Drugs of the Future 1998, 23(4): 437-472

CCC: 0377-8282/98

Information Update

Volume 1-22, Number 4

Estimated developmental phase for this month's updated products:

Phase I

Methosorbinil (symptomatic antidiabetic, aldose reductase inhibitor; Eisai)
Titanocene dichloride (antineoplastic, titanocene complex; Inst. Anorg. Analyt. Chem., Medac)

Phase II

Acetyl-11-keto-β-boswellic acid (antiarthritic; Reg. Res. Lab. Jammu-Tawi)
Arteflene (antimalarial; Roche)
Boswellic acids (antiinflammatory; Reg. Res. Lab. Jammu-Tawi)
Curcumin (antiinflammatory, antineoplastic; Central Drug Res. Inst. Lucknow)
E-6123 (antiallergic/antiasthmatic, PAF antagonist; Eisai)
Examorelin (growth hormone secretagogue; Europeptides)
GEM-91 (anti-HIV; Hybridon)
Lifibrol (hypolipidemic; Klinge Pharma, Merckle)
Lobucavir (antiviral; Bristol-Myers Squibb)
LY-303366 (antifungal; Lilly)
S-4661 (carbapenem; Shionogi)

Phase III

141W94 (anti-HIV, HIV-1 protease inhibitor; Vertex, Glaxo Wellcome, Kissei)
AD-32 (antineoplastic antibiotic; Pharmacia & Upjohn, Anthra, Medeva, Nycomed)
Amiprilose (antiarthritic, immunosuppressant; Boston Life Sciences, Kissei)
Capecitabine (antineoplastic; Roche)
Cefoselis sulfate (cephalosporin; Fujisawa, Johnson & Johnson)
Edelfosine (antineoplastic; Max Planck)
Exemestane (antineoplastic, aromatase inhibitor; Pharmacia & Upjohn)
Ipidacrine hydrochloride hydrate (cognition enhancer, acetylcholinesterase inhibitor; Naucho-Issledovatelsky Inst., Nikken Chem.)
Lomerizine hydrochloride (antimigraine, calcium channel blocker; Kanebo, Pharmacia & Upjohn)
Monatepil maleate (antihypertensive, calcium channel blocker; Dainippon)
Perflenapent emulsion (ultrasound contrast medium; Sonus)
Pimilprost (treatment of peripheral vascular disease; Sumitomo)
Ritipenem acoxil (penem; Pharmacia & Upjohn, Tanabe Seiyaku)
RS-2131 (antiinflammatory; Sankyo)
T-588 (cognition enhancer; Toyama)
Zanamivir (antiviral; Biota Holdings, Glaxo Wellcome)

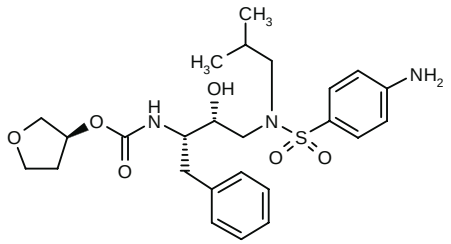
Launched/Year

Budesonide (intestinal antiinflammatory; Astra Pharma)/1981
Butenafine hydrochloride (antifungal; Kaken, Penederm, Schering-Plough)/1992
Famciclovir (antiviral; SmithKline Beecham)/1994
Grepafloxacin hydrochloride (fluoroquinolone antibacterial; Otsuka, Glaxo Wellcome)/1997
Incadronic acid (bone resorption inhibitor, treatment of osteoporosis; Yamanouchi)/1997
Itraconazole (antifungal; Janssen, Kyowa Hakko)/1988
Lamivudine (anti-HIV, reverse transcriptase inhibitor; BioChem Pharma, Glaxo Wellcome, Vion)/1995
Letrozole (antineoplastic, aromatase inhibitor; Novartis, Chugai)/1996
Losartan potassium (antihypertensive, angiotensin II blocker; DuPont Merck Pharm., Merck & Co., Banyu)/1994
Mexiletine hydrochloride (antiarrhythmic, symptomatic antidiabetic; Boehringer Ingelheim)/1996
Mycophenolate mofetil (immunosuppressant; Roche Bioscience)/1995
Nelfinavir (antiviral for AIDS, HIV-1 protease inhibitor; Agouron, Japan Tobacco, Roche)/1997
Penciclovir (antiviral; SmithKline Beecham)/1996
Pramipexole hydrochloride (antiparkinsonian, antipsychotic, antidepressant; Boehringer Ingelheim, Pharmacia & Upjohn)/1997
Pranlukast hydrate (antiallergic/antiasthmatic, leukotriene D_4 antagonist; Ono, SmithKline Beecham)/1995
Raltitrexed (antineoplastic, thymidylate synthetase inhibitor; British Technol. Groups, Ben Venue Labs., Zeneca)/1996
Rifaximin (antibiotic; Alfa Wassermann, Merckle, Salix, Solochem)/1987
Topiramate (anticonvulsant; Janssen-Cilag, Kyowa Hakko)/1995

141W94
VX-478
KVX-478
Amprenavir

Anti-HIV
HIV-1 Protease Inhibitor

EN: 205414



$C_{25}H_{35}N_3O_6S$ **Vertex; Glaxo Wellcome; Kissei**

An open-label, balanced, multiple-dose, three-period study conducted on 24 healthy male volunteers, examining the interactions between 141W94 (1200 mg q12h), rifabutin (300 mg/day) and rifampin (600 mg/day) showed that 141W94 increased the C_{min} for rifampin 3- to 6-fold, rifabutin reduced the C_{max}, AUC and C_{min} for 141W94 by 5, 14 and 10%, respectively, while rifampin reduced them by 67, 81 and 91%, respectively. Results suggest that rifabutin dosage should be lowered when given with 141W94 and rifampin should not be used with 141W94 (1).

The effect of efavirenz (600 mg/day) on 141W94 (1200 mg b.i.d.) in combination with 2 nucleoside analogs was studied in 6 HIV-infected patients. Addition of efavirenz decreased mean AUC_{ss} (36%), C_{max} (39%) and C_{min} (43%) as measured by HPLC. Clinical effects of this decrease are not known (2).

Combination therapy of 141W94 (800 mg t.i.d.) with other protease inhibitors (one of either saquinavir 800 mg t.i.d., indinavir 800 mg t.i.d., or nelfinavir 750 mg t.i.d.) or used alone for 3 weeks followed by zidovudine 300 mg b.i.d. and 3TC 150 mg b.i.d. is being studied in HIV-infected patients with no previous protease inhibitor therapy. Preliminary results on 27 patients revealed that the viral load for 13 of 16 patients reaching week 4 had decreased to < 400 copies/ml from > 10,000 copies/ml. Diarrhea, perioral tingling/numbness, nausea, rash, headache and flatulence were the most common side effects (3).

A randomized, double-blind, multicenter trial in 92 HIV-positive patients followed with real-time RNA monitoring showed that 141W94 alone led to high rates of virologic failure after 12 weeks, while combination therapy with 141W94, 3TC and zidovudine was much more effective (4).

Vertex has reported preliminary results from a phase II study of VX-478/141W94 in combination with Retrovir® (AZT) and Epivir® (3TC) which indicated that the drug combination produced potent antiviral activity and was generally well tolerated (5).

Vertex and Glaxo Wellcome have initiated a phase III trial to evaluate the second-generation HIV protease inhibitor 141W94, also under development by Kissei, in combination with nucleoside reverse transcriptase inhibitor therapy in HIV-infected children (6).

Vertex and Glaxo Wellcome have announced the initiation of a third pivotal phase III clinical trial evaluating the second-generation HIV protease inhibitor VX-478 in combination with a nucleoside reverse transcriptase inhibitor (7).

1. Polk, R.E., Israel, D.S., Patron, R., Sadler, B.M., Chittick, G.E., Symonds, W.T:, Brophy, D., Kristoff, D., Lou, Y., Bye, A. *Pharmacokinetic (PK) interaction between 141W94 and rifabutin (RFB) and rifampin (RFP) after multiple-dose administration.* 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 340.

2. Piscitelli, S., Vogel, S., Sadler, B., Fiske, W., Metcalf, J., Masur, H., Falloon, J. *Effect of efavirenz (DMP 266) on the pharmacokinetics of 141W94 in HIV-infected patients.* 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 346.

3. Eron, J., Haubrich, R., Richman, D., Lang, W., Tisdale, M., Myers, R., Pagano, G. *Preliminary assessment of 141W94 in combination with other protease inhibitors.* 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 6.

4. Murphy, R., Degruttola, V., Gulick, R., D'Aquila, R., Eron, J., Sommadossi, J.P., Smeaton, L., Currier, J., Tung, R., Kuritzkes, D. *141W94 with or without zidovudine/3TC in patients with no prior protease inhibitor or 3TC therapy-ACTG 347.* 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 512.

5. *Promising preliminary phase II data reported for VX-478/141W91.* Prous Science Daily Essentials October 20, 1997.

6. *HIV protease inhibitor enters phase III pediatric trial.* Prous Science Daily Essentials July 15,1997.

7. *Third pivotal trial of VX-478 commences.* Prous Science Daily Essentials October 1, 1997.

Original monograph - Drugs Fut 1996, 21: 347.

Additional References

Ferry Fugett, M.J. *Preparation of (2S, 3S)-N-protected-3-amino-1,2-epoxy-4-phenylbutane - A key intermediate in hydroxyethylamine-based HIV protease inhibitor 141W94.* 213th ACS Natl Meet (April 13-17, San Francisco) 1997, Abst ORGN 456.

Yanagi, T. et al. *Synthesis of the HIV protease inhibitor KVX-478 (1).* 117th Annu Meet Pharm Soc Jpn (March 26-28,Tokyo) 1997, Abst 27(P1) 13-10.

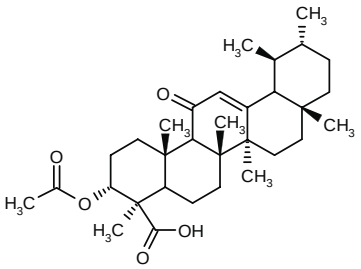
Yanagi, T. et al. *Synthesis of the HIV protease inhibitor KVX-478 (2).* 117th Annu Meet Pharm Soc Jpn (March 26-28,Tokyo) 1997, Abst 28(A3) 11-3.

Polk, R.E. et al. *Effects of ketoconazole (KCZ) and 141W94 on P450 (CYP)3A4 activity measured by the erythromycin breath test (ERMBT).* 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 341.

De Pasquale, M.P. et al. *Mutations selected in HIV plasma RNA during 141W94 therapy.* 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 406a.

Acetyl-11-Keto-β-Boswellic Acid *Antiarthritic*

EN: 150518



$C_{32}H_{48}O_5$ **Reg. Res. Lab. Jammu-Tawi (IN)**

A study of the effect of acetyl-11-keto-β-boswellic acid (AKBA) on HL-60 and CCRF-CEM cells showed that cell counts and [^{3}H]-thymidine incorporation were markedly decreased in a dose-dependent fashion compared to controls. Morphological changes were seen with AKBA treatment, as well as an additive effect with CD-95 receptor cross-linking. AKBA was also shown to inhibit topoisomerase in calf thymus *in vitro*, suggesting that it induces apoptosis through topoisomerase inhibition (1).

Inhibition of SK-MEL 28 human metastatic malignant melanoma cell line growth by acetyl-11-keto-β-boswellic acid (AKBA) and betulinic acid (BA) was examined in concentrations of 3-30 μM. Dose-dependent inhibition was seen with AKBA (93% at 30 μM), while BA showed only moderate inhibition (25% at various concentrations) (2).

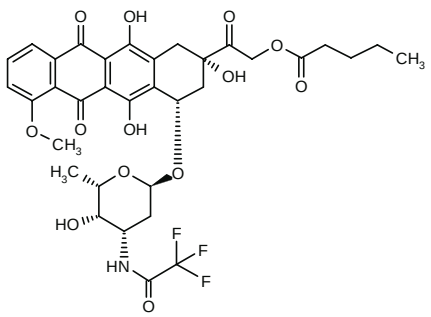
1. Hoernlein, R.F., Orlikowsky, T., Zehrer, C., Niethammer,D., Sailer, E.R., Dannecker, G.E., Ammon, H.P.T. *Acetyl-11-keto-β-boswellic acid induces apoptosis in HL60 and CCRF-CEM cells and inhibits topoisomerase I.* Proc Amer Assoc Cancer Res 1997, 38: Abst 1291.

2. Bogenrieder, T., Glaessl, A., Bosserhoff, A.-K., Sailer,E.-R., Landthaler, M., Ammon, H.P.T., Stolz, W. *Analysis of pentacyclic triterpene-mediated antiproliferative effects on malignant melanoma cells.* Proc Amer Assoc Cancer Res 1997, 38: Abst 1458.

Original monograph - Drugs Fut 1993, 18: 307.

AD-32 *Antineoplastic Antibiotic*
NSC-246131

EN: 090162



$C_{34}H_{36}F_3NO_{13}$ **Pharmacia & Upjohn; Anthra; Medeva; Nycomed**

AD-32 was given to 32 patients with transitional cell carcinoma of the bladder in 6 weekly doses (200-900 mg) intravesically. Very little systemic absorption occurred, and local bladder irritation was the main adverse effect, with the highest tolerable dose being 800 mg. Complete response to therapy occurred in 13 patients; 8 were disease free for 12.1-38.5 months (1).

