been launched by Roberts Pharmaceutical in the U.S. for the treatment of essential thrombocythemia; supplied as capsules, 0.5 mg active ingredient (4).

Roberts has filed an NDA supplement with the FDA seeking approval to expand the current indication for Agrylin™ (anagrelide hydrochloride) to include polycythemia vera (5).

1. Petrides, P.E. *Treatment of essential thrombocythemia with Anagrelin®: The German experience.* Brit J Haematol 1996, 93(Suppl. 2): Abst 892.

2. Petrides, P.E. *Treatment of essential thrombocythemia with Agrelin®: Hematological and clinical responses in 60 patients from Germany.* Proc Amer Soc Clin Oncol 1997, 16: Abst 123.

3. Petrides, P.E., Trapp, O., Beykirch, M.K. *Anagrelide for treatment of patients with chornic myelogenous leukemia and a high platelet count.* Blood 1997, 90(10, Suppl. 1, Part 2): Abst 4009.

4. *New product intros.* Drug News Perspect 1997, 10(3): 150.

5. *Roberts seeks to broaden market for Agrylin.* Prous Science Daily Essentials January 13, 1998.

Original monograph - Drugs Fut 1980, 5: 117.

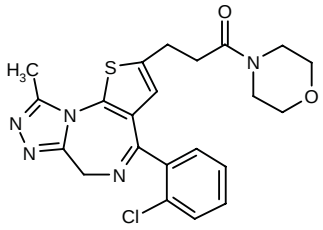
Additional Reference

Roberts seeks European approval of Agrylin. Prous Science Daily Essentials July 11, 1997.

Apafant

Antiallergic/Antiasthmatic
PAF Antagonist

EN: 125474



$C_{22}H_{22}ClN_5O_2S$

Boehringer Ingelheim; Discovery Labs.

Results of fertility and reproduction studies in male and female rats have shown that oral doses of apafant up to 1000 mg/kg were well tolerated and did not significantly influence fertility or the development of embryos and offspring, including function, behavior and reproductive capability (1).

Reproduction and teratology studies in rats administered oral doses of apafant (20, 250 and 1000 mg/kg) during organogenesis showed that the no toxic doses in dams and F1 offspring were 250 and 1000 mg/kg, respectively (2).

Based on perinatal and postnatal reproduction studies in rats, the no toxic effect dose of oral apafant for dams and offspring was determined to be 500 mg/kg/day (3).

Results of a study in rats showed that apafant at a concentration of 1 μg/ml dose-dependently inhibited PAF- and antigen-induced increases in bronchial inflation pressure, pulmonary artery perfusion pressure, microvascular permeability, as well as the increases in thromboxane B_2 and leukotriene production (4).

Studies in guinea pigs showed that apafant, like ketotifen and ozagrel, prevented histamine-induced bronchial hyperreactivity, isoproterenol-induced decrease in the relaxation of lung parenchymal strips and a reduction in the number of β-adrenergic binding sites in lung membrane preparations (5).

In a teratology study of apafant in rabbits, oral doses of 20 and 70 mg/kg did not produce maternal or fetal toxicity. A higher dose of 250 mg/kg was not toxic to offspring but did cause maternal weight loss and abortions (6).

1. Nishimura, M., Matsuo, A., Niggeschulze, A., Katsuki, S. *Fertility and reproduction studies of apafant (WEB 2086 BS) in rats dosed orally.* Pharmacometrics 1996, 52(3-4): 185.

2. Matsuo, A., Nishimura, M., Niggeschulze, A., Katsuki, S. *Reproduction and teratology study of apafant (WEB 2086 BS) in rats dosed orally during the period of organogenesis.* Pharmacometrics 1996, 52(3-4): 201.

3. Matsuo, A., Nishimura, M., Niggeschulze, A., Katsuki, S. *Reproduction studies of apafant (WEB 2086 BS) in rats dosed orally during prenatal and postnatal period.* Pharmacometrics 1996, 52(3-4): 215.

4. Akagi, M., Nishioka, E., Kanoh, R., Tachibana, M., Fukuishi, N. *Inhibitor effect of apafant on bronchopulmonary responses to platelet activating factor and to antigen in rats.* Arzneim-Forsch-Drug Res 1997, 47(12): 1364.

5. Sugimoto, Y., Mihara, T., Hayakawa, T., Nakayama, Y., Kishida, H., Kamei, C. *Effect of apafant on bronchial hyperresponsiveness and down-regulation of β-adrenoceptors induced by endotoxin in guinea pigs.* Arzneim-Forsch-Drug Res 1997, 47(7): 837.

6. Matsuo, A., Nishimura, M., Niggeschulze, A., Katsuki, S. *Teratology study of apafant (WEB 2086 BS) in rabbits dosed orally during the period of organogenesis.* Pharmacometrics 1996, 52(3-4): 209.

Original monograph - Drugs Fut 1988, 13: 242.

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Hayakawa, T. et al. *Effects of apafant and antiasthmatic drugs on bronchial hyperresponsiveness induced by endotoxin in guinea pigs.* Jpn J Pharmacol 1997, 73(Suppl. 1): Abst O-229.

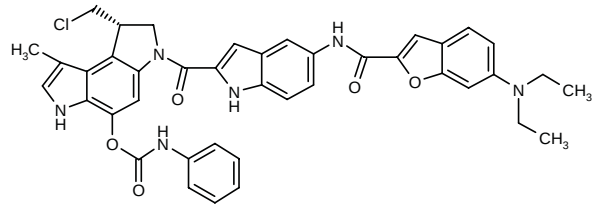
O'Connor, B.J. et al. *Airway and systemic responses to inhaled PAF in humans are inhibited by an oral but not an inhaled PAF receptor antagonist.* Amer J Respir Crit Care Med 1996, 153(4, Part 2): A348.

Sugimoto, Y. et al. *Effects of apafant on PAF-induced down-regulation of β-adrenoceptors in guinea pigs.* Meth Find Exp Clin Pharmacol 1997, 19(8): 547.

Carzelesin

Antineoplastic
Alkylating Agent

EN: 149876



$C_{41}H_{37}ClN_6O_5$

Pharmacia & Upjohn

The degradation of carzelesin was shown to follow first-order kinetics, and neither buffer components nor ionic strength significantly affected the degradation rate. Carzelesin was most stable at a pH of 1-4 (1).

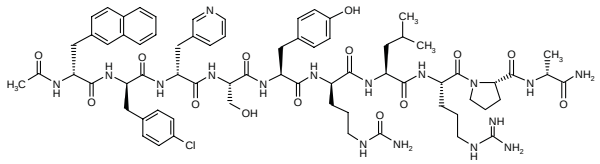
1. Jonkman-de Vries, J.D., Doppenberg, W.G., Henrar, R.E.C., Bult, A., Beijnen, J.H. *Systematic study on the chemical stability of the prodrug antitumor agent carzelesin (U-80,244).* J Pharm Sci 1996, 85(11): 1227.

Original monograph - Drugs Fut 1996, 21: 245.

Cetrorelix

Antineoplastic
LHRH Antagonist
Treatment of BPH

EN: 148387



$C_{70}H_{92}ClN_{17}O_{14}$

Asta Medica; Nippon Kayaku; Shionogi

The inhibitory effects of cetrorelix on tumor growth in nude mice xenografted with DU-146 prostate cancer cell line were suggested to be due, in part, to downregulation of epidermal growth factor and luteinizing hormone-releasing hormone receptors (1).

In vivo studies in nude mice xenografted with PC-3 human prostate cancer cell line showed that both cetrorelix and RC-3940-II significantly reduced tumor cell volume and decreased the number of epidermal growth factor (RGF) receptors detected in tumor membranes. The results suggest that both drugs inhibit tumor growth through downregulation of EGF receptors (2).

Preliminary findings from a randomized, placebo-controlled, double-blind phase II study in 79 men with symptomatic benign prostatic hyperplasia showed that daily treatment with cetrorelix (1 mg s.c.), compared to placebo, improved symptoms, increased peak flow rate and reduced prostate volume. These effects were maintained for up to 3 months posttreatment (3).

In a study in 29 previously untreated patients with inoperable prostate cancer or planning to undergo radical prostatectomy, both slow and fast release formulations of cetrorelix (50 or 60 mg starting dose followed by 60 or 120 mg every 3-4 weeks) resulted in immediate (within 24 h) and continuous suppression of testosterone to castration levels. Both formulations were well tolerated (4).

A study enrolled 79 men with BPH symptoms who were randomized to treatment with placebo or 2 different doses of cetrorelix (group A: 1 mg s.c. once daily; group B: loading dose of 10 mg/day x 5 days followed by 1 mg s.c. once daily) for a total of 4 weeks. Patients were followed for at least 3 months thereafter. Patients in the active treatment group B had decreased sexual function, with testosterone levels suppressed to castration limits. In group A, in contrast, testosterone levels decreased by 43%, to a level below the normal lower limit but above castration levels, and impact on sexual function was minimal. Serum gonadotropins and sex steroids were suppressed in a dose-dependent fashion in cetrorelix-treated patients. BPH symptoms improved in both active drug groups, as seen by increased Q_{max}, decreased prostate size and improved quality of life (5).

In one clinical trial, 3 different cetrorelix treatment regimens were compared in 29 patients with locally confined or advanced prostate cancer. Cetrorelix depot (cetrorelix pamoate, 60 mg i.m. every 3-4 weeks) was given alone or in combination with a loading dose of cetrorelix acetate (50 mg s.c. plus 60 or 120 mg i.m. cetrorelix pamoate). Treatment continued for up to 6 months. Immediate and continued chemical castration was achieved in approximately 50% of the patients treated with cetrorelix, and in the remainder castration was not attained due to low plasma drug levels. The compound was well tolerated, and effectively reduced PSA and prostate volume. In order for routine use of cetrorelix in prostate cancer patients to be feasible, however, improved galenical formulations are needed (6).

1. Jungwirth, A., Pinski, J., Galva, G., Halmos, G., Szepeshazi, K., Cai, R.Z., Groot, K., Vadillo Buenfil, M., Schally, A.V. *Inhibition of growth of androgen-independent DU-145 prostate cancer in vivo by luteinising hormone-releasing hormone antagonist cetrorelix and bombesin antagonists RC-3940-II and RC-3950-II.* Eur J Cancer 1997, 33(7): 1141.

2. Jungwirth, A., Galvan, G., Pinski, J., Halmos, G., Szepeshazi, K., Cai, R.Z., Groot, K., Schally, A.V. *Luteinizing hormone-releasing hormone antagonist cetrorelix (SB-75) and bombesin antagonist RC-3940-II inhibit the growth of androgen-independent PC-3 prostate cancer in nude mice.* Prostate 1997, 32(3): 164.

3. Lepor, H., Dixon, C. *A randomized double blind placebo controlled phase II study of the safety and efficacy of cetrorelix in men with BPH.* J Urol 1997, 157(4, Suppl.): Abst 531.

4. Tunn, U.W., Melamed, R.J., Schnaars, Y., Riethmüller-Winzen, H., Romeis, P., Reissmann, T., Engel, J. *Tolerability and hormonal suppression of the LHRH-antagonist cetrorelix in patients with prostate cancer.* J Urol 1997, 157(4, Suppl.): Abst 551.

5. Riethmüller-Winzen, H., Schnaars, Y. *The GnRH antagonist cetrorelix and proof of concept in patients with benign prostatic hyperplasia.* Aging Male 1998, 1(Suppl. 1): Abst 040.

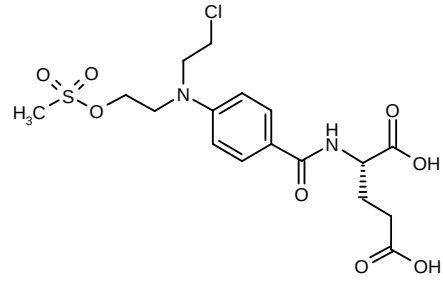
6. Tunn, U.W., Melamed, R.J. *The GnRH antagonist cetrorelix as new concept for the treatment of locally confined or advanced CAP.* Aging Male 1998, 1(Suppl. 1): Abst 041.

Original monograph - Drugs Fut 1994, 19: 228.

CMDA

Antineoplastic

EN: 159448



$C_{17}H_{23}ClN_2O_8S$

Inst. Cancer Res. (GB)

Human tumor cell lines (colon and breast carcinomas and ovarian adenocarcinomas) expressing carboxypeptidase G_2 (CPG_2) were found to be 8- to 150-fold more sensitive to the mustard prodrug CMDA than nonexpressing cell lines. Total cell kill occurred when only 2-31% of the cells expressed CPG_2 on their surface (1).

1. Springer, C.J., Spooner, R., Light, Y., Martin, J., Stribbling, S., Niculescu-Duvaz, D., Niculescu-Duvaz, I., Davies, L., Friedlos, F., Marais, R. *Extracellular expression of the carboxypeptidase G_2 enzyme for activation of a mustard prodrug in gene-directed enzyme prodrug therapy (GDEPT).* Proc Amer Assoc Cancer Res 1997, 38: Abst 2551.

Original monograph - Drugs Fut 1993, 18: 212.

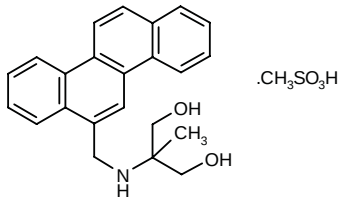
Additional Reference

Marais, R. et al. *GDEPT (gene-direct enzyme prodrug therapy) with the carboxypeptidase G_2 enzyme in combination with a mustard prodrug.* Cancer Gene Ther 1996, 3(6, Suppl.): Abst P-79.

Crisnatol Mesilate

Antineoplastic
DNA Topoisomerase II Inhibitor

EN: 128342



$C_{23}H_{23}NO_2.CH_4O_3S$ **Glaxo Wellcome; Ilex Oncology; Janssen; Sanofi-Winthrop**

Results of a phase I trial of crisnatol mesylate administered as a 72-h continuous i.v. infusion in 17 children with malignant brain tumors showed that the dose-limiting toxicity was neurologic, with 4 patients experiencing generalized tonic-clonic seizures, 2 of whom were treated at the highest dose level tested (3600 mg/m^2). All toxicity was rapidly reversible upon discontinuation of treatment. One patient with brain stem glioma showed clinical improvement and another with glioblastoma multiforme showed stable disease following 6 and 8 courses, respectively, of 2100 mg/m^2 (1).

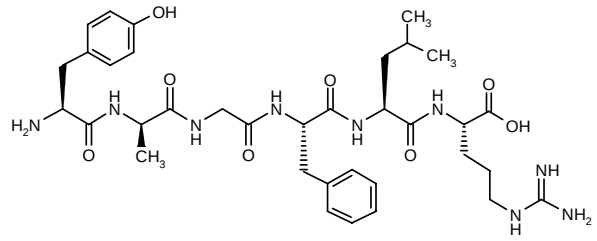
1. Sato, J.K., Siegel, S.E., Villablanca, J.G., Fields, S.,Kuhn, J., Sharpe, A., McGinty, K., Britt, B., Von Hoff, D.D. *Phase I trial of crisnatol mesylate (CM) in pediatric brain tumors.* Proc Amer Soc Clin Oncol 1997, 16: Abst 758.