Medeva has acquired an exclusive U.S. marketing license from Anthra to AD-32 (2).

Nycomed has obtained exclusive marketing rights to Anthra's AD-32 for 31 countries in Europe. According to the agreement, Anthra will be responsible for registration in Europe and Nycomed for distribution and sales (3).

Medeva has filed an NDA with the U.S. FDA for AD-32 for the treatment of refractory carcinoma *in situ* of the bladder (4).

1. Greenberg, R.E., Bahnson, R.R., Wood, D. et al. *Initial report on intravesical administration of N-trifluoroacetyladriamycin-14-valerate (AD 32) to patients with refractory superficial transitional cell carcinoma of the urinary bladder.* Urology 1997, 49(3): 471.

2. *Medeva acquires license to anthracycline derivative for the treatment of bladder cancer.* Prous Science Daily Essentials July 21, 1997.

3. *Nycomed licenses new anthracycline from Anthra.* Prous Science Daily Essentials October 16, 1997.

4. *U.S. marketing application submitted for AD-32.* Prous Science Daily Essentials January 14, 1998.

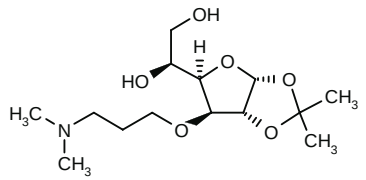
Original monograph - Drugs Fut 1980, 5: 171.

Additional Reference

Koseki, Y. et al. *In vitro synergism of N-trifluoroacetyladriamycin-14-valerate (AD 32) with low dose irradiation against human parenteral and platinum-resistant squamous carcinoma cells.* Proc Amer Assoc Cancer Res 1997, 38: Abst 2216.

Amiprilose *Antiarthritic*
Therafectin® *Immunosuppressant*

EN: 090564



$C_{14}H_{27}NO_6$ **Boston Life Sciences; Kissei**

Boston Life Sciences has reported results from a double-blind, placebo-controlled phase III trial of amiprilose (Therafectin®) for the treatment of rheumatoid arthritis. Preliminary analysis indicated that there was no statistically significant difference between amiprilose and placebo in the percentage of patients achieving therapeutic success (40% *vs.* 33%), with the primary endpoint defined as a return to baseline or better in the number of painful joints, swollen joints and global assessments at the final visit. The secondary endpoint, defined as the number

of painful joints and swollen joints, the patient's global assessment and the physician's global assessment, among other parameters, was highly statistically significantly better in those patients receiving Therafectin®. No significant adverse effects attributable to the drug were reported (1).

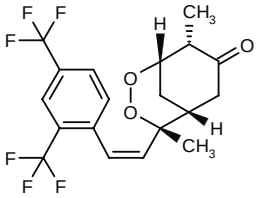
1. *Boston Life Sciences reports phase III results for Therafectin.* Prous Science Daily Essentials October 2, 1997.

Original monograph - Drugs Fut 1985, 10: 301.

Arteflene

Antimalarial

EN: 150164



$C_{19}H_{18}F_6O_3$ **Roche**

Ro-42-1611 (30 ml of 5% suspension) was administered to 16 volunteers who received 2 (G2), 4 (G4) or 6 (G6) doses. Parasitological, laboratory and EKG evaluations were carried out on Days 0, 1, 2, 3 and 7. Two patients did not clear the asexual parasitemia (G2) and only 2 cures (G6) were seen. Mild to moderate side effects included nausea, vomiting, diarrhea and flatulence (1).

1. Uchôa, R., Silva, D., Veloso, M., Alves, A., De Souza, J.M. *RO 42-1611 a new weapon to fight P. falciparum resistant strains.* 14th Int Cong Trop Med Malar (Nov 17-22, Nagasaki) 1996, Abst O-26-8.

Original monograph - Drugs Fut 1995, 20: 341.

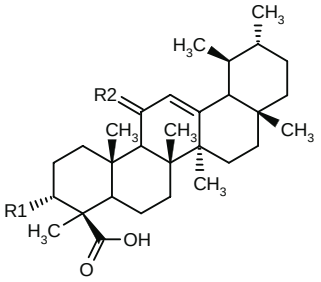
Additional Reference

O'Neill, P.M. et al. *The biomimetic iron-mediated degradation of arteflene (Ro-42-1611), an endoperoxide antimalarial: Implications for the mechanism of antimalarial activity.* Tetrahedron Lett 1997, 38(24): 4263.

Boswellic Acids

Antiinflammatory

EN: 150514



β-Boswellic acid: R_1=OH, R_2=H_2
Acetyl-β-boswellic acid: R_1=OAc, R_2=H_2
11-Keto-β-boswellic acid: R_1=OH, R_2=O
Acetyl-11-keto-β-boswellic acid: R_1=OAc, R_2=O

Reg. Res. Lab. Jammu-Tawi (IN)

Boswellin has been shown to markedly inhibit HL-60 cell growth in culture and to decrease DNA, RNA and protein synthesis. Further studies of its 4 related triterpene acids revealed a dose-dependent inhibition of HL-60 cell DNA, RNA and protein synthesis. The most potent inhibitor, 3-*O*-acetyl-11-keto-β-boswellic acid, had an irreversible inhibitory effect on DNA synthesis (1).

Boswellin, when applied topically (1.2-3.6 mg) with TPA to CD1 mice, was shown to markedly inhibit TPA-induced changes and to decrease skin tumor development as determined by number of skin tumors per mouse, number of mice with skin tumors and latency of tumor formation (2).

A clinical trial of lipophilic boswellic acids in 12 patients with malignant glioma undergoing neurosurgery showed that preoperative drug treatment for 7 days (3x1200 mg p.o.) reduced perifocal edema (mean reduction 30%) in 83% of patients. Neurological deficits improved in 75% of patients, while 1 patient deteriorated (3).

1. Huang, M.-T., Shao, Y., Ma, W., Badmaev, V., Chin, C.-K., Ho, C.-T. *Antitumor activity of β-boswellic acid and its related triterpene acids from the gum resin exudate of the tree Boswellia serrata.* Proc Amer Assoc Cancer Res 1997, 38: Abst 2465.

2. Huang, M.-T., Badmaev, V., Xie, J.-G., Lou, Y.-R., Lu, Y.P., Ho, C.-T. *Inhibitory effect of an extract of the gum resin exudate of Boswellia serrata on 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced skin tumor promotion in mice.* Proc Amer Assoc Cancer Res 1997, 38: Abst 2464.

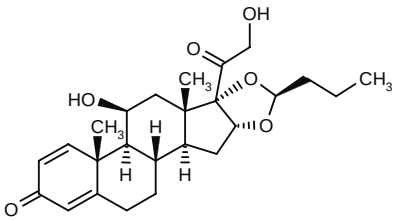
3. Winking, M., Böker, D.K., Simmet, T. *Boswellic acid as an inhibitor of the perifocal edema in malignant glioma in man.* J Neuro-Oncol 1996, 30(2): Abst P-39.

Original monograph - Drugs Fut 1993, 18: 307.

Budesonide
Entocor®

Intestinal Antiinflammatory

EN: 091057



$C_{25}H_{34}O_6$ **Astra Pharma**

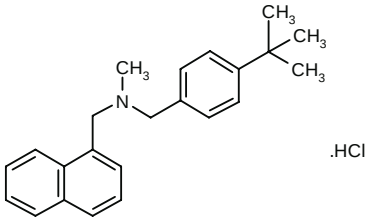
Astra Pharma has received approval from Health Canada for Entocort® (budesonide) capsules, for use in the treatment of mild to moderate Crohn's disease affecting the small intestine and colon (1).

1. *New hope for Crohn's disease sufferers. Canadian team helps research first new drug in five years.* Astra Pharma, Inc. Press Release 1997, April 2.

Original monograph - Drugs Fut 1980, 5: 179.

Butenafine Hydrochloride *Antifungal*
Mentax®
Volley®

EN: 133451



$C_{23}H_{27}N.HCl$ **Kaken; Penederm; Schering-Plough**

Penederm has received regulatory approval from the Health Protection Branch of Health Canada for butenafine hydrochloride 1% cream as an over-the-counter medication for tinea pedis. The drug will be marketed in Canada by Schering-Plough under its own brand names. Kaken developed butenafine and markets the drug in Japan, while Penederm has exclusive rights in North, Central and South Amercia for topical use against all skin and nail fungus (1).

1. *Penederm announces Canadian OTC approval of butenafine HCl for athlete's foot: Schering-Plough Corporation's Canadian Business Units to market.* Penederm, Inc. Press Release 1997, May 8.

Original monograph - Drugs Fut 1989, 14: 315.

Additional References

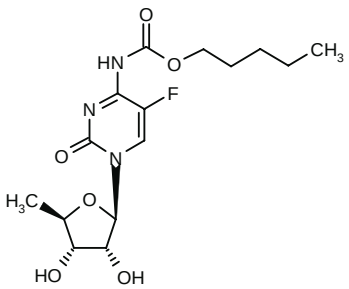
New topical antifungal combination therapy provides cure of tinea pedis with only one week of treatment. Favorable clinical data reported at Dermatology Seminar in Santa Fe, Mexico. Skin Disease Education Foundation Press Release 1997, October 16.

Greer, D.L. et al. *A randomized trial to assess once-daily topical treatment of tinea corporis with butenafine, a new antifungal agent.* J Amer Acad Dermatol 1997, 37(2, Part 1): 231.

Penederm and Mylan to copromote Mentax. Prous Science Daily Essentials December 22, 1997.

Capecitabine *Antineoplastic*
Xeloda®

EN: 211639



$C_{15}H_{22}FN_3O_6$ **Roche**

Results of studies using CXF280, HCT116 and COLO 205 human colon cancer xenograft models demonstrated that oral capecitabine was tumor-selective, producing high concentrations of 5-FU in tumor tissues (1).

In studies in nude mice, capecitabine (360 mg/kg/day p.o.) was found to be more active than FUra (20 mg/kg/day i.p.) against human ileocecal xenografts HCT-8 and HCT-8/FU2h (Fura-resistant cell line). When capecitabine was administered in combination with leucovorin (200 mg/kg/day), its antitumor activity in HCT-8 was potentiated, whereas in HCT-8/FU2h it was not (2).

In human cancer xenograft models, capecitabine was more effective, and over a wider dose range, than 5-FU and UFT, inhibiting tumor growth by more than 90% in 7/23 models as compared to 1/23 (4.3%) and 5/22 (23%) for 5-FU and UFT, respectively (3).

In a study in 19 colorectal cancer patients with liver metastasis and/or requiring surgical resection of primary tumor, oral administration of capecitabine (1255 mg/m^2 b.i.d.) for 5-7 days prior to surgery resulted in higher 5-FU concentrations in primary tumor than in liver metastasis, indicating the drug's high tumor selectivity (4).

A randomized phase II study in 101 outpatients with advanced colorectal cancer evaluated the efficacy and safety of 3 different schedules of capecitabine treatment: arm (a), 1331 mg/m^2 day continuous; arm (b), 2510 mg/m^2 day intermittent; and arm (c), 1657 mg/m^2 day plus leucovorin 60 mg/day p.o. intermittent. Based on overall response rate (7/36, 9/32 and 8/33 for arms a, b and c, respectively), median time to progression (17, 30 and 24 weeks for arms a, b, and c, respectively) and safety, the 2510 mg/m^2 day intermittent schedule was chosen for phase III studies (5).

Roche has submitted capecitabine (Xeloda™) for approval in the U.S. and the European Union (6).

Roche has received accelerated approval from the FDA to market Xeloda™ for the treatment of patients with metastatic breast cancer whose tumors are resistant to standard chemotherapy with paclitaxel and an anthracycline-containing regimen (7).

1. Ishikawa, T., Utoh, M., Sawada, N., Sekiguchi, F., Ishitsuka, H. *Xeloda™ (capecitabine): An orally available tumor-selective fluoropyrimidine carbamate.* Proc Amer Soc Clin Oncol 1997, 16: Abst 727.

2. Cao, S., Lu, K., Ishitsuka, H., Rustum, Y.M. *Antitumor efficacy of capecitabine against fluorouracil-sensitive and -resistant tumors.* Proc Amer Soc Clin Oncol 1997, 16: Abst 795.

3. Ishikawa, T., Sawada, N., Sekiguchi, F., Fukase, Y., Ishitsuka, H. *Xeloda™, a new oral fluoropyrimidine carbamate with an improved efficacy profile over other fluoropyrimidines.* Proc Amer Soc Clin Oncol 1997, 16: Abst 796.

4. Schüller, J., Cassidy, J., Reigner, B.G., Durston, S., Roos, B., Ishitsuka, H., Utoh, M., Dumont, E. *Tumor selectivity of Xeloda™ in colorectal cancer patients.* Proc Amer Soc Clin Oncol 1997, 16: Abst 797.

5. Findlay, M. et al. *A randomised phase II study of Xeloda™ (capecitabine) in patients with advanced colorectal cancer.* Proc Amer Soc Clin Oncol 1997, 16: Abst 798.

6. *First oral, tumor-activated anticancer drug filed by Roche.* Prous Science Daily Essentials October 31, 1997.

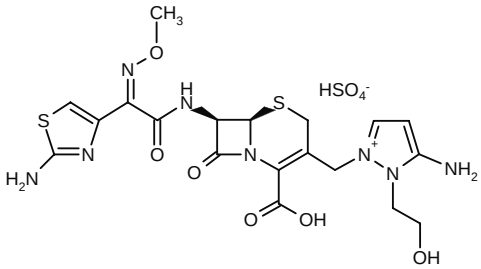
7. *FDA grants accelerated approval for Xeloda*. Prous Science Daily Essentials May 4, 1998.

Original monograph - Drugs Fut 1996, 21: 358.

Cefoselis Sulfate
Wincef®

Cephalosporin

EN: 176375



$C_{19}H_{22}N_8O_6S_2.H_2SO_4$ **Fujisawa; Johnson & Johnson**

A paper describing the synthesis of FK-037 as originally reported in this journal and its antibacterial activity has been published (1).

Results of *in vitro* studies against 230 multiresistant Gram-negative isolates have shown that the activity of cefepime was superior to that of cefoselis and cefpirome (2).

1. Ohki, H., Kawabata, K., Inamoto, Y., Okuda, S., Kamimura, T., Sakane, K. *Studies on 3'-quaternary ammonium cephalosporins - IV. Synthesis and antibacterial activity of 3'-(2-alkyl-3-aminopyrazolium)cephalosporins related to FK037.* Bioorg Med Chem 1997, 5(8): 1685.

2. Tympanidou, C., Tsitsika, A., Grecka, P., Mandaraka, A.,Giamarellou, H., Giamarellos-Bourboulis, E.J. *Comparative in vitro activity of FK037 (cefoselis, FK), cefepime (CF) and cefpirome (CP) on 230 multiresistant Gram-negative isolates.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-186.

Original monograph - Drugs Fut 1994, 19: 325.

Additional References

Climo, M.W. et al. *Comparison of the in-vitro and in-vivo efficacy of FK037, vancomycin, imipenem and nafcillin against staphylococcal species.* J Antimicrob Chemother 1997, 40(1): 59.

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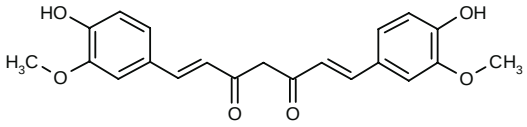
Curcumin

Antiinflammatory
Antineoplastic

EN: 119974



$C_{21}H_{20}O_6$ **Central Drug Res. Inst., Lucknow (IN)**

A study of the cytotoxic effects of curcumin in breast cancer, leukemic cell lines, human melanoma (drug-resistant and -sensitive) and normal skin and breast cells revealed that it has differential cytotoxicity in normal and tumor cells, it induces G_2 block and apoptosis, has its highest IC_{50} values for normal cells (less for drug-sensitive and -resistant tumor cells), and its fluorescence is localized in the Golgi region. Curcumin has chemopreventive and anticarcinogenic properties, probably based on its collateral sensitivity in normal and tumor cells (1).

A recent study has shown that curcumin exhibits *in vitro* growth inhibition of several breast tumor cell lines (hormone-dependent, hormone-independent and multidrug-resistant). Curcumin's effect was both time- and dose-dependent and correlated with ornithine decarboxylase inhibition. Cells were arrested preferentially in the G_2/S phase, and cell death was not related to apoptosis or to changes in apoptosis-related genes (2).

A study of the effect of curcumin on diethylnitrosamine-induced liver cancer in mice showed that mice given diethylnitrosamine and fed a curcumin-enriched diet developed no liver tumors by 16 weeks and had one-third fewer preneoplastic foci than mice without curcumin. At 34 weeks, curcumin-fed mice had a 30% smaller total tumor mass than animals not receiving curcumin (3).

Several studies involving Sprague-Dawley rats examined the effects of curcumin and other compounds on the development of colonic cancer. No protective effect was observed based on measures of colonic cell proliferation, aberrant crypt foci and multiple immune functions (4).

Recent studies from several laboratories have shown that the anticarcinogenic effects of curcumin and tea polyphenols may be mediated, at least in part, by a modulation of mitotic signal transduction (5).

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5. Lin, J.-K. *Modulation of mitotic signal transduction by curcumin and tea polyphenols and their implication for cancer chemoprevention.* 213th ACS Natl Meet (April 13-17, San Francisco) 1997, Abst AGFD 183.

Original monograph - Drugs Fut 1987, 12: 331.

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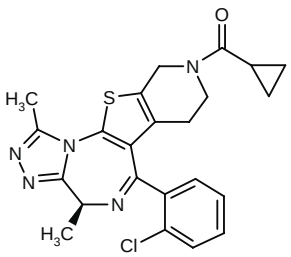
E-6123

Antiallergic/Antiasthmatic
PAF Antagonist

EN: 163799



$C_{23}H_{22}ClN_5OS$ **Eisai**

E-6123 has been found to enhance the sensitivity of human non-small cell lung cancer cells to cisplatin, apparently by enhancing apoptosis induced by the chemotherapeutic agent (1).

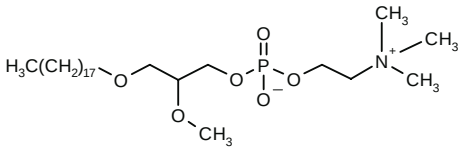
1. Heki, U., Kasahara, K., Bando, T., Shibata, K., Shirsaki, H., Matsuda, T. *Modulation of sensitivity to CDDP by platelet activating factor receptor antagonist: E6123 in PC9 and PC9/CDDP cell line.* 56th Annu Meet Jpn Soc Cancer Res (Sept 25-27, Kyoto) 1997, Abst VAP-119.

Original monograph - Drugs Fut 1991, 16: 310.

Edelfosine

Antineoplastic

EN: 090480



$C_{27}H_{58}NO_6P$ **Max Planck**

ET-18-OCH_3 induced apoptosis in human tumor cell lines and in primary human tumor cell cultures, but not in normal cells. This effect appeared to be dependent on its glycerol backbone and was correlated with its uptake. Binding of ET-18-OCH_3 to platelet-activating factor receptor was not related to its apoptotic effect; it induced *c-myc* expression, and its effect was abrogated by gene transfer-produced overexpression of *bcl-2* and *bcl-x(L)* (1).

A study of ET-18-OCH_3 enhancement of merocyanine 540-mediated photoinactivation showed that such combination purging is effective against some solid tumors (neuroblastoma and rhabdomyosarcoma) while ineffective against breast cancer cells, and thus may be used to eliminate such solid tumor cells from autologous stem cell grafts without too much effect on normal hematopoetic stem cells (2).

The addition of ET-18-OCH_3 (3 times/week for 2 weeks) and iron to the diet of male athymic nude mice injected with human breast cancer cells and fed a fish oil diet resulted in decreased tumor growth rate and mitotic index and increased cytotoxic index in tumors, without any negative effects on the host mice (3).

1. Mollinedo, F., Fernandez Luna, J.L., Gajate, C., Martin Martin, B., Benito, A., Martinez Dalmau, R., Modolell, M. *Selective induction of apoptosis in cancer cells by the ether lipid ET-18-OCH_3 (edelfosine): Molecular structure requirements, cellular uptake, and protection by Bcl-2 and Bcl-X(L).* Cancer Res 1997, 57(7): 1320.

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3. Hardman, W.E., Barnes, C.J., Knight, C.W., Cameron, I.L. *Effects of iron supplementation and ET-18-OCH_3 on MDA-MB 21 breast carcinomas in nude mice consuming a fish oil diet.* Brit J Cancer 1997, 76(3): 347.

Original monograph - Drugs Fut 1987, 12: 341.

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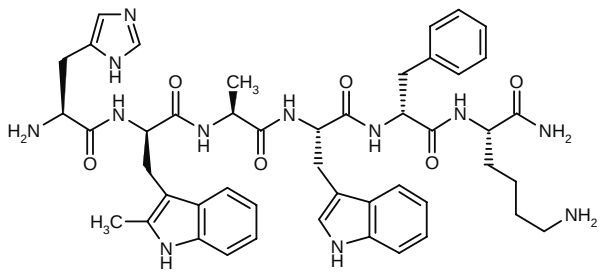
Fujiwara, K. et al. *Expression of heat shock protein (HSP) 27 and cytoplasmic keratin 18 in the nuclei of BG-1 human ovarian cancer cells following ET-18-OCH_3 treatment.* Proc Amer Assoc Cancer Res 1997, 38: Abst 640.

Examorelin Hexarelin®

Growth Hormone Secretagogue

EN: 222476



$C_{47}H_{58}N_{12}O_6$ **Europeptides**

In anti-GHRH treated rats undergoing low-flow ischemia and reperfusion, administration of hexarelin (80 μg/kg b.i.d., s.c.) for 15 days reversed the impaired somatotropic function and improved cardiac function. Furthermore, cardiac ischemic damage was counteracted, and left ventricular developed pressures were higher than in control rats (1).

In a comparison of the ACTH- and cortisol-releasing effects of hexarelin (2.0 μg/kg i.v.) and human GRH (2.0 μg/kg i.v.) in 12 normal subjects and 17 Cushing's syndrome patients, it was found that hexarelin and hCRH produced similar ACTH and cortisol responses in normal patients. Patients with Cushing's syndrome showed a greater response to hexarelin than hCRH, while in patients with adrenal adenoma or ectopic ACTH-induced Cushing's syndrome, hexarelin and hCRH lost their effect on ACTH and cortisol. Hexarelin produced a higher peak GH in normals than in Cushing's syndrome patients (2).

1. Colonna, V.D., Rossoni, G., Bernareggi, M., Muller, E.E., Berti, F. *Cardiac ischemia and impairment of vascular endothelium function in hearts from growth hormone-deficient rats: Protection by hexarelin.* Eur J Pharmacol 1997, 334(2-3): 201.

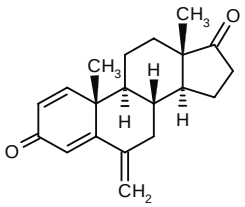
2. Ghigo, E., Arvat, E., Ramunni, J., Colao, A., Gianotti, L., Deghenghi, R., Lombardi, G., Camanni, F. *Adrenocorticotropin- and cortisol-releasing effect of hexarelin, a synthetic growth hormone-releasing peptide, in normal subjects and patients with Cushing's syndrome.* J Clin Endocrinol Metab 1997, 82(8): 2439.

Original monograph - Drugs Fut 1996, 21: 366.

Exemestane

Antineoplastic
Aromatase Inhibitor

EN: 129640



$C_{20}H_{24}O_2$ **Pharmacia & Upjohn**

An open, phase I study evaluated escalating doses of exemestane in 13 postmenopausal women with advanced breast cancer. Exemestane dosage was increased every 2 weeks over 12 weeks. Patients were maintained on the highest tolerable dose until disease progression was seen (median time 63 weeks). Maximal suppression of plasma estradiol (14.6% pretreatment) and estrone (5.8% pretreatment) occurred at 10 mg/day; 25 mg/day suppressed estrone sulfate (8.9% pretreatment). Urinary estrone was maximally suppressed by 5 mg daily, but urinary estradiol was further suppressed by doses of 50-200 mg daily (1).

A double-blind, dose-finding study for the minimally effective dose of exemestane to suppress estrogen in breast cancer patients showed that, in 20 evaluable postmenopausal advanced breast cancer patients, the estrogen suppressive effect was dose-related, and the drug was ineffective at doses of 0.5 and 1 mg. Circulating estrogens were suppressed with doses of 2.5 and 5 mg and the drug was well tolerated (2).

A phase II multicenter, multinational study examined the effects of exemestane (200 mg/day p.o.) in 78 postmenopausal advanced breast cancer patients who progressed on aminoglutethimide after previous tamoxifen therapy. Using Peer Review Assessment, a 28% overall objective response rate was seen, and a further 11% of patients had disease stabilization of at least 24 weeks. Mild to moderate side effects included nausea, hot flushes, dizziness, asthenia, increased sweating, androgenic symptoms and edema; only 2 patients stopped therapy due to adverse events (3).

Exemestane has shown potent inhibition of plasma estrogen at doses starting at 5 mg/day, with maximal suppression at 10-25 mg/day. Clear antitumor activity has been seen in noncontrolled phase II studies with more than 400 patients. An objective response rate of 24%, and disease stabilization for at least 24 weeks was seen in 24% of 62 patients progressing on aminoglutethimide (at least 500 mg/day). Less than 3% of patients discontinued treatment due to side effects, which are usually of mild to moderate severity (4).

Eighty postmenopausal advanced breast cancer patients showing progression on aminoglutethimide (at least 500 mg) were enrolled in a phase II study of exemestane (200 mg/day p.o.). Seventy-eight patients (33 resistant to aminoglutethimide, 39 showing progression after initial response and 6 with an unevaluable or unavailable response to aminoglutethimide) were treated with exemestane; 68 patients had also received tamoxifen, 6 had received tamoxifen and other hormones, and 55% had prior chemotherapy. Metastatic disease was visceral in 34 cases, bone in 27 and soft tissue in 17. Overall objective response rate was 26% by Peer Review Assessment, with an overall success rate of 39%. Only mild to moderate toxicity was reported, with 2% discontinuing because of side effects (5).