Original monograph - Drugs Fut 1993, 18: 216.

Dalargin

Antiulcerative
Antianginal

EN: 105694



$C_{35}H_{51}N_9O_8$ **Acad. Med. Sci. (RU); All Union Cardiol. Res. Center (RU)**

When administered i.p. (1-10 μg/day) to rats, dalargin favorably influenced the quinuclidinyl benzilate-induced central anticholinergic syndrome, and in rats subjected to aversive stimulation it provided protection against the noradrenergic toxin DSP-4 in active avoidance tests (1).

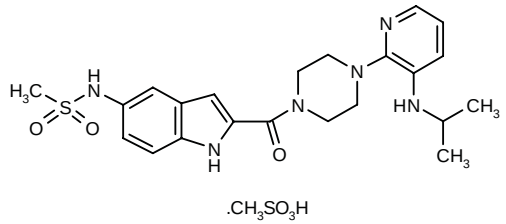
1. Koupilová, M., Patocka, J., Barth, T. *The effect of dalargin on cholinergic and noradrenergic dysfunction in rats.* Pharmacol Toxicol 1997, 80(Suppl. 1): Abst 30.

Original monograph - Drugs Fut 1991, 16: 203.

Delavirdine Mesilate
Rescriptor®

Antiviral for AIDS
Reverse Transcriptase Inhibitor

EN: 196540



$C_{22}H_{28}N_6O_3S.CH_4O_3S$ **Pharmacia & Upjohn**

Protein binding analysis of plasma samples from 67 HIV-1 infected patients showed that binding of both delavirdine mesylate and *N*-desalkyl delavirdine was linear over total trough plasma concentrations of 3-50 μM (1).

Results of studies in mice have indicated that induction of pseudopregnancy by delavirdine is mediated via the mouse-specific metabolite PNU-88703, which is species-specific and not expected to affect humans treated with the drug (2).

A population pharmacokinetics model for delavirdine mesylate and its metabolite *N*-desalkyl delavirdine was developed by analyzing 594 plasma samples from 73 HIV-infected patients taken over 6 months. Results

showed that delavirdine clearance was saturable, with median predicted total oral clearance of 7.7, 4.0 and 2.8 l/h, respectively, at drug concentrations of 10, 30 and 50 μM (3).

Results from a randomized, parallel-group, pharmacokinetic trial in 30 healthy volunteers showed that the combination of delavirdine (400 mg t.i.d. group 1 on days 8-21; group 2 for 28 days) and saquinavir (600 mg t.i.d. group 1 for 21 days; group 2 on days 15-28) resulted in saquinavir concentrations approaching those achieved with saquinavir monotherapy (7200 mg/d) (4).

A pharmacokinetic study in 14 healthy adult volunteers showed that the combination of delavirdine mesylate (400 mg t.i.d.) and indinavir sulfate (400 or 600 mg) resulted in indinavir concentrations similar to or higher than those achieved with the higher dose of indinavir sulfate 800 mg t.i.d. (5).

In a randomized, parallel group study in 30 healthy volunteers, no pharmacokinetic interaction was observed between ritonavir (300 mg b.i.d.) and delavirdine (400-600 mg b.i.d.) and the doses recommended for further study of the combination in HIV-1 patients were 1200 mg/day for each drug (6).

Results of a 2-week, randomized, parallel-group study in 24 healthy volunteers have demonstrated that the metabolic clearance of nelfinavir (750 mg t.i.d.) is inhibited when administered in combination with delavirdine (400 mg t.i.d.). Since 4 subjects withdrew from the study due to treatment-related neutropenia, monitoring for neutropenia is advisable in patients receiving this combination (7).

In a 3-way crossover, single-dose study in 12 HIV-1 infected patients, concurrent administration of delavirdine mesylate (400 mg) and didanosine buffered tablets (125-200 mg) was shown to cause a reduction in the $AUC_{(0-\infty)}$ of both drugs, which could be avoided when didanosine was given 1 h after delavirdine (8).

Oral delavirdine mesylate administered to HIV-positive patients either as escalating doses (200, 300 and 400 mg q8h) or as repeated administration of the same dose (300 mg q8h) caused a marked reduction in hepatic CYP3A activity, indicating that the drug will probably exhibit drug-drug interactions when coadministered with other CYP3A substrates (9).

In a pharmacokinetic study in 12 HIV-positive patients, delavirdine mesylate (400 mg q8h for 30 days) administered alone and in combination with rifampin (600 mg/day on days 16-30) was well tolerated. In patients treated with rifampin, the oral clearance of delavirdine was increased, resulting in almost negligible steady-state trough concentrations after 2 weeks of dosing, and the elimination half-life was significantly shortened. Based on these findings, rifampin is contraindicated in patients being treated with delavirdine mesylate (10).

Results from a study in 9 evaluable HIV-positive patients receiving 21 days of concurrent therapy with ritonavir (600 mg b.i.d.) and delavirdine mesylate (400 mg t.i.d.) indicated that the combination was well tolerated. Furthermore, the metabolism of delavirdine to *N*-desalkyl delavirdine appeared to be unchanged during treatment (11).

The addition of delavirdine mesylate to combination therapy in 46 HIV-1 positive patients failing triple protease inhibitor therapy resulted in a rapid and sustained improvement in CD4 counts and viral load in 20-30%% of patients which lasted for more than 6 months. Significant clinical improvement was observed, and the most frequently reported adverse events included skin rash (27%), nausea (10%), kidney stones and diarrhea (8%) and flank pain with proteinuria (2%) (12).

In a drug combination study in 544 HIV-1 infected patients, the 3-drug combination of delavirdine mesylate, zidovudine and didanosine was shown to be significantly better than 2-drug combinations of delavirdine + zidovudine, delavirdine + didanosine and zidovudine + didanosine in producing mean increases in CD4 counts and mean decreases in HIV-1 RNA levels (13).

Results of a study in 13 HIV-1 positive patients with CD4 counts of 186-480 cells/mm^3 demonstrated that the steady-state pharmacokinetics of delavirdine (300 mg q8h for 30 days) were not significantly affected by coadministration of fluconazole (400 mg q.d. on days 16-30), indicating that no dose adjustment of either drug is necessary when the two drugs are taken together (14).

The influence of rifabutin (300 mg once daily on days 16-30) on the steady-state pharmacokinetics of delavirdine (400 mg q8h for 30 days) was evaluated in 12 HIV-positive patients. After concomitant administration of the drugs for 2 weeks, there was a 5-fold increase in the oral clearance of delavirdine, resulting in lower steady-state plasma concentrations of the drug. Statistically significant differences were observed for all delavirdine pharmacokinetic parameters on day 30. These results indicate that, in patients taking both medications, dose adjustments may be necessary to maintain therapeutic concentrations of delavirdine (15).

Data from a study in 12 HIV-infected patients suggested that antiretroviral therapy using delavirdine combined with didanosine or a triple-drug combination of delavirdine, AZT and didanosine can be effective in restoring the neutralizing activity of patients' sera (16).

In a pharmacokinetic evaluation in 6 HIV-1 patients who were stabilized on rifabutin (300 mg/day), the addition of delavirdine (400-1000 mg t.i.d.) was shown to inhibit rifabutin clearance and produce a >200% increase in rifabutin exposure. These results indicate that combination therapy with the two drugs should not be used on a routine basis due to possible adverse events associated with increased exposure of rifabutin (17).

Results from a phenotypic sensitivity analysis of viral isolates from more than 190 randomly selected HIV patients participating in a phase III, 1200-patient, blinded study showed that 100% of isolates from patients receiving 400 mg t.i.d. delavirdine plus zidovudine remained highly sensitive to zidovudine after 24 weeks of therapy, and that delavirdine sensitivity remained below median trough levels in 88% of isolates. Viral isolates from a phase II delavirdine plus zidovudine trial with experienced

zidovudine patients demonstrated resensitization to zidovudine, with a 85-fold decrease in zidovudine IC_{50} during 6 months therapy) (18).

Delavirdine mesylate (Rescriptor™) has been launched in the U.S. for the treatment of HIV-1 infection in combination with other anti-HIV medications and is supplied as 100-mg tablets (19, 20).

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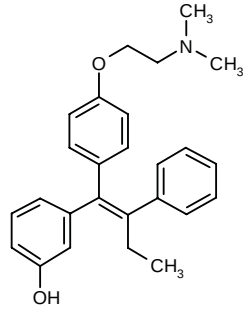
Droloxifene

Antineoplastic
Antiestrogen

EN: 090075 *Treatment of Osteoporosis*



$C_{26}H_{29}NO_2$ **Klinge Pharma; Fujisawa; Pfizer**

A study in ovariectomized rats with established osteopenia showed that 4 and 8 weeks of treatment with droloxifene (10 mg/kg/day via gavage) induced significant increases in bone mineral density and inhibited bone turnover; however, in comparison to estradiol, it had no effects on uterine stimulation (1).

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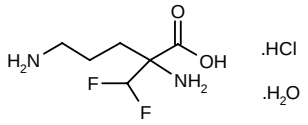
Eflornithine Hydrochloride

Antineoplastic

Ornidyl® *Ornithine Decarboxylase Inhibitor*

EN: 090024



$C_6H_{12}F_2N_2O_2.HCl.H_2O$ **Natl. Cancer Inst. (US); Ilex Oncology**

A double-blind, randomized, placebo-controlled phase IIB trial in 119 healthy subjects aged 40-80 years who had colonic polyps removed during the previous 5 years has evaluated the safety and biochemical effects of very low doses (0.075, 0.20 and 0.40 g/m^2/day p.o.) of eflornithine given for 1 year. The results demonstrated an excellent safety profile, as well as dose-dependent and continuous suppression of polyamine levels in the rectal mucosa. The highest dose reduced putrescine levels to 10% of those in the placebo group, and similar results were observed for the ratio spermidine/spermine. These effects were reversed after discontinuation of eflornithine. Long-term follow-up of these subjects continues. A daily dose of 0.1-0.2 g/m^2 is recommended for phase III trials of the potential of eflornithine for preventing colon cancer (1).

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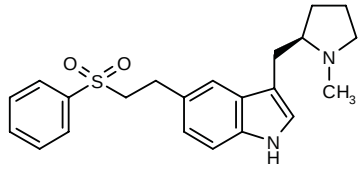
Eletriptan

Antimigraine
5-HT$_{1D}$ Agonist

EN: 223823



$C_{22}H_{26}N_2O_2S$ **Pfizer**

Pfizer has described the design and synthesis of the selective 5-HT$_{1D}$-like receptor partial agonist eletriptan, now in phase III clinical trials for the treatment of migraine. In clinical trials, the compound has shown rapid oral absorption, a relatively long half-life, good bioavailability and rapid relief of migraine headache after oral administration (1, 2).

In radioligand binding studies, eletriptan exhibited a 4- to 8-fold higher affinity for human recombinant 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors as compared to sumatriptan (pK_is = 8.0 and 8.9 *vs.* 7.4 and 8.0, respectively) and had an equally high affinity for the rat recombinant 5-HT$_{1F}$ receptor subtype (pK_is = 8.3 for eletriptan and 8.2 for sumatriptan). In functional studies, eletriptan produced potent and concentration-dependent contractions in dog isolated basilar artery (pEC_{50} = 7.0), further confirming the drug's partial agonist properties (3).

Results of a study comparing the permeability of antimigraine agents across human colonic adenocarcinoma Caco-2 cell monolayers indicated that eletriptan may be more rapidly absorbed in humans than the other drugs tested (4).

Results of double- and single-blind, randomized, placebo-controlled, crossover studies in healthy male volunteers administered single doses of eletriptan (1.5-120 mg p.o. and 1.67-102 μg/kg i.v.) demonstrated linear pharmacokinetics over the dose ranges studied. Eletriptan was rapidly absorbed after oral administration (t_{max} = 1.0 h) and showed an absolute bioavailability of approx. 50%. Tolerance was good after both oral and i.v. dosing. Mild and transient treatment-related adverse events were reported with higher oral doses (90-120 mg) and consisted of stiff neck and heavyheadedness (5).

Results from a crossover study of the pharmacokinetics of oral eletriptan (30 mg) in 34 migraineurs during a migraine attack and during a migraine-free phase demonstrated that the rate of absorption of the drug was significantly slowed and the mean C_{max} and AUC_{0-8} were reduced during a migraine attack. However, 18/34 (52.9%) patients reported a clinically significant reduction in headache severity within 2 h after dosing (6).

In two double-blind studies in patients with acute migraine with or without aura, intravenous eletriptan (16.7, 50 or 102 μg/kg as a 15-min infusion), compared to placebo, produced rapid and significant reductions in headache severity and associated symptoms. The drug was well tolerated in both studies, and only mild to moderate side effects were reported (7).

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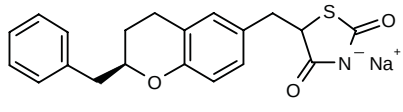
Englitazone Sodium

Antidiabetic

EN: 161743



$C_{20}H_{18}NNaO_3S$ **Pfizer**

Englitazone sodium has been submitted to *in vitro* testing in order to determine its effects on ion channel activity in the CRI-G1 insulin-secreting cell line. The com-

pound was found to inhibit K_{ATP} channel activity and Ca^{2+}-activated nonselective cation channels in a concentration-dependent and voltage-independent, equipotent manner. The K_{ATP} channel-blocking effect of englitazone occurred at a site distinct from that utilized by sulfonylurea antidiabetic drugs (1).

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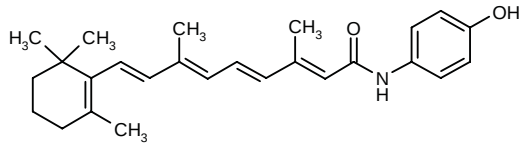
Fenretinide

Antineoplastic

EN: 090670



$C_{26}H_{33}NO_2$

Johnson & Johnson; Natl. Cancer Inst. (US)

Time lapse photomicroscopy studies showed that treatment with liposome-encapsulated fenretinide resulted in a dose- and time-dependent suppression of human neuroblastoma cell growth via induction of apoptosis (1).

Results from a 3-month study of the pharmacokinetics and pharmacodynamics of fenretinide (200, 300 or 400 mg/day) in 11 patients with actinic keratosis demonstrated an overall decrease in the total area of all actinic keratosis, although the magnitude of the decrease did not correlate with dose or mean plasma concentrations of fenretinide, 4-MPR or retinol (2).

A pilot trial of fenretinide (200 mg/day) in combination with tamoxifen (20 mg/day) in 24 women at high risk of developing invasive breast cancer showed that the treatment was well tolerated, with most toxicities such as hot flashes (20/24 patients), mucocutaneous (14/21) and visual symptoms (9/24) being generally mild. Adequate tissue for biomarker studies was obtained in 19/20 patients using a core biopsy technique (3).