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2. Bajetta, E., Zilembo, N., Noberasco, C. et al. *The minimal effective exemestane dose for endocrine activity in advanced breast cancer.* Eur J Cancer 1997, 33(4): 587.

3. Thürlimann, B., Paridaens, R., Serin, D. et al. *Third-line hormonal treatment with exemestane in postmenopausal patients with advanced breast cancer (ABC) progressing on aminoglutethimide (AG): A phase II, multicenter, multinational study.* Proc Amer Soc Clin Oncol 1997, 16: Abst 527.

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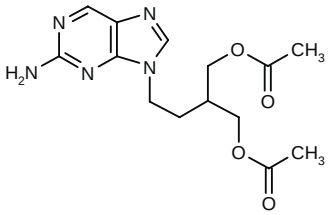
Original monograph - Drugs Fut 1992, 17: 278.

Famciclovir
Famvir®

Antiviral

EN: 126242



$C_{14}H_{19}N_5O_4$ **SmithKline Beecham**

SmithKline Beecham's famciclovir (Famvir™) has been approved in the U.K. for use in the suppression of genital herpes (herpes simplex). This drug was previously approved in the U.K. for the treatment of herpes zoster (shingles) and genital herpes and in the U.S. for the treatment of recurrent genital herpes and zoster (shingles) in immunocompetent individuals. The FDA is currently reviewing famciclovir for use in the suppression of recurrent genital herpes (1).

SmithKline Beecham has received FDA clearance to market famciclovir (Famvir®) for the suppression of recurrent genital herpes (2).

1. *SmithKline Beecham's Famvir receives U.K. approval for new indication.* Prous Science Daily Essentials May 21, 1997.

2. *Famvir approved by FDA for new indication.* Prous Science Daily Essentials September 22, 1997.

Original monograph - Drugs Fut (CIPS) 1989, 14: 347.

GEM-91
Trecovirsen

Anti-HIV

EN: 203661

Antisense oligodeoxynucleotide phosphorothioate 25-mer, complementary to the gag gene of HIV-1 mRNA at the site of initiation codon (nucleotides 324-348), whose sequence is:
5'-CTCTCGCACCCATCTCTCTCCTTCT-3'

Hybridon

An unblinded, placebo-controlled phase Ib/II clinical trial has evaluated GEM-91 treatment (3.2-4.0 mg/kg/day for 8 days) in 22 HIV-positive patients. Results showed a considerable decrease in cellular viremia in GEM-91-treated patients after day 4 through the end of treatment, whereas placebo-treated patients showed a continued increase in cellular viremia. In patients with more advanced disease, there were pronounced decreases in cellular viremia (of up to 1.3 logs, 90% reduction) after 8 days of treatment. Plasma concentrations of viral RNA showed a moderate increase during treatment, which was suggested to reflect the release of incomplete virus from lymphatic tissues (1).

Hybridon has terminated further development of GEM-91 based on a preliminary review of new data from an open-label phase II clinical trial in patients with advanced HIV infection. In this trial, 3 of the 9 subjects tested experienced decreases in platelet counts that required dose interruption on a dose of 3.2 mg/kg/day. Furthermore, the data showed inconsistent responses to the treatment and failed to confirm the decrease in cellular viremia observed in an earlier trial. The company decided to stop further development of GEM-91 because these results indicated that, even if efficacy could be demonstrated, chronic therapy with the product in combination with other antiretroviral agents would likely require periodic interruption of drug to allow platelet levels to increase, whereas the successful management of AIDS patients requires uninterrupted combination therapy to suppress viral replication (2).

Trecovirsen is the new proposed international nonproprietary name for GEM-91 (3).

1. *Hybridon unblinds clinical trial results of GEM®91 showing activity against advanced HIV: Up to 90% decreases in cellular viremia observed in HIV-positive patients.* Hybridon, Inc. Press Release 1997, April 3.

2. *Hybridon suspends development of GEM-91 for AIDS.* Prous Science Daily Essentials July 28, 1997.

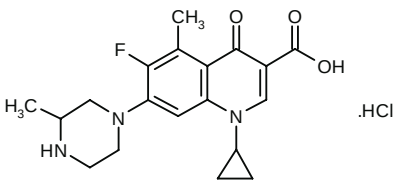
3. *Proposed international nonproprietary names (Prop. INN): List 77.* WHO Drug Inform 1997, 11(2): 102.

Original monograph - Drugs Fut 1995, 20: 344.

Grepafloxacin Hydrochloride
Lungaskin®
Raxar®
Vaxar®

Fluoroquinolone Antibacterial

EN: 176384



$C_{19}H_{22}FN_3O_3.HCl$ **Otsuka; Glaxo Wellcome**

An *in vitro* antibacterial study of 2385 clinical isolates showed that grepafloxacin, compared to other fluoroquinolone antibacterial agents, has higher activity against Gram-positive cocci and pathogens isolated from respiratory tract infections (1).

A study of grepafloxacin's activity against 250 bacterial strains isolated from acute or chronic maxillary sinusitis showed that the drug was superior to sparfloxacin and loracarbef (MIC_{90}s = 0.25, 0.5 and 1.0 mg/l, respectively) against *Streptococcus pneumoniae* and was more effective than loracarbef, cefuroxime axetil, amoxicillin and amoxicillin/clavulanic acid, but comparable to sparfloxacin and clarithromycin, against *Staphylococcus aureus*. The drug's activity was comparable to other antibiotics against anaerobic strains and was equal to sparfloxacin against *Enterobacteriaceae* or nonfermentative Gram-negative bacilli (2).

A study of the antibacterial activity of grepafloxacin against 333 multiresistant *Streptococcus pneumoniae* strains and 305 viridans streptococci strains showed that the drug had excellent activity against both groups (MIC_{90} = 0.12 and 0.25 μg/ml, respectively) and was more effective than cefriaxone (MIC_{90} = 1.0 and 2.0 μg/ml, respectively), ofloxacin (MIC_{90} = 2.0 and 4.0 μg/ml) and ciprofloxacin (MIC_{90} = 2.0 and 2.0 μg/ml, respectively) (3).

Results of a study evaluating the activity of grepafloxacin compared to ciprofloxacin, levofloxacin, sparfloxacin, amoxicillin/clavulanate and clarithromycin against penicillin-resistant, -intermediate and -susceptible pneumococci strains, showed that grepafloxacin was bactericidal against all strains at the lowest concentration tested (≤ 0.5 μg/ml), indicating its usefulness in the treatment of pneumococcal infections (4).

Results of a study on the antibacterial activity of grepafloxacin against 146 clinical penicillin-susceptible or -resistant and ofloxacin-susceptible or -resistant *Streptococcus pneumoniae* isolates indicate that the drug's activity is comparable to that of sparfloxacin and better than that of ofloxacin, levofloxacin and ciprofloxacin (5).

Results of a study evaluating the *in vitro* postantibiotic effect and human monocyte activity of grepafloxacin showed that the drug was superior to rifampicin and sparfloxacin against erythromycin-resistant *Legionella pneumophila* strains and was more effective that ciprofloxacin, sparfloxacin and clarithromycin against erythromycin-resistant *Legionella* strains other than *L. pneumophila*. Grepafloxacin, like the other antibiotics tested, inhibited the growth of erythromycin-resistant and -susceptible *L. pneumophila* and *Legionella* strains other than pneumophila in human monocytes; however, only grepafloxacin and ciprofloxacin prevented the regrowth of killed *L. pneumophila* after the removal of the antimicrobial agent (6).

An evaluation of the *in vitro* activity of grepafloxacin against clinical isolates and several reference strains of *Mycoplasma* species showed that the drug was as active as sparfloxacin and doxycycline, more active than ofloxacin and ciprofloxacin and less active than erythromycin (7).

The *in vitro* activity of grepafloxacin against 1200 bacterial strains responsible for respiratory tract infections was examined using a microdilution method with Mueller Hinton broth (with appropriate supplementation). Grepafloxacin was active against all respiratory pathogens tested, showing superiority over cefixime, amoxicillin and roxithromycin for *H. influenzae* and *H. parainfluenzae*, *M. catarrhalis* and *K. pneumoniae*, and had more activity than ciprofloxacin against *S. aureus*, *S. pyogenes*, *S. pneumoniae*, *M. pneumoniae* and *L. pneumophila* (8).

Grepafloxacin has shown greater activity against Gram-positive organisms than current quinolones, and resistant mutants develop less commonly, with the increase in MIC being less when mutants develop (although absolute values remain the same). Gram-positive bacteria are killed with grepafloxacin concentrations slightly above MIC (9).

Grepafloxacin's *in vitro* effectiveness was examined against respiratory pathogens collected from 15 U.K. laboratories. Approximately 10% of pathogens showed macrolide resistance, and 12% of *H. influenzae* produced β-lactamase. Fluoroquinolones and macrolides were highly effective against *Moraxella catarrhalis*. No quinolone-resistant pathogens were seen, and grepafloxacin, at an MIC_{90} of 0.25 mg/l, had a 4- to 8-fold greater activity than ciprofloxacin (10).

Grepafloxacin's *in vitro* activity against *Chlamydia pneumoniae*, *Chlamydia trachomatis*, *Mycoplasma pneumoniae*, *Mycoplasma hominis* and *Ureaplasma urealyticum* was compared to that of other drugs. For the *Chlamydia* spp., grepafloxacin showed activity about equal to doxycycline, 8-16 times greater activity than ofloxacin, and equal to or 2- to 4-fold less activity than clarithromycin. Against the *Legionella* spp., grepafloxacin was equal in activity to ofloxacin, clarithromycin and rifampicin. Compared to ofloxacin, grepafloxacin showed 4 times greater activity against *M. pneumoniae* and *U. urealyticum*, and 16 times greater activity against *M. hominis* (11).

A comparative pharmacokinetic study of grepafloxacin isomers in rats showed that stereoselective transport of the glucuronides occurs, with biliary clearance of the *R*-GPFX-Glu being twice that of *S*-GPFX-Glu. This effect is absent in mutant strain Eisai-hyperbilirubinemia rats, suggesting that it is likely mediated by the bile canalicular multispecific organic anion transport system (12).

A study comparing the joint toxicity of grepafloxacin (10, 30 or 100 mg/kg/day i.v. for 7 days) with that of ofloxacin and ciprofloxacin in male juvenile beagle dogs showed that ciprofloxacin and ofloxacin produced blisters on the surface of joints at lower doses than grepafloxacin (10 and 30 mg/kg/day *vs.* 100 mg/kg/day) and at lower plasma concentrations (3.80 and 4.24 μg/ml *vs.* 18.69 μg/ml) (13).

Preclinical studies of grepafloxocin show a toxicological profile like other fluoroquinolones: weak photosensitizing effect, no convulsions when given to mice with fenbufen, transient arrhythmias at 10 mg/kg and ventricular tachycardia at 30 mg/kg i.v. in rabbits, and joint cartilage lesions in juvenile dogs at 100 mg/kg/day i.v. Tolerance of grepafloxacin appears similar to that of other fluoroquinolones, but nausea, vomiting and taste perversion have occurred with rather high frequency in early clinical trials, particularly at the higher dose of 600 mg daily (14).

Photoxicity of grepafloxacin (400 and 600 mg/day), ciprofloxacin (500 mg b.i.d.) and placebo was compared

in a double-blind trial in 32 healthy subjects using minimal erythemal dose as the target measure. Grepafloxacin and ciprofloxacin showed a similar weak, UVA-dependent phosensitivity, which was rapidly reversible (15).

Grepafloxacin pharmacokinetics following single oral doses (200-1200 mg) and repeated oral doses of (400 and 800 mg) were studied in healthy male subjects. Peak plasma levels occurred within 2 h, with biexponential decline following. Grepafloxacin showed a half-life of 12 h (single doses) and 15 h (repeated doses), a high apparent volume of distribution with metabolic breakdown, no urinary excretion and nonlinear kinetics (not clinically significant at therapeutic doses). Steady state is reached in 5 days with repeated doses. Of the fluoroquinolones, grepafloxacin has the longest half-life and largest apparent volume of distribution (16).

A study of 48 healthy volunteers (half male) ranging in age from 40 to over 70 years, showed no clinically significant effects of age or gender on grepafloxacin pharmacokinetics. While some differences were observed between males and females, these were related to differences in lean body mass. Therefore, no grepafloxacin dosage adjustments are needed based on age or gender (17).

Two studies with 16 healthy male volunteers showed no effects of food and gastric pH on grepafloxacin pharmacokinetics. No difference was seen when one dose of grepafloxacin (600 mg) was given in the fasting state as compared to after a standard high-fat meal. Similarly, attempts to change gastric pH with famotidine (20 mg infusion, repeated as needed to keep gastric pH above 6) resulted in no changes in grepafloxacin pharmacokinetics (400 mg dose) (18).