Electroretinogram studies in 24 women treated with fenretinide (200 mg/day for a median of 30.5 months) and 18 untreated controls from a phase III intervention trial showed that treatment with the drug caused only subtle changes in retinal function (4).

A phase II chemoprevention trial in 22 men at high risk for prostate cancer showed that treatment with oral fenretinide for 12 cycles of 28 days each was well tolerated, with no major toxicities observed. However, the study was terminated early due to the detection of positive prostate biopsies in 8 patients who had entered the study with negative biopsies (5).

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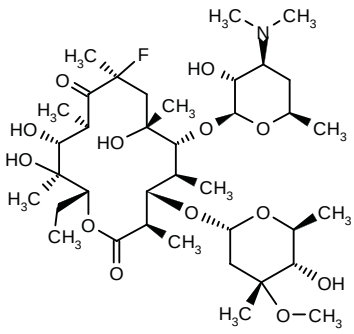
Flurithromycin
Flurizic®
Mizar®
Ritro®

Macrolide Antibiotic

EN: 090756



$C_{37}H_{66}FNO_{13}$

Pharmacia & Upjohn; Fournier Pierrel Farma; Mediolanum; Poli Ind. Chimica

In a 14-day, multicenter, parallel-group, randomized study in 320 patients with upper respiratory tract infections, treatment with flurithromycin (375 mg b.i.d.) was shown to be as effective and well tolerated as clarithromycin (250 mg b.i.d.). At treatment completion, success rates were 95.6% and 91.3% in the flurithromycin and clarithromycin groups, respectively (1).

Flurithromycin has been launched in Italy by Mediolanum (Flurizic®), Fournier Pierrel Farma (Ritro®) and Poli Industria Chimica (Mizar®) for the treatment of flurithromycin-sensitive infections, including upper and lower respiratory tract infections and odontostomatological infections. It is supplied as tablets, 375 mg (2).

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Follitropin Beta
Org-32489
Follistim®
Puregon®

Treatment of Female Infertility

EN: 194492

Organon

Results of an open-label, prospective, randomized, multicenter study in 195 infertile, pituitary-suppressed women undergoing controlled ovarian hyperstimulation by Puregon® showed no significant differences between intramuscular *versus* subcutaneous administration in regard to local tolerance symptoms (63.6 *vs*. 68.6%), the number of oocytes recovered (9.8 *vs*. 10.4) and ongoing pregnancy rates (27.1 *vs*. 26.1%) (1).

Organon was cleared by the FDA to market Follistim® for use in the development of multiple follicles in infertile patients treated by *in vitro* fertilization (IVF) and for the induction of ovulation (2).

1. Out, H.J., Reimitz, P.E., Bennick, H.J.T.C. *A prospective, randomized study to assess the tolerance and efficacy of intramuscular and subcutaneous administration of recombinant follicle-stimulating hormone (Puregon®).* Fertil Steril 1997, 67(2): 278.

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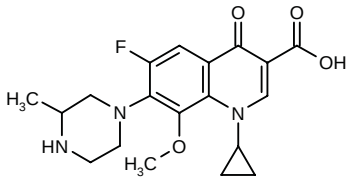
Gatifloxacin AM-1155

Fluoroquinolone Antibacterial

EN: 137307



$C_{19}H_{22}FN_3O_4$

Kyorin; Bristol-Myers Squibb; Grünenthal; Handok

Gatifloxacin was shown to have higher inhibitory activities than ciprofloxacin, ofloxacin, norfloxacin and enoxacin against various bacterial type II topoisomerases, indicating its higher selectivity for these topoisomerases (1).

Results of *in vitro* studies demonstrated that CG-5501 had high activity against a wide range of clinical isolates, including *Streptococcus pneumoniae* (MIC_{90} = 0.5 mg/l), *Staphylococcus aureus* (MIC_{90} = ≤ 4 mg/l) and *Bacteroides fragilis* (MIC_{90} = 0.25 mg/l) (2).

Results of an *in vitro* study against 55 clinical isolates of *Neisseria gonorrhoeae* showed that the antimicrobial activity of AM-1155 was more potent than those of tosufloxacin and fleroxacin against highly fluoroquinolone-resistant, moderately fluoroquinolone-resistant and quinolone-susceptible strains (3).

Gatifloxacin has been reported to have comparable activity to tosufloxacin and superior activity to levofloxacin and ofloxacin against clinical isolates of *Chlamydia trachomatis*, and it has been shown to penetrate well into cervix uteri tissue. When given at daily doses of 200 or 300 mg for 7-14 days to 12 patients with chlamydial cervicitis, good to excellent efficacy was obtained in all patients. *Chlamydia* were eradicated in all cases and no recurrence was observed for up to 56 days after treatment (4).

In vitro studies demonstrated that AM-1155 was highly active against *Prevotella intermedia*, *Porphyromonas gingivalis*, *Fusobacterium* spp., *Clostridium perfringens* and *Mobiluncus* spp. (MIC_{90}s = ≤ 0.39 mg/l) and showed modest activity against *Prevotella bivia* and *B. fragilis*. *In vivo*, the drug was effective against *B. fragilis* and *Escherichia coli* strains in rat granuloma pouch, whereas tosufloxacin was effective only against *E. coli* (5).

Excellent photostability has been observed for gatifloxacin, and it appeared to have less phototoxic potential compared to other quinolones in guinea pigs (6).

In vivo studies in rats with chronic airway infection with *Pseudomonas aeruginosa* showed that treatment with AM-1155 (25 mg/kg s.c.) was as effective as ciprofloxacin (25 mg/kg s.c.) in suppressing excessive immune responses and thereby preventing progression of airway damage (7).

The pharmacokinetics of gatifloxacin have been assessed in elderly patients administered a single oral dose of 100 mg. Compared to healthy young volunteers, the AUC was larger and the $t_{1/2}$ longer in elderly patients; the longer half-life was attributed to reduced renal and apparent body clearance. The results indicate that gatifloxacin should be administered with caution in the elderly and that dose should be adjusted according to renal function in this population. A dose regimen of 100 mg b.i.d. is suggested for elderly patients with impaired renal function (8).

Data from a study examining the bactericidal activity of gatifloxacin in 53 subjects indicate that a single oral dose of 200 or 400 mg of the drug will be efficacious in treating susceptible urinary tract pathogens such as *Staphylococcus saprophyticus*, *E. coli*, *Proteus mirabilis* and *Enterococcus faecalis*. *P. aeruginosa*, on the other hand, may require an increased dose or multiple dosing (9).

The safety and tolerance of single (200-800 mg) and multiple (400 and 600 mg) oral doses of gatifloxacin were evaluated in 3 phase I studies in 107 healthy Caucasian volunteers. In one of the studies, the effect of concomitant food intake on drug bioavailability was also evaluated and results showed no significant alterations in plasma C_{max} or AUC. Clinical and biological tolerance was good in all 3 studies, and treatment-related adverse events were limited to tiredness, headache, dizziness and abdominal pain (10).

In a double-blind, placebo-controlled, parallel-group study of gatifloxacin in 36 healthy male Caucasian volunteers, pharmacokinetic evaluation after multiple oral doses of 400 and 600 mg showed that the C_{max} and t_{max} did not change significantly over the 15-day study period. Total clearance remained stable for both dose groups, indicating linear kinetics (11).

The clinical efficacy and safety of gatifloxacin (100, 150 or 200 mg once or twice daily) have been investigated in 45 patients with eye infections, after it was shown to penetrate well into ocular tissues. Excellent clinical efficacy was obtained in 36 patients, good in 6, fair in 2 and poor in 1 patient, for an overall efficacy rate of 93.3%. One case of transient epigastric discomfort was reported (12).

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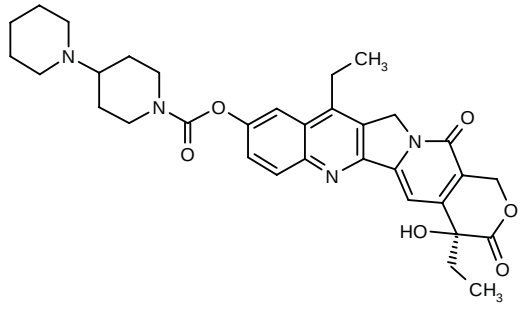
Irinotecan *Antineoplastic*

Campto®
Camptosar®
Topotecin®

EN: 103766



$C_{33}H_{38}N_4O_6$

Yakult Honsha; Daiichi Pharm.; Pharmacia & Upjohn; Prodesfarma; Rhône-Poulenc Rorer

A new asymmetric synthesis of irinotecan has been reported: The reaction of 2,6-dihydroxypyridine-4-carboxylic acid (I) with hot $POCl_3$ and trimethylammonium chloride gives 2,6-dichloropyridine-4-carboxylic acid (II), which by a Grignard condensation with ethylmagnesium bromide in THF is converted into the propanone (III). The ketalization of (III) with ethyleneglycol and trimethylsilyl chloride (TMS-Cl) affords the dioxolane (IV), which by reaction with sodium methoxide in refluxing methanol gives the monomethoxy-pyridine derivative (V). The carbonylation of (V) with butyl lithium and DMF affords the pyridine-carbaldehyde (VI), which is reduced to the methanol (VII) with $NaBH_4$. The protection of the hydroxy group of (VII) with benzyl bromide and potassium *tert*-butoxide in THF affords the benzyl ether (VIII), which is treated with CO, K_2CO_3, palladium acetate and 1,3-bis(diphenylphosphino)propane (DPPP) in propanol/DMF giving the propyl ester (IX). The treatment of (IX) with trifluoroacetic acid yields the propanone (X), which is treated with methyltriphenylphosphonium bromide and potassium bis(trimethylsilyl)amide (KHMDS) in DMF to afford the expected methylene derivative (XI). The oxidation of (XI) with OsO_4 in *tert*-butanol gives the racemic diol (XII), which is submitted to optical resolution with PS-30 catalyst (*Pseudomonas cepaica* lipase over Celite 521) to give the corresponding (*S*)-enantiomer (XIII). The oxidation of (XIII) with NaOCl affords the 2(*S*)-hydroxybutyraldehyde (XIV), which is submitted to cyclization by debenzylation with H_2 over Pd/C in methanol giving the cyclized diol (XV). The oxidation of (XV) with NaOCl in dichloromethane affords the hydroxylactone (XVI), which is treated with trimethylsilyl chloride and NaI to give the pyridone (XVII). A new cyclization of (XVII) with *tert*-butyl acrylate (XVIII) by means of Cs_2CO_3 in DMSO yields the tricyclic *tert*-butyl ester (XIX), which is decarboxylated with trifluoroacetic acid in refluxing toluene to afford the tricyclic trione (XX). The cyclization of (XX) with 2-amino-5-hydroxypropiophenone (XXI) by means of *p*-toluenesulfonic acid in hot toluene/acetic acid gives the camptothecin derivative (XXII), which is finally acylated with 4-(1-piperidyl)piperidine-1-carbonyl chloride (XXIII) in pyridine (1). Scheme 1.

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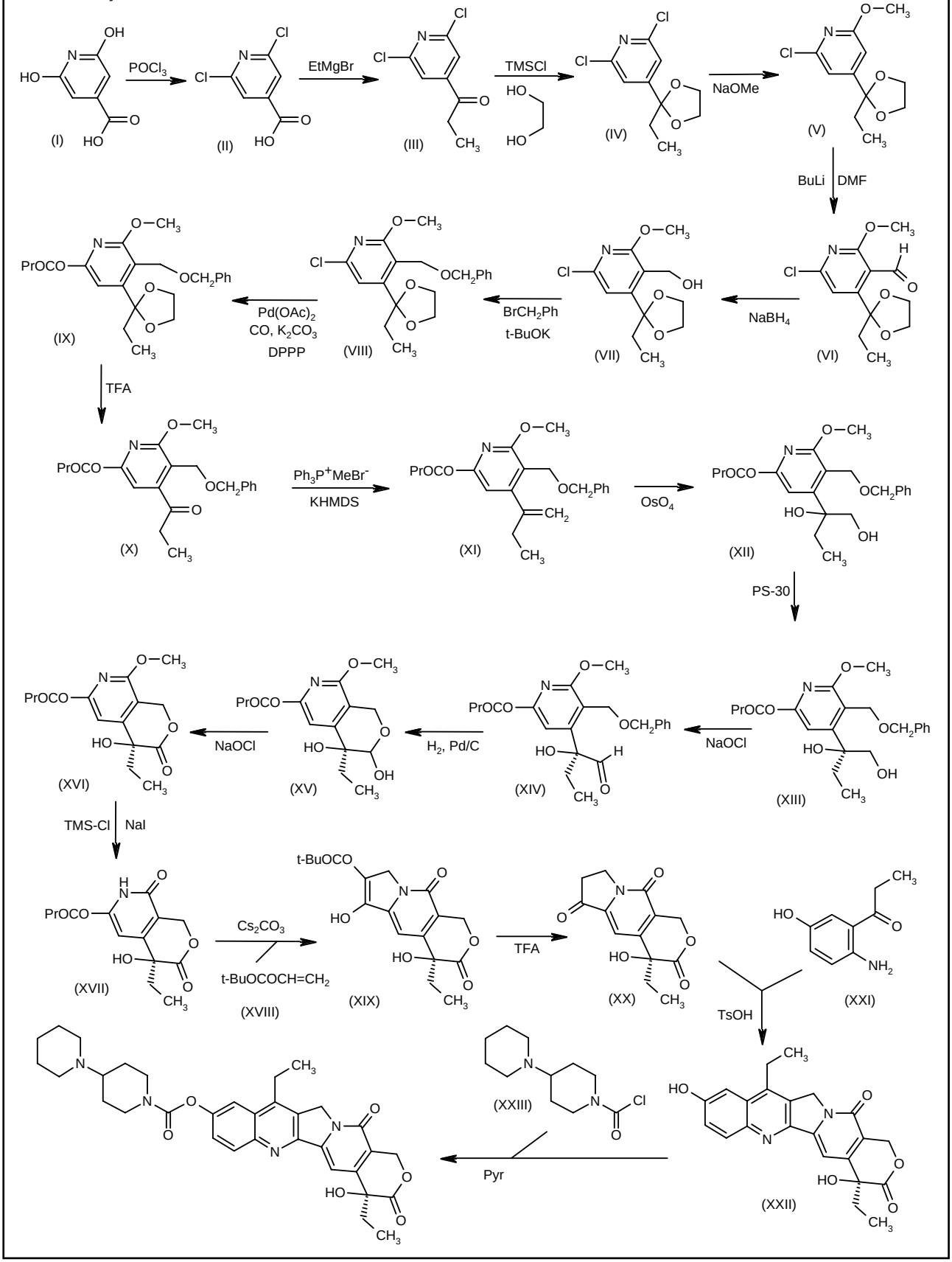
Scheme 1: Synthesis of Irinotecan



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Liposome-Encapsulated Hemoglobin

EN: 170574 *Blood Substitute*

NeXtar

Recent findings have indicated that LPS binds to the surface of liposome encapsulated hemoglobin in a biologically active form and that the binding is mediated by adherent hemoglobin (1).

In vesicles incubated with normal human serum, liposome encapsulated hemoglobin-induced complement activation was associated with increases in serum C4d and Bb levels and appeared to involve both the classical and alternative pathways (2).

Results of platelet distribution studies in rats demonstrated that complement-depleted rats treated with liposome encapsulated hemoglobin (LEH) did not undergo thrombocytopenia, indicating a correlation between complement activation and LEH-induced thrombocytopenia (3).

Experiments examining tissue-specific cytokine accumulation in normovolemic mice found that animals treated with both liposome encapsulated hemoglobin (LEH) and intraperitoneal LPS had significantly increased levels of IL-4 in serum, liver, spleen and lung, as compared to animals treated with LEH or LPS alone (4).

Lung uptake studies in rats following a 40% exchange transfusion with one of several hemoglobin-based blood substitutes showed that the oxygen carrying capacity for human liposome encapsulated hemoglobin (LEH) was significantly greater than that for bovine LEH and free bovine hemoglobin (5).

In anesthetized rabbits, an intravenous infusion of liposome encapsulated hemoglobin caused rapid increases in right ventricular blood pressure and pulmonary vascular resistance, slight increases in mean arterial blood pressure and cardiac output, and a slight reduction in systemic vascular resistance. There were no effects on ventilation or heart rate. All of the effects appeared to be transient and less severe than with previous LEH preparations (6).

In studies in awake, normovolemic cynomolgus monkeys, an infusion of liposome encapsulated hemoglobin had no significant effect on mean arterial pressure or heart rate, although it did cause significant elevations in total white blood cell count and total serum cholesterol which were suggested to be caused by the liposome vehicle (7).

In studies in anesthetized hemodiluted dogs, human liposome encapsulated hemoglobin was found to be an effective substitute for circulating red blood cells in delivering oxygen to peripheral tissues and maintaining normal oxygen metabolism, indicating its potential use in the treatment of massive hemorrhage (8).

A study in dogs with irreversible hemorrhagic shock showed that fewer transfusions of liposome encapsulated hemoglobin, as compared to blood, were needed to increase oxygen transport efficiency and consumption, thereby compensating the reduction of cardiac output (9).

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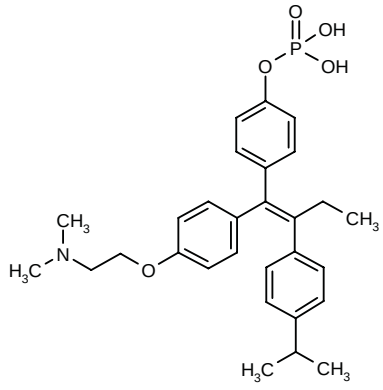
Miproxifene Phosphate *Antineoplastic*
TAT-59

EN: 141699



$C_{29}H_{36}NO_5P$ **Taiho; Synphar**

Findings from a study examining the relationship between hormone-dependent tumor cells and DP-TAT-59, the active metabolite of TAT-59, indicate that the suppressive effects of the compound on human mammary carcinoma growth may be due, at least in part, to the production of growth inhibitory factors and/or the suppression of growth factor production from estrogen receptor-positive cells (1).

In vitro and *in vivo* mutagenicity studies of TAT-59, using the reverse mutation test with *Salmonella typhimurium* strains and *Escherichia coli* WP2 uvrA, the chromosomal aberration test in Chinese hamster lung cells and the micronucleus test in BDF1 female mice, showed that the drug had little or no mutagenic potential (2)

In studies examining the compatibility of TAT-59 with various excipients, the addition of polyethyleneglycol 6000 using the melting granulation method was found to be useful for the stabilization of the drug (3).

Miproxifene has been reported to induce apoptosis in human breast cancer MCF-7 cells (4).

Single-dose toxicity studies of orally administered TAT-59 revealed species, but not gender, differences in LD_{50} values for mice and rats, which were 1940 and 1800 mg/kg for male and female mice, respectively, and 835 and 785 mg/kg for male and female rats, respectively (5).

A study of changes in body weight, hematology, blood chemistry, organ weight and histopathology of rats administered repeated oral doses of TAT-59 (0.001, 0.04, 1.6 and 64 mg/kg/day for 13 weeks followed by 5-week recovery) showed the nontoxic dose to be approximately 0.001 mg/kg, with most treatment-related changes returning to normal during the recovery period (6).

A toxicity study of TAT-59 (0.0005, 0.01, 0.2 and 4.0 mg/kg/day) orally administered for 52 weeks in female Sprague-Dawley rats determined the nontoxic dose to be 0.0005 mg/kg. Most dose-related changes returned to pretreatment levels during the 5-week recovery period (7).

A fertility study of TAT-59 (0.0002, 0.001 and 0.005 mg/kg/day) orally administered to male Sprague-Dawley rats 64 days prior to mating, and to female Sprague-Dawley rats 14 days prior to mating showed that the drug decreased implantation rate, disordered the estrus cycle, decreased fertility rate and decreased body weight in females at the higher doses. In males, the drug increased body weight but did not produce reproductive toxicity. In fetuses, the drug retarded growth, increased embryo-fetal death, but did not increase external, visceral or skeletal abnormalities. The results determined the nontoxic doses for general toxicity and for reproductive function/fetal toxicity to be 0.001 and 0.0002 mg/kg/day, respectively (8).

A teratological study of TAT-59 (0.1, 1.0 and 10.0 μg/kg/day) administered by oral gavage to pregnant Sprague-Dawley rats on days 7-17 of gestation showed that the highest dose decreased body weight, food consumption, birth rate and increased embryo-fetal mortality, but did not produce changes in development, function, behavior or reproductive ability. The results indicated that the nontoxic dose for general toxicity and reproduction in the dams and fetuses is 1.0 μg/kg/day and 10.0 μg/kg/day in the offspring (9).

Results of a peri- and postnatal study of TAT-59 (0.001, 0.01, 0.1 mg/kg/day p.o.) in female Sprague-Dawley rats from day 17 of gestation through day 21 of lactation indicated that the higher concentrations of the drug reduced body weights and produced vaginal bleeding in dams. In F1 neonates, the drug decreased body weight, suppressed weight gain and delayed testis descent, but did not affect emotional, learning or reproductive performance. In F2 neonates, no adverse effects were observed. The general nontoxic dose was found to be 0.001 mg/kg/day for dams and F1 offspring, 0.01 mg/kg/day for maternal reproductive ability and 0.1 mg/kg/day for F2 offspring (10).

Results of an antigenicity study of TAT-59 in BALB/c and C3H/He mice sensitized by oral gavage or intraperitoneally with aluminum hydroxide gel as adjuvant and in female Hartley guinea pigs sensitized by oral gavage or subcutaneously with Freund's complete adjuvant showed that the drug had no antigenicity (11).

A study of changes in blood chemistry, body weight, organ weight, general conditions and histopathology of male and female dogs administered repeated oral doses of TAT-59 (0.001, 0.04, 1.6 and 64 mg/kg/day for 13 weeks followed by 5-week recovery) determined the approximate nontoxic dose to be 0.001 mg/kg/day, with most dose-related changes returning to pretreatment levels during the recovery period (12).

In a repeated-dose toxicity study TAT-59 (0.0005, 0.01, 0.2 or 4.0 mg/kg/day) was orally administered for 52 weeks to female Beagle dogs. Results of histopathological, hematological and biochemical analysis determined that the nontoxic dose was 0.0005 mg/kg/day. Lesions in reproductive tissues were attributed to sex hormone imbalances and most dose-related changes returned to pretreatment levels during the 5-week recovery period (13).

A teratological study in pregnant NZW rabbits orally administered TAT-59 (0.001, 0.01, 0.1 mg/kg/day) on days 6-18 of gestation showed that the drug reduced fecal mass, body weight, food consumption and produced death and premature birth at the higher doses. In fetuses, it increased embryo-fetal deaths, but did not produce teratogenetic or developmental retardation. The results determined the nontoxic dose to be 0.001 mg/kg/day and 0.01 mg/kg/day for reproductive and fetal toxicity (14).

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6. Kitagaki, T., Suzuki, T., Kito, S. *A 13-week oral repeated dose toxicity study of miproxifene phosphate (TAT-59) in rats.* Jpn Pharmacol Ther 1997, 25(Suppl. 2): 11.

7. Imai, K., Yamaguchi, K., Ikeda, H. et al. *A 52-week oral repeated dose toxicity study of miproxifene phosphate (TAT-59) in rats.* Jpn Pharmacol Ther 1997, 25(Suppl. 2): 87.

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10. Koida, M., Shinomiya, M., Yamakita, O., Izumi, K., Ikebuchi, K., Nakagawa, F., Nonaka, N., Sato, T. *Reproductive and developmental toxicity study of miproxifene phosphate (TAT-59) (4) - Peri- and postnatal study in rats by oral administration.* Jpn Pharmacol Ther 1997, 25(Suppl. 2): 181.

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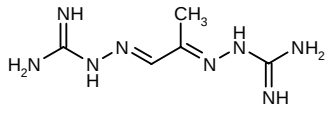
Original monograph - Drugs Fut 1991, 16: 217.

Mitoguazone
Zyrkamine®

Antineoplastic

EN: 090048



$C_5H_{12}N_8$

Natl. Cancer Inst. (US);
Ilex Oncology; Sanofi Winthrop

In 8 patients with AIDS-related primary CNS lymphoma, mitoguazone dihydrochloride (600 mg/m^2 i.v. on days 1 and 8, then every 2 weeks) administered in combination with radiation therapy produced partial remissions in 4 patients, 3 of whom had survived for more than 6 months at the time of publication. Toxicity consisted of facial flushing in all 8 patients and mild hematologic toxicity in 4 patients (1).

The FDA's Oncologic Drugs Advisory Committee did not recommend approval of Ilex Oncology's Zyrkamine® (mitoguazone dihydrochloride) injection, stating that there was not substantial evidence that this drug was effective as a second-line treatment for patients with AIDS-related non-Hodgkin's lymphoma. The company intends to meet with Sanofi, their development partner for Zyrkamine®, to review their options (2).

1. Levine, A., Tulpule, A., Espina, B.M., Von Hoff, D., Tessman, D. *Mitoguazone (MGBG) with radiation therapy in AIDS-related primary CNS-lymphoma.* 11th Int Conf AIDS (July 7-12, Vancouver) 1996, Abst Th.B.184.

2. *FDA advisory committee withholds recommendation of Ilex Oncology's treatment for AIDS-related NHL.* Prous Science Daily Essentials June 26, 1997.

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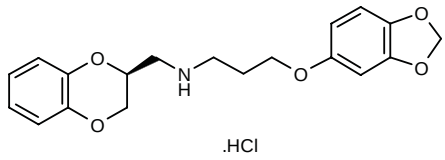
MKC-242
MCI-242

Anxiolytic
Antidepressant
5-HT$_{1A}$ Agonist

EN: 176577



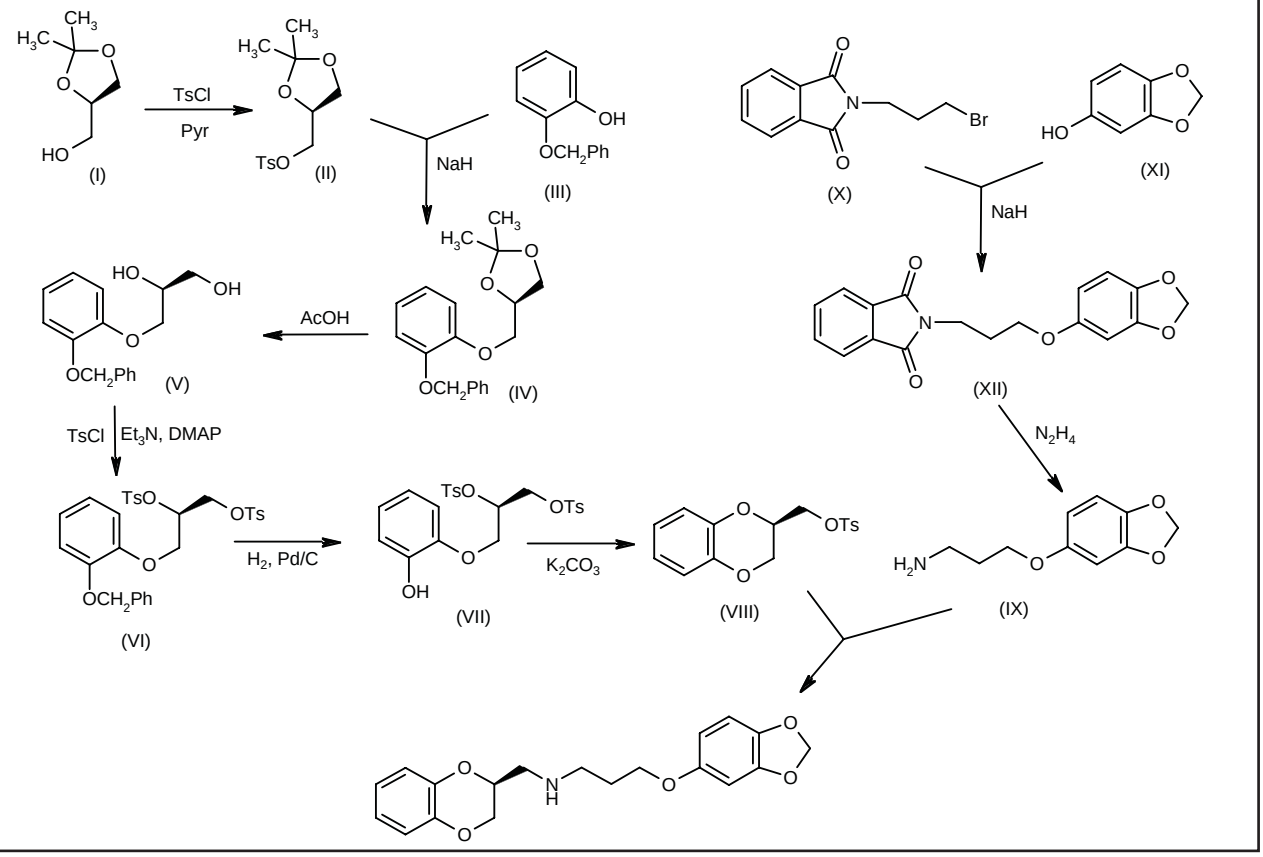
$C_{19}H_{21}NO_5$.HCl

Mitsubishi Chem.; Astra; Hoechst Marion Roussel

A new synthesis of MKC-242 has been described (1): The tosylation of 2, 2-dimethyl-1,3-dioxolane-4(*R*)-methanol (I) with tosyl chloride in pyridine gives the expected tosylate (II), which is condensed with pyrocatechol monobenzyl ether (III) by means of NaH in *N*-methylpyrrolidone (NMP) yielding 4(*S*)-(2-benzyloxyphenoxymethyl)-2,2-dimethyl-1,3-dioxolane (IV). The hydrolysis of the dioxolane ring with hot acetic acid affords the diol (V), which is tosylated with tosyl chloride, triethylamine and dimethylaminopyridine (DMAP) in dichloromethane to give the ditosylate (VI). The debenzyl-ation of (VI) with H_2 over Pd/C in methanol/ethyl acetate yields the phenol (VII), which is cyclized by means of K_2CO_3 in NMP affording 2(*R*)-(tosyloxymethyl)-1,4-benzodioxane (VIII). Finally, this compound is condensed with 3-(1,3-benzodioxol-5-yloxy)propylamine (IX) by means of ethyl diisopropylamine in NMP. The amine (IX) used as second starting compound has been obtained as follows: The condensation of *N*-(3-bromopropyl)phthalimide (X) with 5-hydroxy-1,3-benzodioxole (XI) by means of NaH in hot NMP gives *N*-[3-(1, 3-benzodioxol-5-yloxy)propyl]phthalimide (XII), which is then treated with hydrazine in refluxing methanol to obtain amine (IX). Scheme 2.