Interactions between grepafloxacin and theophylline or warfarin were examined in two phase I trials in 16 healthy volunteers. For theophylline, peak concentrations and area under the concentration-time curve increased significantly while on treatment with grepafloxacin 600 mg/day for 10 days, while theophyline clearance decreased 50%. For warfarin, no changes were observed in pharmacokinetics. The results indicate that theophylline dosage should be decreased by 50% during grepafloxacin treatment, with monitoring of theophylline levels (19).

A multicenter, double-blind, randomized study comparing the antibacterial activity of grepafloxacin (600 mg/day for 10 days) with clarithromycin (250 mg b.i.d. for 10 days) in 494 patients with community-acquired pneumonia showed that the two treatment groups were equivalent in clinical cure rate, radiographic analysis and bacteriological cures. Both drugs were well tolerated; however, grepafloxacin produced a significantly higher rate of taste perversion, nausea, vomiting and dizziness (20).

Grepafloxacin (400 and 600 mg/day) was compared to amoxycillin (500 mg t.i.d.) in the treatment of acute exacerbations of chronic bronchitis in a randomized, prospective, double-blind, multicenter study of 656 patients treated for 7-10 days. Clinical success rates were equivalent, and microbiological success rates were significantly better at end of treatment for both dosages of grepafloxacin, and at follow-up (2 weeks) for grepafloxacin 600 mg/day. Mild to moderate side effects (most commonly taste perversion, nausea and headache) were similar in all three groups (21).

A randomized, prospective, open-label, multicenter study compared single-dose grepafloxacin (400 mg) to single-dose cefixime (400 mg) in the treatment of uncomplicated gonococcal urethritis in 380 female patients (1/3 of documented cases also had pharyngeal and/or rectal involvement). Grepafloxacin had a significantly higher clinical response rate; mild to moderate adverse effects, most commonly vaginitis, nausea and vomiting, occurred in both groups (22).

In a double-blind, double-placebo study with 227 enrolled patients, grepafloxacin (200 mg/day) was compared to ofloxacin (200 mg t.i.d.) for the 7-day treatment of erysipelas, cellulitis, furuncles, furunculosis and carbuncles. No significant differences were found in clinical efficacy, overall improvement, usefulness, safety and bacteriologic response (23).

In a double-blind comparative study of grepafloxacin (300 mg/day) and ofloxacin (200 mg t.i.d.) in the treatment of obstetrical and gynecological infections in 244 patients, both drugs were found to be equivalent in relation to clinical efficacy, bacteriological effect, safety, adverse effects and usefulness (24).

An open-label noncomparative study of grepafloxacin 600 mg q.i.d. for 10 days in the treatment of community-acquired pneumonia was conducted in 273 patients. Of the assessable patients completing the study, the clinical success rate 4-6 weeks after the last dose was 89%. An eradication rate of 95% was seen in microbiologically assessable patients. Treatment was highly effective for community-acquired pneumonia associated with *Streptococcus pneumoniae*, *H. influenzae*, *H. parainfluenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Mycoplasma pneumoniae* and *Legionella pneumophila*; the drug was well tolerated, with taste perversion and nausea the most common side effects (25).

Grepafloxacin (once daily for 7 days) was compared to doxycycline (100 mg p.o. b.i.d. for 7 days) for the treatment of uncomplicated chlamydial genital infection in 79 men and 48 women. Based on clinical and bacteriological evaluation before therapy, at 10-15 days and 28-35 days after therapy, grepafloxacin showed at least comparable effectiveness to doxycycline, with minor side effects reported in both groups (26).

Pharmacokinetic studies of grepafloxacin have shown that peak plasma levels following oral administration are reached around 2 h following ingestion, with a biexponential decline resulting in a 12 h extended half-life. Elimination is primarily metabolic with mostly fecal excretion; renal clearance is only 10-15%. Absorption is not affected by food or gastric pH elevation, but gender-related body weight variations and hepatic impairment (but not renal impairment) affect the pharmacokinetics. Warfarin and theophylline (with a dose reduction) can be

given with grepafloxacin. High grepafloxacin concentrations are achieved in lung, genital tract, bile, gall bladder tissues and polymorphonuclear leukocytes (27).

A multicenter, randomized, double-blind, dose-response study of grepafloxacin for the treatment of acute bacterial exacerbations of chronic bronchitis was carried out on 76 patients aged 23-81 years. Daily dosage regimens of 200, 400 and 600 mg for 14 days were compared. Iterative 2-stage analysis was used for population pharmacokinetic analysis and serial 24 h sputum collections were taken for Gram stain and culture. Grepafloxacin showed first-order absorption after a lag for systemic absorption to begin. Measures of response were related to AUIC (AUC/MIC); AUIC > 175 was optimal, while < 75 was inadequate (28).

The safety and efficacy of grepafloxacin (400 and 600 mg/day) were compared to amoxycillin (500 mg t.i.d.) for 7 or 10 days in the treatment of acute bacterial exacerbations of chronic bronchitis in a randomized, double-blind, double-dummy study of 656 patients (86% completed the study). Both doses of grepafloxacin were as safe and effective as amoxycillin, although side effects were higher in the grepafloxacin 600 mg group (29).

Seven- or ten-day regimens of grepafloxacin 600 mg/day were compared to amoxycillin 500 mg t.i.d. for the treatment of community-acquired pneumonia in a total of 264 patients (207 completed). At follow-up (28-42 days after the last dose) grepafloxacin and amoxycillin showed equivalent results in evaluable patients, while grepafloxacin was superior (both clinical and microbiological success) in the intent-to-treat population with a demonstrable pathogen. Safety profiles were identical (30).

Ten-day treatment with grepafloxacin (400 and 600 mg/day) was compared to ciprofloxacin (500 mg b.i.d.) in a randomized, prospective, double-blind, double-dummy multicenter study with 624 patients suffering from acute bacterial exacerbations of chronic bronchitis. Clinical and bacteriological effectiveness of the three treatment regimens was equivalent, with good tolerance. Only mild to moderate adverse effects occurred with grepafloxacin (31).

The effect of liver impairment on grepafloxacin pharmacokinetics (dosage 400 mg/day for 7 days) was studied in two trials involving 36 patients (14 healthy, 10 with mild hepatic dysfunction and 12 with moderate hepatic dysfunction). Hepatic dysfunction decreased grepafloxacin clearance and increased the peak plasma concentrations, area under the concentration-time curve and urinary excretion; a greater effect was observed with more severe hepatic dysfunction. The authors recommend a grepafloxacin dose of 400 mg/day with mild liver dysfunction and avoidance of grepafloxacin with moderate or greater liver dysfunction (32).

An open-label study involving 20 adults (15 with varying degrees of renal impairment) showed that grepafloxacin pharmacokinetics (dosage 400 mg/day) were unaffected by changes in renal function, and therefore, no dosage adjustment is needed when using grepafloxacin in renally impaired patients (33).

The efficacy and safety of two doses of grepafloxacin (400 and 600 mg once daily) and ciprofloxacin (500 mg b.i.d.) given orally for 10 days have been compared in a multicenter, double-blind, randomized trial in patients with acute bacterial exacerbations of chronic bronchitis; 472 patients were evaluable for efficacy. The results demonstrated equivalent efficacy and good tolerance for all three treatments (34).

The efficacy and safety of 7-day courses of grepafloxacin (400 mg once daily) and doxycycline (100 mg b.i.d.) have been compared in a multicenter, double-blind, randomized trial in 451 women with *Chlamydia trachomatis* endocervical infections. Over 96% of evaluable patients showed bacteriological eradication at the end of treatment and at follow-up at 21-28 days. Clinical efficacy rates for grepafloxacin at the end of treatment and follow-up were 89% and 84%, respectively, and respective rates for doxycycline were 81% and 86%. Both treatments were generally well tolerated (35).

The results from a multicenter trial in 251 evaluable patients with community-acquired pneumonia (CAP) given a 10-day course of grepafloxacin (600 mg/day p.o.) demonstrated its high efficacy and good safety both at the end of treatment and at follow-up 4-6 weeks after the last dose. The fluoroquinolone was effective against CAP caused by both typical and atypical pathogens (36).

Grepafloxacin hydrochloride has been evaluated in three studies in patients with respiratory infections. A preliminary dose-comparison trial was conducted in 127 patients in order to determine the optimal dose for treating chronic respiratory tract infections. On the basis of assessments of clinical efficacy, bacterial efficacy, safety and usefulness, the optimal dose for clinical use in treating this type of infection was determined to be 300 mg p.o. once daily, administered in the morning (37).

The clinical efficacy, safety and utility of grepafloxacin hydrochloride (300 mg p.o. q.d.) in chronic respiratory tract infections was assessed in a double-blind study using ofloxacin (200 mg p.o. t.i.d.) as the control drug. Both drugs were administered for 14 days, and 203 patients were enrolled. Bacterial eradication was 72.9% with grepafloxacin and 84.2% with ofloxacin; clinical efficacy rates were 90.3% and 90.7% respectively. Safety was 79.3% with grepafloxacin, compared to 88.8% with ofloxacin. None of these differences were statistically significant. Thus, the clinical usefulness of grepafloxacin was deemed to be equivalent to that of ofloxacin in treating chronic respiratory tract infections (38).

A double-blind study was conducted to evaluate grepafloxacin's clinical efficacy, safety and usefulness in 256 patients with pneumonia. Again ofloxacin served as the control drug; dosages were the same as in the previous study. Clinical efficacy rates were 96.4% and 92.9% for grepafloxacin and ofloxacin, respectively; bacterial eradication rates were 96.4% and 97.0%, respectively. Safety rates for grepafloxacin and ofloxacin were 81.8% and 83.5%, respectively. None of these differences were statistically significant, and as a result the clinical useful-

ness of grepafloxacin in the treatment of pneumonia was considered to be equivalent to that of ofloxacin (39).

Grepafloxacin (Vaxar™) has been launched in Germany for the treatment of community-acquired pneumonia, acute bacterial exacerbation of chronic bronchitis and sexually transmitted diseases, and is supplied as tablets of 400 and 600 mg. The drug originates from Otsuka and will be marketed in Europe, the U.S. and other territories by Glaxo Wellcome (40, 41).

Glaxo Wellcome's Raxar™ (grepafloxacin hydrochloride) has been approved under the European Commission's mutual recognition procedure in 12 member states of the European Union (42).

Glaxo Wellcome's Raxar™ (grepafloxacin hydrochloride) is now available in the U.S. by prescription (43).

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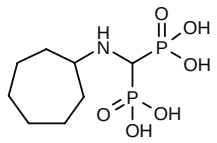

$C_8H_{19}NO_6P_2$ **Yamanouchi**

Findings from a study investigating bone mass and bone mechanical properties in rats treated with YM-175 (0.005-0.15% in drinking water) showed that humeral midshaft failure load, stiffness and ultimate compressive load were significantly increased at higher doses. Treatment for 2 years with YM-175 increased bone mass and mechanical strength, with no decrease in bone mineralization (1).

The drug disposition of incadronate was investigated in nude rats with malignant melanoma-induced bone metastases. Selective uptake was seen around metastatic tumor nests, reaching higher concentrations than required for osteoclast inhibition. Within the tumor nests, drug concentrations were lower than needed to inhibit tumor cells. It was postulated that incadronate inhibits osteoclast activity, thereby preventing osteolysis and metastatic progression (2).

Incadronate disodium at doses of 1, 10, 100 and 1000 μg/kg and a control vehicle were injected into 8-week old ddY female mice. Examination of tibias and femurs the next day showed that osteoclast number/trabecular bone surface increased significantly only with doses of 1 and 10 μg/kg, with weak stimulation of osteoclast and osteoblast formation (3).

Incadronate was given to 6-week old female rats at doses of 10 and 100 μg/kg 3 times a week for 2 weeks prior to fracturing of right femurs. Rats maintained on incadronate (100 μg/kg) showed the most callus formation at 6 and 16 weeks and stronger ultimate strength. However, callus remodelling was delayed in all treatment groups compared to vehicle treatment only (4).

The pharmacokinetics of incadronate (0.025-1.6 mg i.v.) were studied in healthy volunteers and patients with malignancy-associated hypercalcemia. Incadronate showed linear pharmacokinetics, with a delayed clearance in patients due to poor renal function. However, enhanced bone uptake occurred in patients, compensating to a certain extent for the decreased renal clearance (5).

Yamanouchi's injectable formulation of incadronate disodium (Bisphonal®) was introduced for the first in Japan for the treatment of hypercalcemia of malignancy. The product is supplied as ampoules (5 ml) containing 10 mg of the active ingredient (6).

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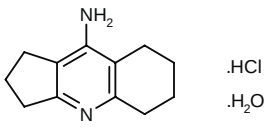

$C_{12}H_{16}N_2.HCl.H_2O$ **Naucho-Issledovatelsky Inst. (RU); Nikken Chem.**

A study comparing the effects of NIK-247 and the cholinesterase inhibitors tacrine and E-2020 showed that all three were strong inhibitors of acetylcholinesterase in human RBCs, producing a mixed inhibition of its activity,

with that of NIK-247 being reversible. Furthermore, all three drugs (0.1-1.0 mg/kg p.o.) improved scopolamine-induced amnesia in rats, but at doses of 1 and 3 mg/kg p.o. did not affect spontaneous movements (1).

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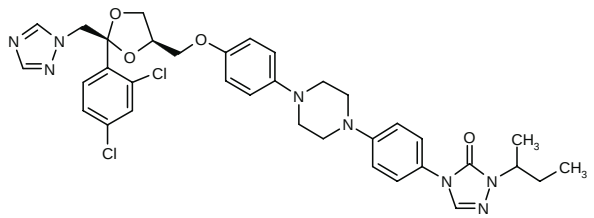

$C_{35}H_{38}Cl_2N_8O_4$ **Janssen; Kyowa Hakko**

A prospective, multicenter, open-label trial in 46 AIDS patients with mild to moderate disseminated histoplasmosis who had successfully completed 12 weeks of induction therapy with itraconazole has evaluated maintenance treatment with itraconazole 200 (42 patients) or 400 mg (4 patients) once daily. During a median follow-up of 87 weeks, only 2 patients relapsed, giving a 1-year relapse rate of 95.3%. These relapses appeared to be due to poor treatment compliance in one patient and concurrent rifampin administration in the other. Treatment was discontinued by 5 patients due to suspected drug toxicity, and 3 of these had possible or probable hepatotoxicity. Thus, itraconazole 200 mg/day appears to be effective and generally well tolerated in preventing relapse of disseminated histoplasmosis in AIDS patients (1).

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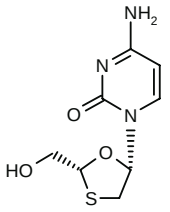

$C_8H_{11}N_3O_3S$ **BioChem Pharma; Glaxo Wellcome; Vion**

A 38-year old female AIDS patient developed severe generalized pruritus and facial uriticaria within 24 h of starting treatment with lamivudine (150 mg b.i.d.) and zidovudine (200 mg t.i.d.). Symptoms cleared upon drug withdrawal and no significant response occurred either with oral zidovudine challenge or skin testing with lamivudine. Oral desensitization with lamivudine in a monitored ambulatory setting was successful (1).

Lamivudine therapy (100 mg/day for 6 months) was evaluated in 8 patients with stable chronic hepatitis delta infection. During therapy, HBV replication was suppressed and HBsAg levels decreased, but ALT levels were not significantly reduced (2).

The results of a phase III trial of Glaxo Wellcome's lamivudine indicate significant efficacy in improving liver histology compared to placebo in patients with chronic hepatitis B. In this multicenter, 1 year study involving 358 Asian patients with chronic hepatitis B, 67% and 59% of patients receiving lamivudine 100 mg and 25 mg orally, respectively, experienced improvements in liver histology compared to 30% of patients receiving placebo. Moreover, fewer lamivudine patients (7% and 10% of patients on 100 mg and 25 mg, respectively) had deterioration of liver histology compared to placebo (32%). In addition, the study also revealed that 16% of patients on lamivudine 100 mg compared to 4% of patients on placebo experienced seroconversion, the conversion being from HBeAg-positive to HBeAg-negative, with undetectable hepatitis B virus (HBV) DNA. This response is indicative of the body's immune system effectively responding to this viral protein. Sustained reductions in the levels of HBV DNA, an important marker of viral replication and viremia (the level of virus in the blood), in the lamivudine treatment arms data in phase II trials. Glaxo Wellcome intends to file for regulatory approval of this drug worldwide with initial petitions to be filed in Asia later this year (3).

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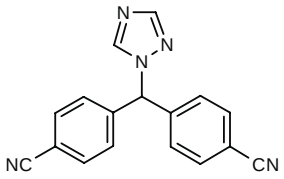
Original monograph - Drugs Fut 1993, 18: 319.

Letrozole
Femara®

Antineoplastic
Aromatase Inhibitor

EN: 164958



$C_{17}H_{11}N_5$ **Novartis; Chugai**

Absorption of a single oral dose of letrozole (2.5 mg) was compared in the fasting and fed states in 12 healthy male volunteers. While absorption rate was decreased in the fed state, extent of absorption remained the same. Due to the drug's long half-life (~ 2 days), the absorption rate change is of no clinical significance for prolonged therapy (1).

In a randomized, open-label clinical trial, letrozole at doses of 0.5 mg or 2.5 mg daily was compared to aminoglutethimide 250 mg b.i.d. plus hydrocortisone or cortisone acetate in 555 women with advanced breast cancer previously treated with antiestrogens. After 33 months, letrozole was clearly superior in relation to TTP and TTF, and showed a trend to improved overall survival. Less than 3% of patients on letrozole dropped out because of side effects (2).

Novartis has launched letrozole tablets (Femara™), a once-a-day therapy for the treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy, in the U.S. (3).

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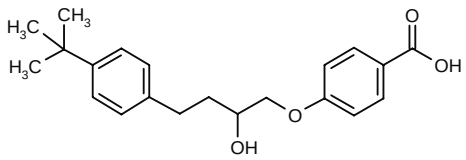
Sinha, S. et al. *Effect of CGS 20267 on ovarian aromatase and gonadotropin levels in the rat.* Breast Cancer Res Treat 1998, 48(1): 45.

Lifibrol

Hypolipidemic

EN: 106850



$C_{21}H_{26}O_4$ **Klinge Pharma; Merckle**

Stable isotope studies of lifibrol were performed in 5 male patients with type IIb hyperlipidemia, treated with lifibrol 450 mg for 12 weeks, and 2 male patients with type IIa hyperlipidemia, tested before and after lifibrol 450 mg and again after lifibrol 600 mg for 4 weeks. In type IIb, total cholesterol decreased 20% and triglycerides 11%, and in type IIa, cholesterol fell 36% and triglycerides 12%. In both types, LDL apoB levels fell, apparently as a result of increased fractional catabolic rates (67%), with only a

slight increase in production (38%), suggesting higher LDL-receptor activity (1).

A randomized, placebo-controlled, crossover study examined the effect of lifibrol (600 mg/day) in 11 adult males with hypercholesterolemia; each study phase lasted 2 months. Reductions were seen in total cholesterol (29%), triglyceride (18%), total apoB (25%) and apoA-I transport rate (9.7%). Mean HDL cholesterol and plasma apoA-I were not reduced, and increased LDL clearance was seen in some patients (2).

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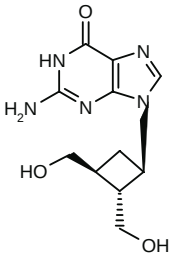
Original monograph - Drugs Fut 1995, 20: 352.

Lobucavir
BMS-180194

Antiviral

EN: 166978



$C_{11}H_{15}N_5O_3$ **Bristol-Myers Squibb**

In a study of lobucavir in the woodchuck model of human chronic hepatitis B, oral doses of 5-20 mg/kg/day were given for 4-12 weeks to woodchucks with chronic WHV infection. Serum levels of WHV DNA were significantly reduced in animals treated with 10 or 20 mg/kg/day, whereas reductions were not significant in the 5 mg/kg/day group. The effective dose to treat chronic WHV infection in this model was determined to be 10 mg/kg/day (1).

A dose-escalating pilot study examined the *in vivo* anti-CMV activity and safety of oral lobucavir (200 mg b.i.d., 200 mg q.i.d. and 400 mg q.i.d. for 28 days) in patients infected with both HIV and CMV. Anti-CMV activity was demonstrated by CMV viruria eradication and semen CMV titer reduction. All doses of the drug were well-tolerated, and no drug-related laboratory or clinical adverse events were observed (2).

A randomized, double-blind, placebo-controlled phase I/II study of 28-day courses of 2 doses of lobucavir (200 mg b.i.d. and 200 mg q.i.d.) was conducted in 22 patients with chronic hepatitis B (with liver transaminases under 5 times ULN). HBV DNA levels decreased 2-4 log with both dosage levels and the treatment was well tolerated; no difference in adverse events was observed between treatment and placebo (3).

Two dose regimens of lobucavir were given to 22 adults with chronic HBV with well-compensated liver disease in a double-blind, placebo-controlled, randomized study for 28 days, with 3 months follow-up. Of the 22 patients, 5 were treated with placebo, 7 with lobucavir 200 mg b.i.d. and 10 with lobucavir 200 mg q.i.d. Serum HBV DNA levels were reduced by 2- to 4-log in lobucavir-treated patients. Patients had few adverse events, with no difference between the groups (4).

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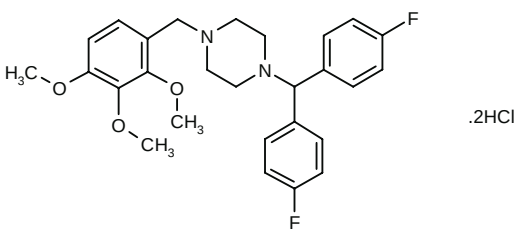
Lomerizine Hydrochloride

Antimigraine
Calcium Channel Blocker

EN: 130942



$C_{27}H_{30}F_2N_2O_3.2HCl$ **Kanebo; Pharmacia & Upjohn**

The effects of lomerizine on potassium- and serotonin-induced contractile responses were examined in isolated canine basilar, mesenteric and coronary arteries. Lomerizine showed stronger inhibition of potassium-induced contraction than of serotonin-induced contraction in basilar arteries, and had stronger inhibition of serotonin-induced contraction in basilar arteries than in mesenteric and coronary arteries. These results suggest that lomerizine has a preferential effect on cerebral arteries, different from that of classical calcium channel blockers (1).

In a study of the effects of lomerizine (0.03-1 mg/kg i.v.) on blood flow and mean arterial blood pressure in anesthetized beagles, the drug was shown to increase arterial blood flow (vertebral, superior mesenteric and femoral) and decrease mean arterial blood pressure dose-dependently. Compared to other calcium channel blockers, lomerizine caused a milder reduction of mean arterial blood pressure and improved cerebral blood flow more than peripheral blood flow, with little change in blood pressure (2).

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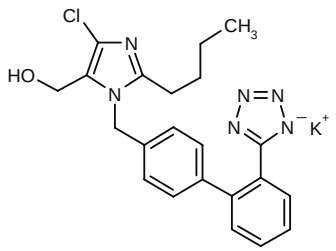
Losartan Potassium *Antihypertensive*
Cozaar® *Angiotensin II Blocker*
Lorzaar®
Lozaprex®

EN: 162288



$C_{22}H_{22}ClKN_6O$ **DuPont Merck Pharm.; Merck & Co.; Banyu**

Losartan (60 mg/l) was administered to 9 uninephrectomized Lewis rats starting 10 days after orthotopic transplantation of a F344 kidney, when excision of the contralateral kidney was carried out. Nine rats served as controls. Treatment resulted in significantly less focal and segmental glomerulosclerosis, suggesting that angiotensin II plays a role in renal allograft injury in this experimental model (1).

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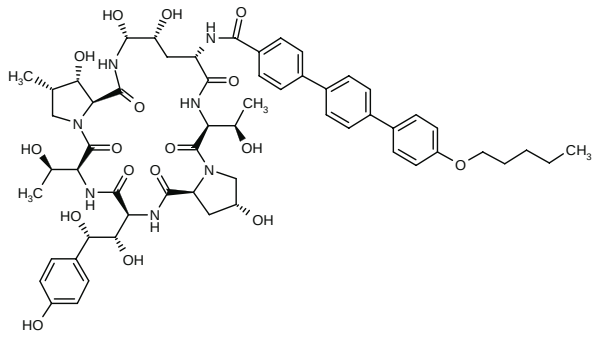
LY-303366 *Antifungal*

EN: 194685



$C_{58}H_{73}N_7O_{17}$ **Lilly**

The *in vitro* activity of LY-303366 was evaluated against 195 strains of filamentous fungi. Results showed that the agent was effective against *Paracoccidoides brasilienis*, *Histoplasma capsulatum*, phaeohyphomycosis agents, with less activity against *Blastomyces dermatitis*, *Penicillium marneffei* and *Coccidoides immitis*, and poor activity against *Sporothrix schenckii*, *Fusarium* spp., *Pseudallescheria boydii*, *Scedosporium prolificans*, *Zygomycetes* and chromoblastomycosis agents (1).

Results of an *in vitro* study comparing the activity of LY-303366 against 145 clinical isolates of *Candida* spp. to amphotericin B and fluconazole showed that the drug is effective against *C. albicans* (MIC_{90} = 0.5 mg/ml), *C. tropicalis* (MIC_{90} = 0.125 mg/ml), *C. krusei* (MIC_{90} = 0.5 mg/ml), *C. norvegenis* (MIC_{90} = 0.5 mg/ml) and *T. glabrata* (MIC_{90} = 1.0 mg/ml), but less effective against *C. parapsilosis* (MIC_{90} = 8.0 mg/ml). Except for *C. parapsilosis*, the drug's activity was better than or comparable to amphotericin B and fluconazole (2).

A comparative study of *in vitro* antifungal activity of LY-303366 and other antifungal agents against 435 clinical yeast isolates of *Candida* and *Saccharomyces cerevisiae* showed high activity for LY-303366 in RPMI-1640 test

medium (comparable to amphotericin B and itraconazole) and more potency in antibiotic medium 3 (16 to > 2,000 times more potent than itraconazole, fluconazole, amphotericin B and 5FC) for all species but *Candida parapsilosis* (3).