Quantitative autoradiographic studies showed that orally administered MKC-242 (0.1-0.5 mg/kg) significantly decreased [^{3}H]-8-OH-DPAT binding in hippocampus and dorsal raphe nucleus sections of rat brain. Binding was not affected in either section after 2 weeks' treatment

Scheme 2: Synthesis of MKC-242



with the drug, suggesting that low-dose MKC-242 passes the blood-brain barrier and binds to 5-HT_{1A} receptors (2).

Results of *in vivo* studies have suggested that systemic injection of MKC-242 (0.5-1.0 mg/kg s.c.) in the rat cerebral cortex facilitates acetylcholine release by activating somadendritic 5-HT_{1A} autoreceptors, and that the mechanism by which the drug affects cholinergic neurons is different from that of 8-OH-DPAT (3).

1. Yamabe, H., Sugano, M., Chaki, H., Abe, M., Tabata, R., Saito, K. *Synthesis and 5-HT_{1A} affinity of an optically active benzodioxane derivative MKC-242; a novel anxiolytic and antidepressant agent.* 214th ACS Natl Meet (Sept 7-11, Las Vegas) 1997, Abst MEDI 019.

2. Asano, S., Matsuda, T., Yoshikawa, T., Somboonthum, P., Tasaki, H., Abe, M., Baba, A. *Interaction of orally administered 5-(3-[((2S)-1, 4-benzodioxan-2-ylmethyl)amino]propoxy)-1,3-benzodioxole (MKC-242) with 5-HT_{1A} receptors in rat brain.* Jpn J Pharmacol 1997, 74(1): 69.

3. Somboonthum, P., Matsuda, T., Asano, S., Sakaue, M., Baba, A. *MKC-242, a novel 5-HT_{1A} receptor agonist, facilitates cortical acetylcholine release by a mechanism different from that of 8-OH-DPAT in awake rats.* Neuropharmacology 1997, 36(11-12): 1733.

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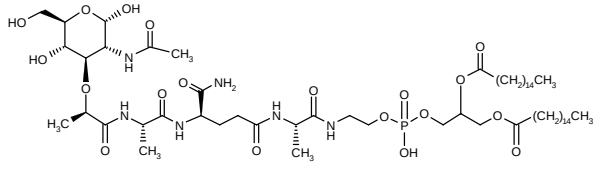
Abe, R., Saito, K. *Effect of MKC-242, a novel 5-HT_{1A} receptor agonist, on restraint-induced stress.* 27th Annu Meet Jpn Soc Neuropsychopharmacol (Oct 21-22, Kagoshima) 1997, Abst P-56.

MTP-PE *Immunostimulant*
CGP-19835A
MLV-19835A
L-MTP-PE
MF-59 (water/oil emulsion)

EN: 108093



$C_{59}H_{109}N_6O_{19}P$ **Novartis; Chiron; Jenner Technologies; NABI**

A recent review of advances in vaccine adjuvants has reported that MF-59 oil-in-water emulsion is potent and safe with several vaccines in human subjects (1).

1. O'Hagan, D.T., Ott, G.S., Van Nest, G. *Recent advances in vaccine adjuvants: The development of MF59 emulsion and polymeric microparticles.* Mol Med Today 1997, 3(2): 69.

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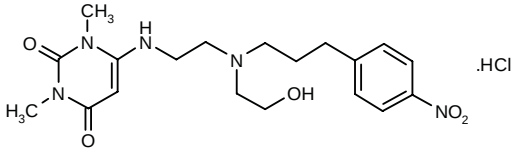
Nifekalant Hydrochloride *Antiarrhythmic*
MS-551 *Potassium Channel Blocker*

EN: 162601



$C_{19}H_{27}N_5O_5.HCl$ **Mitsui Toatsu**

In the coronary artery ligation-reperfusion model in rats, MS-551 (3 and 10 mg/kg), unlike sematilide (10 and 30 mg/kg) and dofetilide (1 mg/kg), prolonged the QT interval and reduced the incidence of sustained ventricular fibrillation after perfusion (1).

Mitsui Pharmaceuticals has submitted MS-551 for an NDA in Japan (2).

1. Chen, J., Komori, S., Li, B., Tamura, K., Hashimoto, K. *IK independent class III actions of MS-551 compared with sematilide and dofetilide during reperfusion in anaesthetized rats.* Brit J Pharmacol 1996, 119(5): 937.

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Sagara, K. et al. *Antifibrillation effect of pure class III antiarrhythmic agent, and mechanism of action.* Jpn Circ J 1997, 61(Suppl. 1): Abst 0415.

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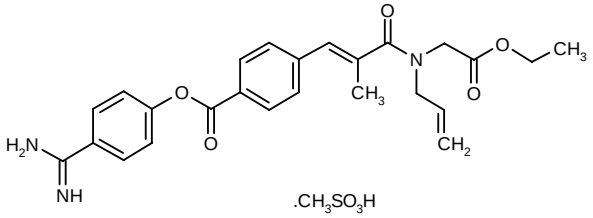
ONO-3403

Protease Inhibitor
Treatment of Pancreas Disorders

EN: 224429



$C_{25}H_{27}N_3O_5.CH_4O_3S$ **Ono**

ONO-3403 was shown to have an inhibitory effect on the proliferation of various cultured human cancer cell lines, with IC_{50}s ranging from 41 ± 18 μg/ml to 71 ± 15 μg/ml (1).

1. Ohgoshi, M., Hiwasa, R., Tsutada, T., Nakagawara, A. *Inhibitory effect of serine protease inhibitor (ONO-3403) on proliferation of cultured human cancer cells.* 2nd Conf Proteases Inhib Pathophysiol Ther (Aug 20-21, Nagoya) 1997, Abst 57.

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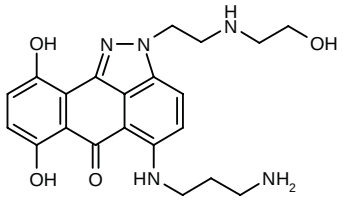
Piroxantrone

Antineoplastic

EN: 116744



$C_{21}H_{25}N_5O_4$ **Parke-Davis; DuPont Merck**

Results of a phase II trial in chemotherapy-naive women with advanced, persistent or recurrent squamous cell carcinoma of the cervix indicated that piroxantrone (160 mg/m^2), administered as a 1-h infusion every 3 weeks, had no beneficial effects. Among the 18 evaluable patients, 6 achieved stable disease and 12 experienced disease progression (1).

1. Lincoln, S., Blessing, J.A., McGehee, R., Lentz, S.S. *Phase II trial of piroxantrone in advanced squamous cell carcinoma of the cervix: A Gynecologic Oncology Group study.* Amer J Clin Oncol Cancer Clin Trials 1997, 20(1): 84.

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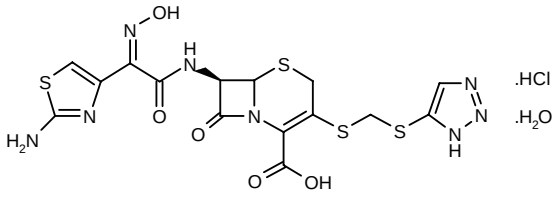
S-1090

Cephalosporin

EN: 189332



$C_{15}H_{14}N_8O_5S_4.HCl.H_2O$ **Shionogi**

Studies in rabbits with experimentally induced mandibular infection showed that drug concentrations of S-1090 (5 mg/kg), measured 12 h after administration, were significantly high in the oral tissues, including the parotid gland and gingiva (1).

1. Satoh, T., Hoshino, H., Yamaguchi, M., Miyasaka, T., Ohmura, M. *Oral tissue transfer of S-1090, a new oral cephalosporin, in rabbit infection models.* Clin Microbiol Infect 1997, 3(Suppl. 2): Abst P394.

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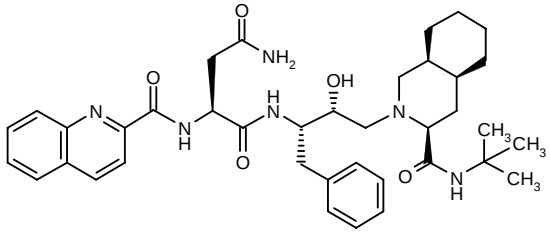
Saquinavir Mesilate *Antiviral for AIDS*
Invirase® *HIV-1 Protease Inhibitor*
Fortovase™ (soft gel capsules)

EN: 168103



$.CH_3SO_3H$

$C_{38}H_{50}N_6O_5.CH_4O_3S$ **Roche**

Results from a randomized, parallel-group, pharmacokinetic trial in 30 healthy volunteers showed that the combination of saquinavir (600 mg t.i.d. group 1 for 21 days; group 2 on days 15-28) and delavirdine (400 mg t.i.d. group 1 on days 8-21; group 2 for 28 days) resulted in saquinavir concentrations approaching those achieved with saquinavir monotherapy (7200 mg/d) (1).

A 3-panel, dose-escalating, placebo-controlled, sequential, pharmacokinetic, 2-period crossover study in 18 healthy subjects showed that the coadministration of saquinavir hard gel (600 mg) or soft gel (800 or 1200 mg) with indinavir (800 mg q8h on days 1-2) caused an approximately 5- to 8-fold increase in the mean AUC and C_{max} of saquinavir (2).

In a 12-week study in 32 HIV-infected patients with CD4 cell counts less than 250, the combination of saquinavir (400 mg b.i.d.) and ritonavir (600 mg b.i.d.) with 2 nucleoside reverse transcriptase inhibitors was shown to be generally safe and effective in reducing viral load by a mean of –2.26 $\log_{10}$ and increasing CD4 cell count by a mean of 72 cells/mm^3 (3).

In an open-label trial in 8 subjects with advanced HIV infection intolerant to the recommended dose of ritonavir (600 mg p.o. b.i.d.) the 4-drug regimen of 2 nucleosides, saquinavir (800 mg p.o. b.i.d.) and ritonavir (400 mg p.o. b.i.d.) was well tolerated and showed reduced plasma HIV RNA levels and an increase in CD4 counts that were sustained for 3 months. The combination was well tolerated, with no significant alterations in laboratory values being observed (4).

The combination of saquinavir plus ritonavir in the treatment of HIV-infected patients with CD4 cell counts of 100-500 resulted in a median decrease in plasma viral load of > 2 $\log_{10}$ at 4 weeks and > 4 $\log_{10}$ at 12 weeks. At 4 weeks, development or improvement in proliferative responses to PHA, p24 Ag and TT were observed in 27/41, 14/41 and 3/8 patients, respectively, demonstrating an immunologic effect which appeared rapidly with the onset of antiviral effects (5).

The regimen of saquinavir alone (600 mg t.i.d. x 7 days), followed by nevirapine alone (200 mg once daily x 14 days, then 200 mg b.i.d. x 14 days) and lastly by the coadministration of saquinavir and nevirapine for the final 7 days was well tolerated in 21 HIV patients and did not produce a clinically significant interaction in the pharmacokinetics of either drug (6).

In 338 HIV-infected patients with $CD4^+$ counts less than 300 cells/mm^3 who had failed or were intolerant to all other antiretroviral agents, no differences in overall antiretroviral effect were noted when saquinavir was administered alone or in combination with one or more nucleosides including d4T, zidovudine and lamivudine (7).

Results from a clinical study involving 3,485 patients from 22 countries indicated that a three-drug therapy comprised of saquinavir mesylate (Invirase) with two nucleoside analogues, ddC (zalcitabine) and AZT (zidovudine), is significantly superior to a standard two-drug regimen in reducing the onset of AIDS. The combination delayed disease progression and prolonged survival in patients without or with limited prior antiretroviral therapy by 50% compared to patients starting therapy with ddC plus AZT alone. Patients who used the triple combination experienced a total of 76 clinical endpoints (first AIDS defining event or death) compared with 142 clinical endpoints in patients receiving ddC and AZT alone. Results from this trial will be submitted to the regulatory authorities in order to update the product labeling for Invirase® (8).

Results of 2 open-label trials in 23 HIV-infected patients, who were protease inhibitor treatment naive, showed that therapy with saquinavir soft gel capsules in combination with AZT/3TC, D4T/3TC or AZT/ddC resulted in a statistically significant reduction in HIV-1 RNA, a progressive increase in percent and absolute number of CD4 T-cells, and a progressive decrease in CD8 T-cells (9).

The safety profile of saquinavir soft gel capsules (1200 mg t.i.d.) in combination with other antiretroviral agents has been demonstrated in a 24-week, multicenter study in HIV-infected patients. Of 444 patients enrolled, 86% completed the study and 14% withdrew because of adverse events or laboratory abnormalities. The major treatment-related adverse events were diarrhea and nausea, and low grade shifts in AST and ALT were the only important laboratory abnormalities reported (10).

Preliminary results from a 24-week, multicenter, open-label study of saquinavir soft gel capsules (1200 mg t.i.d) in combination with AZT (300 mg b.i.d.) and 3TC (150 mg b.i.d.) in 42 HIV-infected patients previously untreated with antiretrovial therapy showed that the regimen was effective in reducing viral load (mean log decrease of 2.17 copies/ml) and increasing CD4 cell count. Treatment was well tolerated and mild adverse events included nausea, headache, dyspepsia, diarrhea, fatigue and loose stool (11).

In an open-label, randomized, crossover study in 14 HIV-infected patients, chronic combination therapy with saquinavir soft gel capsules (800 mg t.i.d.) and nelfinavir

mesylate (750 mg) was shown to provide long-lasting HIV suppression. Treatment was well tolerated and no new protease gene mutations were produced (12).

An open-label, randomized study in 171 treatment-naive HIV-1 patients with ≥ 5000 copies/ml of HIV RNA has evaluated combination therapy consisting of hard gel or soft gel capsule formulations of saquinavir plus 2 nucleoside analogs. Results showed that after 16 weeks of treatment, 43% of the patients treated with saquinavir hard gel capsules (600 mg t.i.d.) had a mean RNA reduction of 1.6 $\log_{10}$ copies/ml, whereas 80% of the patients receiving the soft gel formulation (1200 mg t.i.d.) had a mean RNA reduction of 2.0 $\log_{10}$ copies/ml. The response in patients treated with the soft gel capsules lasted up to 24 weeks (13).

The results of a 20-week, open-label, noncomparative study in 42 antiretroviral-naive HIV-1 patients have shown that combination therapy with saquinavir soft gel capsules (1200 mg t.i.d.), AZT (300 mg b.i.d.) and 3TC (150 mg b.i.d.) was well tolerated and resulted in a mean viral load decrease of 3.34 $\log_{10}$ copies/ml and a mean increase in CD4 count of 259 cells/mm^3. Adverse events were mild and consisted of nausea, headache, dyspepsia, diarrhea and fatigue (14).

The results of a multicenter, open-label, randomized study in 44 evaluable HIV-infected patients demonstrated that the antiretroviral activity of saquinavir soft gel capsules was comparable to that of indinavir when used in triple combination therapy with AZT and 3TC. By week 12, patients in both treatment groups experienced a reduction in HIV RNA of 2.3 $\log_{10}$ copies/ml from baseline, which lasted up to 24 weeks. There was a greater increase in CD4 count from baseline in the saquinavir-treated patients group compared to patients treated with indinavir (124 cells/µl *vs.* 49 cells/µl) (15).

Roche has launched Fortovase™, a new soft gel formulation of the company's protease inhibitor saquinavir mesilate, in the U.S. for the treatment of HIV infection. The drug, approved by the FDA for use in combination with other HIV drugs, is currently under review by regulatory authorities in the European Union and other countries. Fortovase™, administered at the approved dose of 1200 mg 3 times a day with meals, provides an increased drug exposure of 8-10 times compared with Invirase™ (16).

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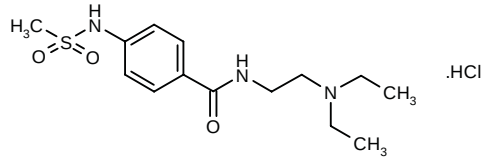
Sematilide Hydrochloride

Antiarrhythmic

EN: 147117



$C_{14}H_{23}N_3O_3S.HCl$ **Berlex; Schering AG; Roussel Morishita**

Sematilide selectively blocked the delayed rectifier current in isolated rabbit ventricular myocytes and enhanced rate dependence of action potential duration *in vivo* in New Zealand white rabbits (1).

In rabbit atrial myocytes, sematilide (10-300 μM) was shown to inhibit the rapidly activating delayed rectifier K^+ current in a concentration-dependent manner (IC_{50} = 25 μM). Application of 100 μM sematilide did not significantly affect the Ca^{2+}-independent transient K^+ and inward rectifier K^+ currents nor the voltage-dependent Na^+ and Ca^{2+} currents, further confirming the selectivity of the compound on membrane currents (2).

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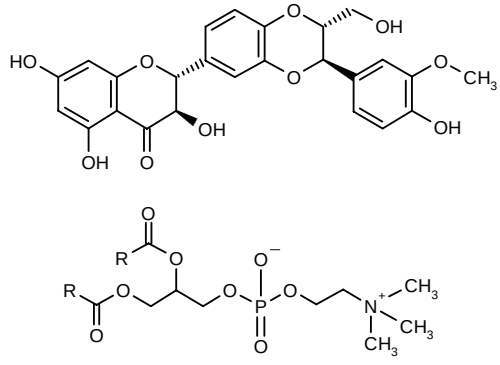
Silipide
IdB-1016

Hepatoprotectant

EN: 158563



For linolenic residues $R=C_{17}H_{31}$

$C_{25}H_{22}O_{10}.C_{44}H_{80}NO_8P$ **Inverni Della Beffa**

A study in rats fed a high cholesterol diet showed that silybin had no effect on total and lipoprotein cholesterol levels, indicating that compounds other than silybin may be responsible for the antihypercholesterolemic effect of silymarin (1).

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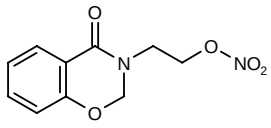
Sinitrodil

Antianginal
Vasodilator

EN: 186706



$C_{10}H_{10}N_2O_5$ **Italfarmaco**

In a randomized, double-blind, placebo-controlled, crossover study in 16 healthy normotensive male subjects, ITF-296 at single oral doses of 10 and 20 mg was found to increase brachial artery compliance without decreasing systemic vascular resistance index. ITF-296, in contrast to isosorbide dinitrate (20 mg), was more selective to large arteries than to resistance vessels and did not cause headache, indicating the drug's usefulness in the treatment of isolated systolic hypertension (1).

In a double-blind, placebo-controlled, crossover study, 16 healthy normotensive male volunteers were randomized to receive ITF-296 (10, 20 and 40 mg), isosorbide dinitrate (20 mg) or placebo. ITF-296 at doses up to 20 mg caused an increase in large artery compliance without decreasing systemic vascular resistance index. Furthermore, headache occurred in 15 subjects receiving isosorbide dinitrate compared to only 1 subject receiving 40 mg ITF-296 (2).

Results of a double-blind, placebo-controlled, parallel-group study in 24 males with chronic stable angina showed that ITF-296 (0.3, 1.0 or 3.0 μg/kg/min i.v.) administered as a 30-min infusion before exercise was effective in increasing exercise time, time to angina threshold and time to 1 mm ST depression, while reducing wall motion abnormality (3).

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3. Khattar, R.S., Senior, R., Sardina, M., Boyce, M., Lahiri, A. *Clinical evaluation of the anti-ischaemic efficacy of ITF-296, a nitric oxide donor, in patients with chronic stable angina.* Circulation 1997, 96(8, Suppl.): Abst 513.

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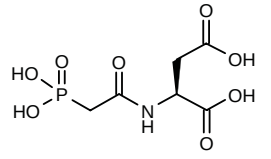
Sparfosic Acid

Antineoplastic
Antiviral

EN: 090055



$C_6H_{10}NO_8P$ **Parke-Davis; US Bioscience**

Results of an 8-week, phase II trial in 23 evaluable patients with advanced gastric adenocarcinoma demonstrated that weekly treatment with low-dose PALA (250 mg/m^2 i.v. bolus) followed 24 h later by a high dose of 5-FU (2600 mg/m^2 i.v. infusion over 24 h) was ineffective at these doses and schedule (1).

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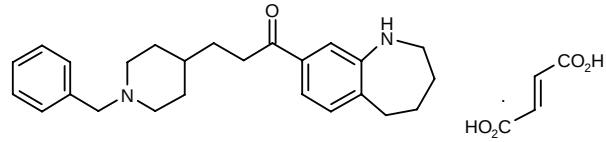
TAK-147

Cognition Enhancer
Acetylcholinesterase Inhibitor

EN: 191111



$C_{25}H_{32}N_2O.C_4H_4O_4$ **Takeda**

In vitro, *in vivo* and *ex vivo* experiments of the effects of TAK-147 in rats showed that the drug inhibited acetylcholinesterase potently and reversibly (IC_{50} = 51.2 nM) in the cerebral cortex, was 2.4 and 3.0 times more potent than physostigmine and tacrine, respectively, did not affect butyrylcholinesterase (BuChE) activity in plasma and accelerated the turnover rates of dopamine, noradrenaline and serotonin at 3 mg/kg p.o. These results suggest that TAK-147 acts by inhibition of AChE without affecting BuChE, and moderately activates the monoaminergic systems, indicating its usefulness in the treatment of Alzheimer's disease (1).

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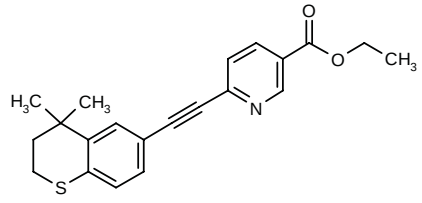
Tazarotene
Tazorac®
Zorac®

Antipsoriatic
Antiacne

EN: 145711



$C_{21}H_{21}NO_2S$ **Allergan**

Hybridization studies showed that tazarotene-induced gene 2 is expressed at high levels in nonlesional psoriatic skin and at lower levels in psoriatic lesions; after topical application of tazarotene to psoriatic lesions, gene expression is upregulated (1).

The downregulating effect of tazarotene on markers of keratinocyte differentiation and proliferation and inflammation associated with psoriasis, as well as its upregulating effect on tazarotene-induced genes 1, 2 and 3, suggest that the drug acts directly on gene expression rather than indirectly on the disease itself (2).

Preclinical safety and tolerability studies have shown topically applied tazarotene (0.05 and 0.1% gel) to be nonmutagenic, noncarcinogenic and nonteratogenic. During clinical trials involving approximately 2000 volunteers with mild to moderate plaque psoriasis, no treatment-related systemic adverse effects were observed for periods of up to 1 year (3).

Analysis of biopsy specimens from 29 patients with psoriasis lesions demonstrated that daily topical application of tazarotene (0.1% gel) reduced interferon inducible protein 10 (IP-10) expression. Additional studies in human foreskin keratinocyte cultures showed that tazarotene blocked induction of IP-10 mRNA by 50% (4).

In a study in 29 patients with stable plaque psoriasis, daily topical application of tazarotene (1.0% gel) for 15 weeks was associated with changes in staining patterns to calgranulin, interferon inducible protein 10, intercellular adhesion molecule, filaggrin and keratin. The results indicate that tazarotene's mechanism of action in psoriasis may be the downregulation of epidermal inflammation, adhesion molecules and differentiation in plaques (5).

Two multicenter, double-blind, randomized trials lasting 6 and 8 weeks were conducted with the objective of establishing the safety and efficacy of topical tazarotene gel in the treatment of mild to moderate plaque psoriasis. Tazarotene was administered twice daily at the concentration of 0.01% or 0.05% (study A), or once or twice daily as 0.05% or 0.1% (study B). Topical application of the 0.01% tazarotene gel did not provide significant benefits as compared to placebo. In contrast, the 0.05% and 0.1% tazarotene gels did provide significant improvements in terms of plaque elevation, scaling, erythema and overall clinical severity, with improvement noted as soon as 1 week after beginning treatment. In study A, success rates were 45% and 13% with 0.05% tazarotene and vehicle, respectively, after 6 weeks of treatment. Success rates at 8 weeks ranged from 48% to 63% with the various treatment regimens in study B. Benefits of topical tazarotene therapy were still evident 8 weeks after stopping treatment in study B. Drug-related adverse effects were mild to moderate, mainly consisted of local irritation and were less frequent using once-daily dosing regimens (6).

A review of controlled clinical trials has demonstrated the efficacy of once-daily topically applied tazarotene (0.05 and 0.1% gel) in improving and reducing the clinical signs and symptoms of plaque psoriasis. Overall, the drug is well tolerated, with adverse events being limited to local irritation (7).

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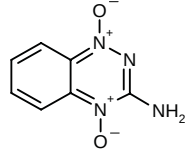

$C_7H_6N_4O_2$

Sanofi Winthrop; SRI Intl.

Isolated nuclei from A549 human lung adenocarcinoma cells treated with tirapazamine (1-50 μM for 1 h) were shown to have ~2.5 times more DNA single strand breaks than whole cells under similar conditions, indicating that the enzymes responsible for the hypoxic toxicity of the drug are located in the nucleus (1).

Studies using a panel of genetically engineered cell lines have indicated that both rapid and delayed apoptosis contribute to the overall cell killing ability of tirapazamine over a range of doses (2).

Baseline fine needle aspirates taken from patients with advanced squamous cell head and neck cancer prior to and after a single infusion of 300 mg/m^2 tirapazamine revealed extensive DNA single strand breakage following drug administration (3).

Results of *in vivo* and *in vitro* studies in mice transplanted with RIF-1 tumors demonstrated that tirapazamine had an additive effect on tumor cell killing when combined with carboplatin, cyclophosphamide, doxorubicin, etoposide and taxol, but not with 5-FU. The enhancement of antitumor activity was greatest with carboplatin (4).

In mice bearing human tumor xenografts, tirapazamine combined with fractionated irradiation produced a greater enhancement of tumor response to fractionated radiation therapy than the combinations of nicotinamide + carbogen or nicotinamide, carbogen and tirapazamine (5).

Results of toxicity studies in mice bearing human melanoma xenografts indicated that combination treatment with tirapazamine and dacarbazine resulted in an approximately 3-fold greater delay in tumor regrowth and a significantly greater cell kill than when either drug was administered alone (6).

A phase I trial has assessed the pharmacokinetics and toxicity of the hypoxic cell radiosensitizer tirapazamine at doses of 36-450 mg/m^2 i.v. every 3 weeks in 28 patients. Ototoxicity was dose-limiting at 450 mg/m^2 and patients who developed ototoxicity usually had higher plasma AUC values for the parent drug and its two major metabolites. The AUC for the two major metabolites showed a greater than dose-proportional increase. No ototoxicity was observed at tirapazamine AUCs of 1252 μg/ml.min or less, and the dose of 330 mg/m^2 was therefore selected for studies in combination with chemotherapy (7).

Results of a phase I study in 22 patients with metastatic tumors of varying histology showed that tirapazamine (220 mg/m^2 i.v. over 2 h) administered 30-90 min prior to radiation treatment did not appear to enhance normal tissue reactions to irradiation except in the esophagus. Because of adverse events such as generalized malaise, fatigue and recurrent nausea, patient acceptance was limited to a maximum of 12 doses over 6 weeks (8).

Results from a phase I trial in 13 previously treated patients with solid tumors showed that the combination of tirapazamine (130-260 mg/m^2 as a 1-h i.v. infusion) administered 3 h prior to cisplatin (75-100 mg/m^2) was well tolerated, with nausea, vomiting, diarrhea, muscle cramping, anorexia and fatigue being the major acute side effects. Two patients experienced a partial response and 1 patient a minor response (9).

An analysis of 5 phase I-II trials in 117 patients has shown that the pharmacokinetics of tirapazamine are predictable over a wide range of doses and schedules, with no evidence of accumulation following multiple dosing. No systematic deviations were observed with regard to age and gender, and interpatient variability was described as moderate (10).

A phase I/II study in 40 patients with untreated advanced head and neck cancer demonstrated that tirapazamine (159 mg/m^2 i.v. 3 times/week for 12 doses) combined with radiotherapy was well tolerated, although it did not appear to enhance the acute effects of radiotherapy. Major acute drug toxicities included muscle cramps, nausea and vomiting, which were manageable with appropriate treatment; 13 and 4 patients, respectively, experienced grade 3 and grade 4 toxicities (11).