In vitro susceptibility testing of LY-303366 and comparators showed that, based on MICs, LY-303366 was effective against *Candida albicans*, *C. glabrata*, *C. tropicalis* and *Aspergillus* species, but was less effective against *C. parapsilosis* and inactive against *C. neoformans* and *B. dermatitidis* (4).

A study of *in vitro* susceptibility to LY-303366 of 191 yeast isolates using the broth microdilution method showed the following MICs at which 50% of isolates were inhibited: 0.125 μg/ml for *Candida tropicalis* and *C. albicans*; 0.25 μg/ml for *C. glabrata*, *C. kefyr* and *C. krusei* and 2.0 μg/ml for *C. parapsilosis* (5).

Using a microdilution method to evaluate the *in vitro* susceptibility of various yeasts (12 different ATCC strains and 245 clinical isolates) to LY-303366, amphotericin B and fluconazole, it was found that LY-303366 showed activity not only against *Candida* species known to be susceptible to fluconazole (*e.g.*, *C. albicans*), but also against strains that are fluconazole-resistant, such as *C. krusei* and *C. glabrata* (6).

An *in vitro* study of LY-303366, fluconazole, flucytosine and amphotericin B against 105 isolates of nine different *Candida* species using a microtiter modification of the NCCLS M27-T proposed standard, showed that LY-303366 is fungicidal and had strong activity against most fungi (at lower concentrations than the comparator drugs) except *C. parapsilosis* and *C. guilliermondi* (7).

Comparison of the *in vitro* antifungal activity of LY-303366, L-743,872 and comparator drugs against 51 clinical isolates of *Aspergillus*, *Fusarium, Rhizopus* and other filamentous fungi showed that LY-303366 was 2-4 times more active against all species (except *P. boydii*) than L-743,872, and both were more active against *Aspergillus* species than itraconazole, amphotericin B and 5-flucytosine, but less active against *Rhizopus*. LY-303366 was more active than L-743,872 and itraconazole against *Fusarium* species (8).

Using a macrobroth doubling dilution checkerboard method, potential synergistic combinations of LY-303366 with other antifungal agents were investigated. Additivity or indifference was shown by LY-303366 in combinations against *Candida* species, except with ketoconazole, which showed antagonism against *C. tropicalis* (9).

A multiple-dose, *in vitro* pharmacodynamic model of LY-303366 activity against *C. albicans* showed that the drug exhibited nondose-dependent activity for all strains at concentrations from 0.1-100 times the MIC. No difference in activity was seen between fluconazole-resistant and fluconazole-susceptible strains (10).

A study of LY-303366's activity against *Aspergillus fumigatus* in a temporarily neutropenic murine model of disseminated aspergillosis revealed that the drug was active against both amphotericin B-susceptible and amphotericin B-resistant infections (11).

An *in vitro* study, using the NCCLS broth microdilution method for MIC determination, compared the antifungal activity of LY-303366, amphotericin B, fluconazole and itraconazole against 75 various fungal isolates, two NCCLS QC isolates and 4 reference isolates. Compared to the other drugs, LY-303366 had greater activity against *C. albicans*, *C. tropicalis* and *C. glabrata*, less activity against *C. neoformans* and *T. beigeli*, and at least equal activity against *Aspergillus flavus*, *A. fumigatus*, *C. parapsilosis* and *C. krusei*, but not *C. guilliermondi* (12).

An *in vitro* study of the activity of LY-303366 against clinical isolates of fluconazole-sensitive and -resistant *C. albicans* showed dose-independent killing (1-2 $\log_{10}$) at various concentrations (1-1000 times the MIC). At their MICs, LY-303366 demonstrated similar fungicidal activity to amphotericin B against the above organisms, *C. glabrata* and *C. krusei*, while stasis or growth occurred with fluconazole (13).

LY-303366 and nikkomycin Z have been evaluated for potential synergy as regards both inhibitory and fungicidal activity against various fungal strains. Strong synergy was found for both inhibition and killing of *Aspergillus fumigatus*, and for *Candida albicans* synergy for inhibition and a trend for synergy for killing were noted. Differential effects were observed for different isolates of *Rhizopus*, *Fusarium*, *Coccidioides* and *Histoplasma capsulatum*. Overall, the results suggest potent synergistic effects for these antifungal agents with different mechanisms of action against certain difficult-to-treat fungal pathogens (14).

In a comparison of the efficacy of LY-303366 and amphotericin B for the treatment of murine pulmonary histoplasmosis, mice treated with LY-303366 survived for 14 days compared to 28 days for amphotericin B. Furthermore, analysis of fungal burdens in spleen and lung following a sublethal inoculum showed that LY-303366 was not effective in this model (15).

A placebo-controlled study comparing LY-303366 (escalating doses 1-20 mg/kg/day) to amphotericin B (1 mg/kg/day) for the treatment of experimental invasive pulmonary aspergillosis in neutropenic rabbits, showed that both drugs decreased pulmonary injury, as measured by infarct score and lung weight, and LY-303366-treated rabbits had significantly better survival (16).

In an open, crossover, single-dose escalation study on 26 healthy volunteers, LY-303366 at doses of 7-100 mg was shown to have linear pharmacokinetics, achieve high plasma concentrations, have a long half-life permitting once daily administration and was well tolerated (17).

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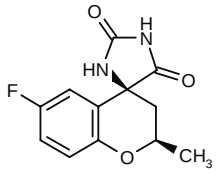
Methosorbinil

Symptomatic Antidiabetic
Aldose Reductase Inhibitor

EN: 090923



$C_{12}H_{11}FN_2O_3$ **Eisai**

The effects of M79175 on retinal vascular changes were investigated in 9-month old male beagle dogs fed either 30% non-nutrient filler or 30% galactose. The galactose-fed animals were split into two groups: one untreated and the other treated with M79175 (average doses of 10 or 16 mg/kg/day). Objective examination of enucleated eyes (one from 4 dogs of each group) revealed that endothelium/pericyte ratios in dogs fed galactose and treated with M79175 (16 mg/kg/day) were no different from controls. All other parameters in treated galactose-fed dogs showed smaller changes than in untreated dogs (1).

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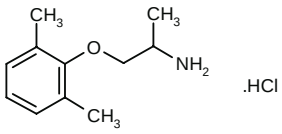
Mexiletine Hydrochloride
Mexitil®

Antiarrhythmic
Symptomatic Antidiabetic

EN: 091522



$C_{11}H_{17}NO.HCl$ **Boehringer Ingelheim**

Mexiletine (450-1200 mg/day) was evaluated in 8 patients with spasmodic torticollis and 2 with blephalospasms. Intensity and frequency of symptoms decreased subjectively and objectively, and patient daily activities improved in all cases. Four patients experienced side effects: GI symptoms, dizziness, ataxia and dysarthria (1).

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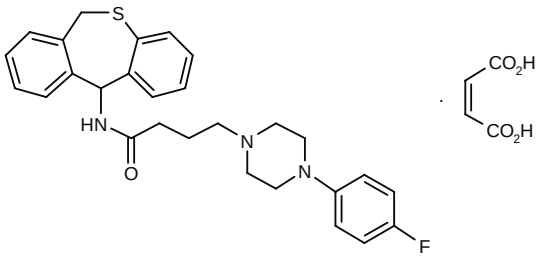
Monatepil Maleate

Antihypertensive
Calcium Channel Blocker

EN: 136016



$C_{28}H_{30}FN_3OS.C_4H_4O_4$ **Dainippon**

The effects of monatepil on LDL receptor activity and expression have been evaluated based on the observation that the compound is associated with a significant decrease in LDL cholesterol levels in hypertensive patients. Using human skin fibroblasts, monatepil at a concentration of 10 μM increased [^{125}I]-LDL binding and internalization by 273% and 298%, respectively, and at a concentration of 20 μM it increased degradation by 45%. A 163% increase in LDL receptor mRNA was detected when fibroblasts were incubated with 20 μM monatepil for 6 h. These results suggest that the hypolipidemic effects of this calcium antagonist may be mediated by increased LDL receptor activity (1).

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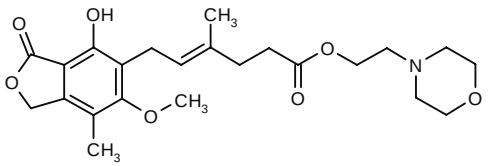
Mycophenolate Mofetil *Immunosuppressant*
CellCept®

EN: 144096



$C_{23}H_{31}NO_7$ **Roche Bioscience**

A pilot study of the use of mycophenolate mofetil (2 g/day p.o.) as an alternative to azathioprine for the treatment of chronically active and perianal Crohn's disease showed that the drug was effective in all 4 patients with perianal disease and could be used as an alternative to azathioprine (1).

Mycophenolate mofetil (2 g/day p.o.) was given to 5 patients with inflammatory bowel disease, 4 of whom were also on continuous 5-ASA. All but 1 patient reported significant symptom reduction within 2 weeks. Main reported adverse events were transient and included increased stool frequency, increased abdominal discomfort and flu-like symptoms (2).

The efficacy of mycophenolate mofetil (CellCept®) in the treatment of rheumatoid arthritis has been evaluated in a series of clinical studies. The compound was administered for periods of up to 2 years at doses ranging from 0.25 g/day to 2 g b.i.d. An overall assessment of the results obtained in these studies shows that at a dose of 1 g b.i.d. mycophenolate mofetil is superior to placebo in terms of efficacy, although with a more frequent incidence of withdrawal due to adverse effects (AEs). At the dose of 2 g b.i.d., the compound was also superior to placebo but not to the 1-g dose. AEs primarily affected the digestive system, such as diarrhea and nausea; no adverse renal, hepatic, hematologic or cardiovascular effects were described. Thus, it appears that at the dose of 1 g b.i.d., mycophenolate is both safe and effective in the treatment of active rheumatoid arthritis (3).

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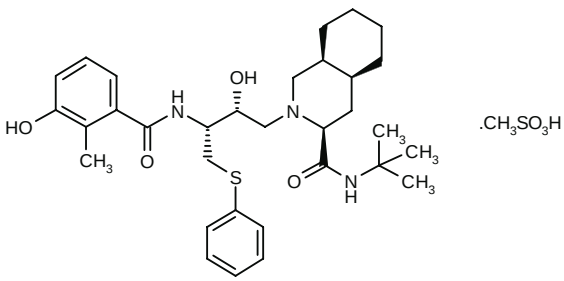
Nelfinavir Mesilate *Antiviral for AIDS*
Viracept® *HIV-1 Protease Inhibitor*

EN: 211732



$C_{32}H_{45}N_3O_4S.CH_4O_3S$ **Agouron; Japan Tobacco; Roche**

A randomized, parallel-group study with 24 healthy volunteers examined the pharmacokinetic drug-drug interaction between delavirdine and nelfinavir. One group received nelfinavir 750 mg t.i.d. for 14 days, with delavirdine 400 mg t.i.d. added on day 8; the other group received delavirdine first, with nelfinavir added on day 8. Results demonstrated that delavirdine decreased nelfinavir's metabolic clearance. Reversible neutropenia caused 4 subjects to drop out; therefore, patients treated with this combination require monitoring for neutropenia (1).

In an open-label, crossover design with 34 healthy volunteers, the pharmacokinetic effect of efavirenz (600

mg/day) on nelfinavir (750 mg q8h) and its metabolite AG-1402 was studied using HPLC. Efavirenz increased nelfinavir's AUC by 20% and decreased that of AG-1402 by 37%. Results indicate that dose modification of nelfinavir is not needed when combined with efavirenz (2).

The safety, activity and pharmacokinetic interactions of stavudine 30-40 mg b.i.d., nelfinavir 750 mg t.i.d. and nevirapine 200 mg/day (increased to 200 mg b.i.d. after 14 days) were studied in 12 patients (of a target of 24 patients) for 9 weeks of treatment. The combination was well tolerated (only 3 of 24 patients dropped out due to adverse events) and strong anti-HIV activity was seen. Pharmacokinetic studies showed no need for any dose adjustments (3).

The pharmacokinetic interaction of nelfinavir and nevirapine was studied in 8 HIV-positive patients. Pharmacokinetic studies were performed when patients reached steady state on nelfinavir (750 mg q8h) and 24 days after nevirapine was begun. Data from 3 patients showed that nevirapine reduced nelfinavir's AUC by a mean of 46% (4).

Combination antiretroviral therapy (d4T, 3TC, ddI and/or nevirapine) including nelfinavir (30 mg/kg q8h) was evaluated in 17 therapy experienced but protease inhibitor naive HIV-infected children. While the median decrease of HIV RNA was good, fewer children than adults appear able to achieve < 500 copies/ml (5).

The pharmacokinetics, safety and efficacy of nelfinavir when combined with nucleoside reverse transcriptase inhibitors was evaluated in 60 HIV-infected children. Dosages of 20-30 mg/kg t.i.d. resulted in steady-state plasma levels similar to adults (oral powder and tablets were equivalent). Median viral RNA decreased by 1.3 log after 10 weeks, with best results occurring with the addition of at least one nucleoside reverse transcriptase inhibitor within 6 weeks. Ater 34 weeks, 55% had no detectable HIV RNA. Only 5 grade 2 or higher adverse events occurred (6).