In a phase II trial in 18 female patients with advanced non-small cell lung cancer, a 2-h infusion of tirapazamine (390 mg/m^2 i.v.) followed 1 h later by cisplatin (75 mg/m^2) once every 21 days resulted in partial responses in 5 patients, with an objective response rate of 28%. This combination showed promising activity, and toxicity was comparable to that with cisplatin alone (12).

In a phase II trial in patients with advanced head and neck carcinomas, tirapazamine (159 mg/m^2 i.v. 3 times/week for 12 doses) administered concurrently with radiotherapy was well tolerated, with 22/24 patients receiving all 12 doses of the drug. Muscle cramps, nausea and vomiting were the major drug toxicities but could be controlled by medication (13).

In a randomized phase II study, a single administration of tirapazamine (300 mg/m^2 i.v) was shown to induce extensive DNA damage in cells removed from neck nodes of previously untreated head and neck cancer patients (14).

Results of an open-label, multicenter, phase II trial of tirapazamine (159 mg/m^2 i.v. 3 times/week for 12 doses) combined with radiation therapy in 54 evaluable patients with glioblastoma multiforme showed that the treatment was well tolerated. Nine patients experienced grade III acute toxicity and 2 patients experienced grade IV nausea or muscle pain. Overall median survival time was 10.6 months (15).

Combination therapy with tirapazamine (260 mg/m^2 i.v. over 2 h) followed by cisplatin (75 mg/m^2 i.v. over 1 h) every 3 weeks for up to 8 cycles was evaluated in a phase II trial in patients with previously untreated advanced stage non-small cell lung cancer. Of 42 evaluable patients, 10 had an objective response (23.8%). Median survival for all patients was 36.9 weeks with a 1-year survival rate of 30.6%. Mild to moderate toxicities included involuntary muscle contractions, vomiting, fatigue, diarrhea, alopecia and transient hearing loss (16).

In a phase II study in 31 chemotherapy-naive patients with advanced cutaneous melanoma, treatment with an

escalated dose of tirapazamine (390 mg/m^2) plus cisplatin (75 mg/m^2 i.v.) over 1 h every 21 days was associated with a higher incidence of gastrointestinal side effects and fatigue compared to the 260 mg/m^2 dose. Myelosuppression was mild and other toxicities included grade 2 neutropenia, grade 2 thrombocytopenia and grade 3-4 fatigue, nausea, muscle cramps, anorexia, vomiting, diarrhea and constipation (17).

In a phase II trial in 48 patients with metastatic melanoma, combination therapy with tirapazamine (260 mg/m^2 i.v. over 2 h) plus cisplatin (75 mg/m^2 i.v. over 1 h) resulted in 9 responses in chemotherapy-naive patients, with an overall response rate of 19%. There were no responders among the 7 patients with choroidal melanoma nor the 16 patients with previously treated cutaneous melanoma. Neutropenia and thrombocytopenia were rare, and common toxicities included fatigue, muscle cramps, peripheral neuropathy and gastrointestinal side effects (18).

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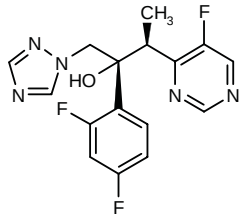

$C_{16}H_{14}F_3N_5O$ **Pfizer**

The *in vitro* antifungal activity of voriconazole has been compared to that of amphotericin B, fluconazole and itraconazole against yeasts and *Aspergillus* spp. Against most of the yeast species tested, voriconazole displayed activity equal to itraconazole, similar to amphotericin B and superior to fluconazole. Its activity against *Aspergillus* spp. was comparable to itraconazole and slightly lower than that of amphotericin B (1).

The *in vitro* activity of voriconazole against 23 species of pathogenic molds was shown to be comparable to or better than that of itraconazole against most of the hyaline and dematiaceous molds tested (2).

Voriconazole exhibited potent activity *in vitro* against clinical isolates of *Aspergillus fumigatus*, *A. flavus* and *A. niger*, with respective MIC_{90}s of 0.25, 0.5 and 0.5 μg/ml. In a rat model of invasive pulmonary aspergillosis, daily oral doses of 30 mg/kg voriconazole were effective in delaying or preventing mortality (3).

Results of *in vitro* studies against clinical and laboratory isolates of *Aspergillus fumigatus* showed no significant difference in activity between voriconazole and itraconazole (ITZ) against ITZ-susceptible strains (mean MICs = 0.83 ± 0.57 and 0.60 ± 0.76 μg/ml, respectively). However, voriconazole had an 8-fold lower mean MIC than itraconazole (1.46 ± 0.59 *vs.* 11.30 ± 4.77 μg/ml) against ITZ-resistant isolates (4).

Results of an *in vitro* macrobroth dilution test of 239 isolates of dimorphic fungi and opportunistic molds and yeasts demonstrated that the MIC values of voriconazole were lower than those for fluconazole, amphotericin B and itraconazole against all of the isolates tested (5).

In vitro, voriconazole was found to be very active (MIC_{90} = ≤ 0.5 μg/ml) against all 400 blood stream isolates of *Candida species* tested. Compared to the other triazole agents evaluated in the study, voriconazole was 2- to 4-fold more active than itraconazole, 16- to 128-fold more active than fluconazole, and 2- to 64-fold more active than amphotericin B and 5-flucytosine (6).

In vitro susceptibility testing has demonstrated good antifungal activity for voriconazole (MIC_{50} and MIC_{90} = 0.5 and 8 μg/ml respectively) against 51 common clinical isolates of filamentous fungi. Voriconazole was generally more active than itraconazole, amphotericin B and 5-flucytosine against the majority of isolates tested (7).

Both voriconazole and itraconazole were shown to be effective in an *in vitro* study against amphotericin B-resistant isolates of *Aspergillus fumigatus*. Both agents had mean MIC values ranging from 0.25 -1 mg/ml, which were 12-fold lower than those for amphotericin B (8).

In *in vitro* studies against *Candida species*, including *C. krusei*, voriconazole exhibited 4- to 16-fold and 2- to 8-fold higher antifungal activity than fluconazole and itraconazole, respectively. Fluconazole- and itraconazole-resistant strains were cross-resistant to voriconazole. Furthermore, when voriconazole and flucytosine were combined, mean fractional inhibitory and lethal concentration indexes were 0.71 and 0.5, respectively (9).

Microdilution testing of 173 pathogenic blood and oral *Candida* isolates showed that voriconazole had potent activity against most isolates, with similar modal and median MIC values at 24 and 48 h. Trailing growth produced higher MICs at 48 h than 24 h for some of the isolates (10).

Voriconazole exhibited potent *in vitro* activity against 33 clinical isolates of *Cryptococcus neoformans*, with no cross-resistance observed between voriconazole and fluconazole, as well as against 40 blood isolates of *Candida* species, including fluconazole-resistant strains (11).

In an *in vitro* study against isolates of *Aspergillus* and *Fusarium*, the respective MICs of voriconazole (measured as the lowest concentration producing 80% reduction in turbidity) were 0.125-2 μg/ml and 0.25-2 μg/ml, and those of amphotericin B (measured as the lowest concentration producing a clear tube) were 0.25-1 μg/ml and 0.5-2 μg/ml, respectively, for *Aspergillus* and *Fusarium* (12).

A study evaluating the *in vitro* activity of antifungal azoles against *Aspergillus fumigatus* isolates from patients and the hospital environment has demonstrated the feasibility and reproducibilty of an agar dilution method for testing voriconazole, amphotericin B and itraconazole. *In vitro* resistance to the three drugs was rare (13).

Voriconazole exhibited greater activity than fluconazole against a wide spectrum of *Candida* species, causing inhibition of cell growth, thinning of cell walls and degradation of cell membrane (14).

Subinhibitory concentrations of voriconazole were shown to completely inhibit ergosterol synthesis of fluconazole-resistant and -susceptible strains of *Candida albicans* and *C. krusei*, whereas fluconazole only partially inhibited ergosterol synthesis. These findings are consistent with the different antifungal potencies of the two compounds (15).

The MICs of voriconazole against 650 clinical isolates of yeasts, molds and dermatophytes were 0.06, 0.74 and 0.10 μg/ml, respectively. Compared to the other drugs tested, voriconazole was more potent than fluconazole against most species, especially molds and dermato-

phytes, had activity comparable to that of amphotericin B against yeasts and molds, and was more active than griseofulvin against the dermatophytes (16).

The *in vitro* activity of voriconazole has been examined against 394 *Candida* clinical isolates and compared to that of fluconazole, itraconazole, amphotericin B and flucytosine. Against all the organisms tested, voriconazole was the most active antifungal agent, giving an MIC_{90} value of 0.5 μg/ml. *Candida albicans* isolates were the most susceptible to voriconazole (MIC_{90} = 0.06 μg/ml) and *Candida glabrata/Candida krusei* the least susceptible (MIC_{90} = 1 μg/ml). Voriconazole was more active than the reference compounds except against *C. glabrata*, flucytosine being the most active. Possible partial cross-resistance with fluconazole and itraconazole was detected; however, the compound has been reported to have good efficacy in guinea pig models of systemic candidiasis caused by azole-resistant strains of *C. albicans*, as well as in clinical trials in patients with fluconazole-resistant oropharyngeal candidiasis (17).

In a neutropenic guinea pig model of *Candida krusei* infection, voriconazole (5 and 10 mg/kg b.i.d. p.o.) was found to be significantly more effective than amphotericin B (1 mg/kg i.p. on alternate days) or fluconazole (20 mg/kg b.i.d. p.o.) in eradicating fungi from the brain, liver and kidney (18).

In a guinea pig model of disseminated invasive aspergillosis, voriconazole (10 mg/kg p.o. b.i.d.) produced more negative cultures than amphotericin B (1.25 mg/kg i.p. once daily), and compared to controls, improved survival by significantly reducing tissue burden in lung, liver, kidney and brain (19).

A multicenter open trial has evaluated the efficacy of voriconazole (initially 3-6 mg/kg i.v. every 12 h followed by 200 mg b.i.d. p.o. for up to 24 weeks) as primary or salvage therapy in immunocompromised patients with invasive aspergillosis. Given the high mortality rate associated with such infections, the complete and partial response rates (17% and 36%, respectively) indicate that further evaluation of the compound is warranted (20).

The successful treatment of a child with chronic granulomatous disease and disseminated *Aspergillus nidulans* infection unresponsive to other therapies, including amphotericin B + itraconazole, with voriconazole has been reported. A dose of 10 mg/kg/day i.v. was associated with disappearance of fever and gradual improvement in radiological lesions. After 4 weeks, oral therapy was instituted and the child was eventually discharged in good condition (21).

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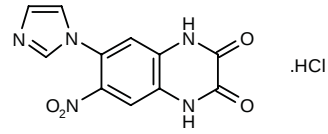

.HCl

$C_{11}H_7N_5O_4$.HCl **Yamanouchi**

YM-90K reduced infarct volume in a stroke model of photothrombotic distal middle cerebral artery occlusion in rats. At a dose of 5 mg/kg/h i.v. for 1 h starting 5 min after occlusion, infarct volume was reduced by 34% compared to vehicle. No significant effect on cerebral blood flow was observed (1).

Results of experimental studies using the rat kindling model of epilepsy demonstrated that pretreatment with YM-90K (7.5, 15 and 30 mg/kg i.p.) 30 min before electrical stimulation dose-dependently delayed the onset of kindling, and in fully-kindled rats, significantly and dose-dependently suppressed seizures (2).

YM90K has been shown to reduce infarct volume in spontaneously hypertensive rats subjected to thrombotic distal middle cerebral artery occlusion. These results indicate the potential of AMPA receptor blockade using compounds such as YM90K in the treatment of acute ischemic stroke (3).

In a rat model of focal cerebral ischemia, a 4-h continuous infusion of YM90K (10 and 20 mg/kg/h) begun immediately after middle cerebral artery occlusion resulted in a dose-dependent reduction in infarct size at 24 h which lasted up to 72 h postocclusion (4).

In gerbils submitted to transient unilateral forebrain ischemia, YM-90K (20 or 25 mg/kg i.p.) administered at 60, 75 and 90 min after reperfusion had a significant neuroprotective effect against neuronal death, as shown by

higher levels of *N*-acetylaspartate in the hippocampal CA1 region in YM-90K-treated animals compared to saline-treated controls (5).

In experimental models of transient global ischemia, YM-90K (15 or 30 mg/kg i.p. x 3) administered 1 h postischemia in gerbils significantly reduced delayed neuronal death up to 4 days after occlusion, and when administered 60 min after reperfusion in rats, markedly prevented the development of delayed neuronal death up to 7 days after occlusion (6).

In studies in healthy male volunteers, single (up to 36 mg i.v.) and multiple (24 mg i.v.) doses of YM-90K administered as a 3-h infusion were shown to be well tolerated, causing only mild changes in kidney function markers. Steady-state plasma drug concentrations were reached during the 3-h infusion and rapidly decreased thereafter. The drug demonstrated linear pharmacokinetics, with no significant differences observed between the first and fifth dose in the repeated-dose study. No significant adverse events or abnormal laboratory and physical findings were reported, indicating the drug's good safety profile (7).

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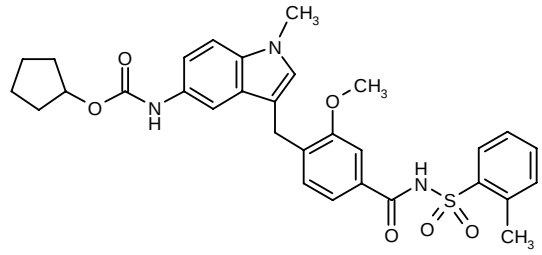

$C_{31}H_{33}N_3O_6S$ **Zeneca**

A randomized, placebo-controlled study in 16 healthy men demonstrated that coadministration of zafirlukast (80 mg p.o. b.i.d. x 10 days) with a single oral dose of warfarin (25 mg on day 5) caused a significant decrease in the clearance of (*S*)-warfarin but had no effect on (*R*)-warfarin. Changes in unbound fraction in plasma of both warfarin enantiomers were clinically nonsignificant (1).

A pharmacokinetic study in 16 healthy male volunteers showed that coadministration of zafirlukast (160 mg p.o. b.i.d.) and terfenadine (60 mg p.o. b.i.d.) resulted in a significant decrease in the C_{max} and $AUC_{(0\text{-}12)}$ of zafirlukast, while terfenadine and terfenadine carboxylate pharmacokinetics were not affected (2).

An open-label, steady-state trial in 8 healthy men showed that coadministration of zafirlukast (160 mg p.o. b.i.d. on days 8-16) with terfenadine (60 mg p.o. b.i.d. on days 1-16) did not produce significant increases in the QTc interval or AUC of terfenadine or its active metabolite terfenadine carboxylate (3).

In a randomized, double-blind, crossover study in 16 healthy males, coadministration of single-dose warfarin (25 mg) with steady-state zafirlukast (80 mg b.i.d.) resulted in a significant increase in AUC of warfarin and a significant increase in prothrombin time enhancement compared to warfarin plus placebo. These results indicate that precaution is necessary when coadministering warfarin with zafirlukast (4).

In a double-blind, randomized, crossover trial in 19 patients with mild asthma, zafirlukast (160 mg b.i.d.), compared with placebo, caused significant reductions in basophils, eosinophils and spontaneous superoxide release from alveolar macrophages 48 h after segmental allergen challenge, demonstrating that the drug not only has antiinflammatory activity but also inhibits eosinophil influx (5).

A single oral dose of zafirlukast (20 mg), but not placebo, was shown to reduce the hyperresponsiveness to an ultrasonic nebulized distilled water (UNDW) challenge in 6 mild drug-naive nonsmoker asthmatics, indicating the role of cysteinyl-leukotrienes in priming the response to UNDW (6).

Data from 62 placebo-controlled trials evaluating various doses and treatment durations of zafirlukast (0.4-160 mg/day p.o. for up to 20 weeks) confirmed the drug's favorable safety profile for use in mild to moderate asthma. The incidence of serious adverse events across all trials was similar in both drug- and placebo-treated groups (1.3% *vs.* 1.1%) (7).

A 2-week, randomized, placebo-controlled study in 198 patients with symptomatic asthma showed that treatment with zafirlukast (20 or 160 mg b.i.d.) improved morning peak flow after 1 week, which was maintained at 2 weeks. Clinic peak flow was also improved within 2 h after the first dose of zafirlukast, demonstrating the drug's early onset of action. There were no differences between either dose of the drug and placebo in regard to adverse events, ECGs or laboratory tests (8).

Results from three 13-week, double-blind, randomized, multicenter trials involving more than 1000 patients with mild to moderate asthma suggested that the efficacy of zafirlukast (20 mg b.i.d.) was similar regardless of age, gender, race and baseline asthma characteristics (9).

In a 13-week, multicenter, double-blind, randomized, placebo-controlled trial in 454 asthmatic patients with moderate airflow obstruction, twice-daily treatment with 20 mg zafirlukast was shown to improve daytime symptom scores, nighttime awakenings, β_2-agonist use and morning PEFR. The drug was well tolerated, with no observed differences from placebo in the frequency of adverse events (10).

A 12-week, double-blind, randomized, placebo-controlled study of zafirlukast administered as a single oral dose (20 mg) in 9 patients with moderate asthma showed that the drug significantly reduced the amount of beclomethasone required by patients in a time-dependent manner. Although there were no significant changes in FEV_1, the use of short-acting β_2-agonists and the frequency of asthma-related night awakings were decreased (11).

Results of a 2-week, randomized, double-blind, placebo-controlled, crossover trial in 18 adolescent patients with asthma demonstrated that treatment with zafirlukast (20 and 80 mg b.i.d.) significantly reduced the severity of exercise-induced bronchoconstriction measured at 4 and 8 h postdose, whereas sodium cromoglycate treatment (10 mg q.i.d.) did not (12, 13).

Results of a randomized, double-blind, placebo-controlled trial in 146 patients with mild to moderate asthma showed that treatment with zafirlukast (20 mg b.i.d.) added to inhaled β-agonists was more effective than β-agonists alone in reducing the number of asthma attacks, days absent from school or work, health care contacts and use of β-agonists (14).

In a double-blind, placebo-controlled trial in 39 adolescent asthmatics, a single dose of zafirlukast (5, 10, 20 or 40 mg) administered 4 h prior to exercise challenge was found to significantly reduce exercise-induced bronchoconstriction. All doses of the drug were well tolerated, and safety assessments did not differ between placebo and zafirlukast groups (15).

In a randomized, double-blind, placebo-controlled trial in 24 nonsmoking asthma patients, zafirlukast (20 or 80 mg b.i.d. for 2 weeks), administered in addition to usual therapy, provided a significant level of protection against exercise-induced asthma which lasted up to 8 h postdose. Adverse events were similar for placebo and both zafirlukast dose groups (16).

In a randomized, placebo-controlled, crossover study in 19 patients with stable asthma, a single dose of zafirlukast (20 or 80 mg b.i.d. x 4 days) was found to exert significant protection against cold air-induced bronchoconstriction. The effect was dose-dependent and lasted for up to 12 h with the 80-mg dose (17).

Results of a 6-week, double-blind, randomized study in 481 patients with mild to moderate asthma demonstrated that oral zafirlukast (20 and 80 mg b.i.d.) produced a comparable response in most patients to that of inhaled beclomethasone dipropionate (200-250 μg b.i.d.). Response rates were 30%, 41% and 47%, respectively, for 20 mg and 80 mg zafirlukast and beclomethasone. Tolerance, asthma-related events and adverse events were similar in all treatment groups (18).

A randomized, placebo-controlled study in 368 symptomatic asthma patients being treated with high doses of inhaled corticosteroids showed that 6 weeks of treatment with oral zafirlukast (80 mg b.i.d.) significantly improved morning peak flow rate from baseline and had beneficial effects on other measures of lung function and asthma symptoms. Treatment was well tolerated and no differences in adverse events between zafirlukast and placebo groups were observed (19).

In a double-blind, crossover trial in 6 asthmatic patients on inhaled corticosteroid therapy, pretreatment with a single dose of zafirlukast (20 mg) was effective in inhibiting leukotriene D_4-induced bronchoconstriction. After zafirlukast, $PC_{20}FEV_1$ and $PD_{20}FEV_1$ were increased 66-fold and 75-fold, respectively, compared with placebo (20).

A 4-week, open, crossover study comparing oral zafirlukast (20 mg b.i.d.) with inhaled beclomethasone (200 or 250 μg b.i.d.) in 152 evaluable stable asthmatics showed overall patient preference for zafirlukast (55% *vs.* 27%). Patients also found zafirlukast easier to administer and had fewer dislikes with the drug than with beclomethasone (21).

Results of a 13-week, randomized, double-blind, parallel-group trial in 454 asthmatic patients with moderate airflow obstruction demonstrated that zafirlukast (20 mg p.o. b.i.d.) was more effective than placebo in providing clinically meaningful improvements in daytime symptoms, nighttime awakenings, morning peak flow rate and β_2-agonist use. The drug was well tolerated, and no differ-

ences in adverse events or results of laboratory tests were noted between treatment groups (22).

Results of a 13-week, multicenter, randomized, double-blind, placebo-controlled study in 762 patients with mild to moderate asthma showed that zafirlukast (20 mg b.i.d) administered as maintenance therapy produced early and sustained decreases in daytime asthma symptom scores, nighttime awakenings, mornings with asthma and β-agonist use. The drug was well tolerated and type and frequency of adverse events were similar in both drug- and placebo-treated groups (23).

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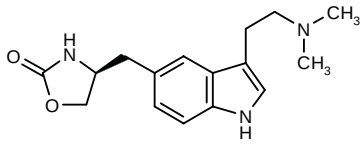

$C_{16}H_{21}N_3O_2$ **Zeneca**

A study of the receptor specificity and trigemino-vascular inhibitory actions of zolmitriptan showed that the drug is a potent partial agonist at the 5-HT_{1B}-like receptor that mediates vascular contraction ($p[A_{50}] = 6.79 \pm 0.06$) in rabbit saphenous vein. The drug produced concentration-dependent contractions of primate basilar artery (p[A50] = 6.92 ± 0.07) and human coronary artery rings (p[A50] = 7.3 ± 0.1), displayed high affinity at human recombinant 5-HT_{1D} ($pIC_{50} = 9.16 \pm 0.12$) and 5-HT_{1B} ($pIC_{50} = 8.32 \pm 0.09$) receptors, and caused a dose-dependent (3-30 µg/kg i.v.) inhibition of [^{125}I]-albumin extravasation within the ipsilateral dura mater of anesthetized guinea pigs. The results show that the drug exhibits a high degree of pharmacological specificity which is equal to or more potent than sumatriptan (1).

Results of studies in anesthetized cats and guinea pigs have suggested that the antimigraine mechanism of action of zolmitriptan may be related to its ability to inhibit central and peripheral components of the trigemino-vascular system (2).

Results of a randomized, open-label, crossover, pharmacokinetics study of zolmitriptan (3.5 mg i.v. or 10 mg p.o. or 25 mg [^{14}C]-labeled p.o.) in 18 healthy volunteers determined that the drug undergoes first-pass metabolism, which is more extensive in men than women, and the drug has bioavailability suitable for use as an antimigraine agent (3).

A randomized, placebo-controlled, crossover study in 12 healthy volunteers showed that multiple doses of zolmitriptan (5 or 10 mg x 5 over 24 h) were as well tolerated as single doses (10 mg), with no significant differences in blood pressure after the first and last doses of the multiple dose regimen. The only significant changes in pharmacokinetic parameters after 10 mg compared with 5 mg, and after the last dose compared to the first dose was an expected rise in peak plasma concentration and slight increase in renal clearance (4).

The cardiovascular effects of zolmitriptan (20 mg p.o.) administered alone or in combination with ergotamine (2 mg p.o.) were evaluated in a randomized, double-blind, placebo-controlled study in 12 healthy volunteers. No significant changes in cardiac output, stroke volume, heart rate or ECG were recorded, although both compounds produced a small degree of peripheral vasoconstriction which was not clinically important. Zolmitriptan at doses up to 8 times the therapeutic dose were generally well tolerated when administered alone and in combination with ergotamine (5).

Results from a double-blind, randomized, crossover study in 12 healthy volunteers showed that dihydroergotamine (5 mg p.o. b.i.d. for 10 days) administered concomitantly with zolmitriptan (10 mg p.o.) produced no significant effects on the pharmacokinetic parameters of zolmitriptan, indicating that no special precautions are needed when the two drugs are used together (6).

In a double-blind, randomized, two-period, crossover study in 13 healthy volunteers, oral pizotifen (1.5 mg) administered once daily for 8 days did not significantly affect the pharmacokinetics of oral zolmitriptan (10 mg p.o.). Tolerance to zolmitriptan was equally good when the drug was administered alone or in combination with pizotifen, indicating that no dose adjustments are necessary when the drugs are administered concomitantly (7).

Results from a double-blind, randomized, crossover study in 12 healthy volunteers administered a single dose of zolmitriptan (10 mg) indicated that pretreatment with propranolol (160 mg/day x 7 days) caused inhibition of

biotransformation of zolmitriptan but had no effect on the small pressor response (8).

In two multicenter, double-blind, randomized, placebo-controlled trials in outpatients, significant migraine relief was observed within 1 h in 40% and 44% of patients treated with 2.5 and 5 mg zolmitriptan, respectively, *versus* 26% of those treated with placebo; the response rate increased at 2 (64% and 67%, respectively, *vs.* 35%) and 4 h (73% and 77%, respectively, *vs.* 34%). Furthermore, significantly fewer patients treated with zolmitriptan required rescue medication. Thus, zolmitriptan is an effective antimigraine agent with a rapid onset of action (9).

In a multicenter, double-blind, placebo-controlled trial in 1,258 patients with migraine, 33%, 45%, 52% and 59% of patients treated with zolmitriptan at doses of 1, 2.5, 5 and 10 mg, respectively, were pain-free at 4 h compared to 11% on placebo. In a similar study in 327 patients, 38% of those treated with zolmitriptan 2.5 mg were pain-free at 4 h compared to 13% on placebo. Zolmitriptan was also associated with significant subjective meaningful migraine relief and impact on normal activities compared to placebo in these studies (10).

A multicenter, double-blind study in outpatients with migraine randomized to either 2.5 mg oral zolmitriptan (n = 200) or placebo (n = 101) showed that headache response was significantly greater with zolmitriptan than with placebo at 2 and 4 h postdose (62% *vs.* 36% and 70% *vs.* 37% at 2 and 4 h, respectively). The most common adverse events were nausea, dizziness, paresthesia, chest tightness and somnolence, but were of mild to moderate intensity. No clinically relevant cardiovascular or laboratory changes were observed (11).

Five clinical studies of varying design have assessed the safety and efficacy of zolmitriptan (1-25 mg) in more than 4000 patients with single or multiple migraine attacks. Overall results have shown that the drug's efficacy and tolerability are optimal at doses of 2.5 and 5 mg. In dose-ranging studies, 60-70% of patients reported reduction in headache pain as early as 1 h postdose and more than 40% of patients were completely pain free at 4 h postdose. Adverse events were dose-related, transient and usually mild to moderate across all studies. No clinically significant effects on laboratory or hemodynamic parameters were reported (12).

Results of a long-term study in >300 patients with migraine have demonstrated that treatment with zolmitriptan (5 mg) produces a consistently high headache response for initial attacks as well as for recurrent headaches. 91% of the patients treating more than 30 attacks reported some improvement and no change in the magnitude of headache relief across the attacks (13).

In two multicenter, randomized, double-blind, placebo-controlled trials in patients with migraine, zolmitriptan (2.5 mg) was shown to be as effective for migraine on awakening (2-h response rates of 62 and 65%) as for migraine developing during waking hours (2-h response rates of 70% and 59%) (14).

In a multicenter, double-blind, placebo-controlled, dose-finding study of oral zolmitriptan (1, 2.5, 5 or 10 mg) in 999 evaluable patients with severe or moderate migraine headaches, headache response rates with doses ≥ 2.5 mg at 1, 2 and 4 h were 44-51%, 65-67% and 75-78%, respectively, suggesting that the optimal initial dose for the acute treatment of migraine attacks is 2.5 mg (15).

Results of a randomized, double-blind, placebo-controlled trial in 327 patients with moderate or severe migraine attacks demonstrated good tolerance and clinical efficacy of zolmitriptan 2.5 mg. Headache responses at 2 and 4 h were 62 and 70% for zolmitriptan, compared to 36 and 37% for placebo (16).

In a study comparing the pharmacokinetics of single-dose zolmitriptan (10 mg) in 15 patients with moderate or severe renal failure not requiring dialysis with an age-and sex-matched group of healthy controls, only minimal changes to the pharmacokinetics were observed in renally impaired subjects. Adverse events were similar for both groups and consisted of dry mouth, nausea, headache and vertigo. The results indicate that dose adjustment of zolmitriptan is not necessary in patients with renal impairment (17).

Zeneca has launched zolmitriptan (Zomig®) in the U.K. for the treatment of acute migraine and is supplied as tablets, 2.5 mg. The drug, administered by a simple oral dosing regimen, has demonstrated consistent efficacy and rapid relief of symptoms within 1 h of dosing (18, 19).

The Medical Products Agency in Sweden cleared Zeneca's zolmitriptan (Zomig®) for marketing for the treatment of acute migraine (20).

Zeneca has introduced zolmitriptan (AscoTop®) in Germany for use in the treatment of migraine with or without aura. It is supplied as tablets of 2.5 mg (21).

The FDA has cleared zolmitriptan (Zomig®) for the treatment of acute migraine with or without aura in adults (22).

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