Pharmacokinetic interactions between nelfinavir (750 mg q8h) and saquinavir hard gel (600 mg q6h) were studied in 6 HIV-positive patients using HPLC. Addition of nelfinavir resulted in approximately 5-fold increases of saquinavir's geometric mean C_{max} and $AUC_{0\text{-}8h}$ when added to patients on saquinavir at steady state. Thus, oral bioavailability of saquinavir is increased 5-fold with nelfinavir (7).

The antiviral effect, safety and multiple-dose pharmacokinetics of saquinavir hard gel alone and with nelfinavir were studied in 20 HIV-positive patients in a 2-period longitudinal study; b.i.d. and t.i.d. dosing was also compared. Preliminary results showed significant increases in saquinavir total and peak plasma exposures by 12.7- and 10-fold, with larger increases occurring in cases with lower baseline saquinavir levels (8).

Analysis of long-term virologic data from a randomized, multicenter clinical trial of nelfinavir in 297 patients with no previous antiretrovirus therapy, showed that 62% of patients treated for 1 year with nelfinavir at 750 mg t.i.d., along with AZT and 3TC, had no detectable plasma viral RNA using a highly sensitive HIV-RNA PCR assay (detection limit of < 50 copies/ml), with an average change from baseline of –29 log10 HIV-RNA copies/ml (9).

A randomized, open-label, 2-group, comparative trial of nelfinavir (1250 mg b.i.d. and 750 mg t.i.d.) with standard doses of 3TC and d4T is under way at 24 European sites with 279 patients enrolled. Pharmacokinetic studies in 21 patients showed no significant differences between the b.i.d. and t.i.d. doses after 4 weeks. Similarly, viral load data and $CD4^+$ counts showed no significant differences after 16 weeks of treatment (10).

An open-label pilot study of two b.i.d. dosing regimens of nelfinavir (1000 mg and 1250 mg) combined with 2 nucleoside reverse transcriptase inhibitors (AZT/3TC or d4T/3TC) is ongoing. Preliminary results showed reductions of HIV RNA with both dosing regimens, with the 1250 mg b.i.d. regimen showing a significant reduction (92% of 12 patients below detectable HIV RNA levels) and the 1000 mg b.i.d. regimen showing 80% below detectable levels (< 400 copies/ml) (11).

Agouron and Japan Tobacco have granted Roche exclusive marketing rights to the HIV protease inhibitor nelfinavir mesilate (Viracept®) for several Asian countries (12).

Agouron's second-generation HIV protease inhibitor nelfinavir mesilate (Viracept®) has been granted marketing approval by the European Commission for the treatment of HIV infection in adults and children in combination with an antiretroviral nucleoside analog (13).

The Japanese Ministry of Health and Welfare has approved Viracept® (nelfinavir mesilate), Agouron's HIV protease inhibitor (14).

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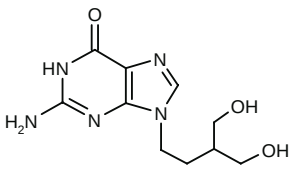
Penciclovir
Denavir®
Vectavir®

Antiviral

EN: 107044



$C_{10}H_{15}N_5O_3$

SmithKline Beecham

An *in vitro* study in 6 human fibroblast cell lines comparing penciclovir's activity against CMV wild strains and CMV strain AD169 using a plaque reduction assay showed that the IC_{50} of penciclovir was significantly higher than those for acyclovir, ganciclovir and foscarnet (1).

A study comparing the efficacy of Zovirax cream (5% acyclovir, applied b.i.d.) to Vectavir Cold Sore Cream (1% penciclovir applied q.i.d.) in the treatment of cutaneous herpes simplex virus in guinea pigs showed that Zovirax, started 2 h after experimental infection and continued for 4 days was clearly superior, but that both drugs were equally effective when started 18 h after infection and continued for 3 days (2).

Four blinded, untreated- or placebo-controlled studies compared Zovirax cream (5% acyclovir, applied b.i.d.) and Vectavir Cold Sore Cream (1% penciclovir, applied b.i.d. or q.i.d.) in the the HSV orofacial mouse model. Acyclovir was clearly superior to penciclovir in relation to suppression of lesion severity and prevention of lesion development (3).

The pharmacokinetics of intravenous penciclovir and its oral prodrug famciclovir were characterized in 11 patients following allogeneic bone marrow or peripheral blood stem cell transplants. From 7 days before transplant to 30 days after, patients received penciclovir (10 mg/kg i.v. infusion for 1 h q8h), followed by oral famciclovir (750 mg t.i.d.) for 2 months. Analysis by reversed HPLC after solid-phase extraction showed that the pharmacokinetics of penciclovir were kidney function-dependent (as in healthy volunteers), and oral famciclovir resulted in plasma penciclovir levels equal to penciclovir i.v. infusion (4).

A phase I/II trial in 11 patients (either CMV seropositive or receiving transplants from a CMV seropositive donor) who received penciclovir (10 mg/kg i.v. infusion q8h) for 7 days before either allogeneic bone marrow or peripheral blood stem cell transplantation, and then for 30 days afterward, followed by oral famciclovir (750 mg t.i.d.) for 2 more months, showed that this regimen was ineffective in preventing CMV antigenemia (55% developed it). However, no patients developed CMV disease (5).

A randomized, double-blind, placebo-controlled, 2-arm, parallel clinical trial examined the use of topical 1% penciclovir cream in patients with a history of herpes labialis. Treatment consisted of cream application within 1 h of the first sign or symptom and continued every 2 h while awake for 4 days. Penciclovir-treated patients showed faster healing, less pain and less lesion virus shedding, independent of when therapy was initiated, with no significant adverse events (6).

A double-blind, acyclovir-controlled (5 mg/kg q8h) study of the use of penciclovir (5 mg/kg q8h or q12h) for the treatment of mucocutaneous HSV infections in 342 immunocompromised patients, beginning within 72 h of onset and continuing for no more than 7 days, showed that there was no significant differences between the 3 treatments regarding new lesion formation, viral shedding, time for complete healing and pain. Adverse effects were also similar and all three regimens were well tolerated (7).

SmithKline Beecham has launched Denavir™ (penciclovir cream) 1%, the first and only topical antiviral cream to be approved by the FDA for the treatment of recurrent cold sores. Denavir™ acts by blocking the activity of herpes simplex virus type 1 (8).

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Perflenapent Emulsion
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Ultrasound Contrast Medium

EN: 202607

2% w/v Dodecafluoropentane emulsion stabilized with fluorosurfactant (0.6% w/v) in a 30% w/v solution of sucrose in water

Sonus

Sonus Pharmaceuticals has announced that it will begin phase III clinical trials of EchoGen® (perflenapent emulsion) as an ultrasound contrast agent for use during stress echocardiography (1).

The FDA has notified Sonus that approval of the company's NDA for EchoGen® requires additional information relating to the manufacturing processes, including chemistry and analytical methods validation. Reanalysis of some of the animal and clinical data is also required (2).

1. *EchoGen enters phase III trials.* Prous Science Daily Essentials August 22, 1997.

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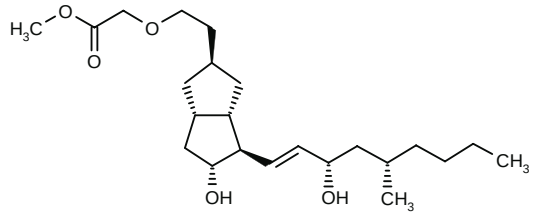
Pimilprost *Treatment of Peripheral Vascular Disease*

EN: 173922



$C_{23}H_{40}O_5$ **Sumitomo**

The affinity for [^{3}H]-iloprost binding sites (using radioligand binding) and the effect on cAMP synthesis of SM-10902 and SM-10906 was examined in human platelets and endothelial cells. It was found that SM-10906 binds to [^{3}H]-iloprost binding sites, and that by increasing intracellular cAMP, the drug produces its antiplatelet and cytoprotective actions (1).

A study of the relationship between serum SM-10902 (and its metabolite SM-10906) concentration and blood pressure, pulse rate and platelet aggregation was conducted in 11 patients with skin ulcers. SM-10906 was detected in the serum of only 7 patients (detection limit 10 pg/ml). No clinically significant relationship between drug blood concentration and blood pressure, pulse rate and platelet aggregation was observed, and no adverse reactions or changes in laboratory tests were seen (2).

A pharmacokinetic and safety study of SM-10902 was carried out in 11 healthy volunteers. SM-10902 ointment (0.15, 0.5, 1.5, and 5 μg/g) was applied as a single occlusive application for 8 h on the forearm skin. While chemical analysis showed skin absorption, serum and urine concentrations of the drug and its main metabolite were below detection limits. Skin blood flow measured by laser-doppler showed marked increase with the highest doses in 5 of 8 cases. A warm feeling, mild itching or a tingly feeling at the application site was reported in 4 cases, and erythema was seen at higher doses (3).

A controlled safety evaluation of SM-10902 ointment at concentrations of 0.00005, 0.000015 and 0.00015% was carried out in 30 healthy volunteers and 11 patients with skin diseases. Twenty-minute closed patch testing showed no contact urticaria and no delayed reactions were seen with 48-h closed patch testing. Skin irritant indices increased with concentration in the 48-h closed patch test in volunteers and photo patch testing showed no photosensitivity reactions (4).

A placebo-controlled study of the safety and pharmacokinetics of SM-10902 ointment (1.5 μg/g applied occlusively for 7 h b.i.d. for 2 days and then once daily for 7 days) was undertaken in 8 healthy volunteers. Skin reactions (mild to moderate erythema) were seen in 3-5 of the 6 active treatment cases each day, with slightly persisting erythema in 2/3 of the cases on the second day, lasting to the next morning. No systemic drug or metabolites were detected, and a marked skin blood flow increase was seen (5).

The safety and efficacy of SM-10902 ointment (0.15, 0.5 and 1.5 μg/g b.i.d.) for the treatment of skin ulcers were evaluated in 108 patients. Povidone iodine solution was used to sterilize ulcers prior to application of ascending concentrations of SM-10902. Final overall efficacy rate was 70.5%, with a 69.5% useful or better rating. Only mild side effects were seen in 5.6% of patients and consisted of tingling sensation, increased ulcer-related pain and diarrhea (6).

A placebo-controlled, double-blind study was conducted in 398 patients to determine the optimal concentration of SM-10902 ointment (1.5, 0.5 and 0.15 μg/g) for skin ulcer therapy. When adjusted for initial ulcer severity, only the highest concentration was significantly better than placebo in final global improvement rating. Usefulness ratings of useful and better were 75% for the two highest concentrations. The optimal SM-10902 concentration appears to be 1.5 μg/g (7).

In a study of the effect of SM-10902 ointment (0.5 and 1.5 μg/g) on skin temperature and skin microcirculation for the treatment of decubitus ulcers in 12 patients, it was found that skin temperature increased significantly after 1 h, plateaued at 2 h and remained elevated after 3 h. Similar changes were seen in skin microcirculation. After 2 weeks, no local or systemic side effects occurred and decubitus ulcer size decreased (8).

The efficacy, safety and utility of pimilprost were compared to those of bucladesine sodium in a group of 276 patients with pressure sores, burn ulcers and leg ulcers. Both compounds were administered as ointment formulations. Moderate or better final global improvement was reported by 81.3% and 69.5% of patients on pimilprost and bucladesine, respectively. Improvement was unusually high in both treatment groups among patients with mild sores, but tended to decrease with increased severity; this decrease was less significant, however, in the pimilprost group. Pimilprost was also significantly superior to bucladesine with respect to improvement in moderate cases. Mild side effects were noted at the site of application in 4.5% and 1.5% of patients on pimilprost and bucladesine, respectively; overall safety was 95.5% and 98.5%, respectively. Pimilprost was suggested to be safe and extremely useful in the treatment of pressure sores and other skin ulcers in this phase III study (9).

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Pramipexole Hydrochloride
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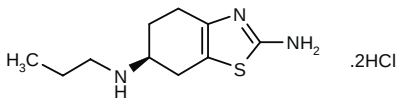

$C_{10}H_{17}N_3S.2HCl$

Boehringer Ingelheim; Pharmacia & Upjohn

The pharmacokinetics of concomitant administration of pramipexole, levodopa and carbidopa were examined in 10 healthy subjects (5 male, 5 female). Following a single dose of Sinemet (25/250 mg), pramipexole was given q8h on a dose escalation scheme to 1.5 mg t.i.d. An open-label, randomized, crossover design was used to give either pramipexole 1.5 mg alone or with Sinemet. Pramipexole pharmacokinetics were unaltered by carbidopa/levodopa, but levodopa absorption rate was increased by pramipexole (statistically significant only in females) (1).

Using HPLC concentration measurement, the steady-state pharmacokinetics of pramipexole at 4 dose levels were studied in 16 healthy subjects. Pramipexole concentrations were proportional to dose, with a gender difference observed which was explainable by different creatinine clearance levels seen with age. Renal clearance of pramipexole was 80% of total oral clearance, with a significant correlation between renal and creatinine clearance (2).

The steady-state pharmacokinetics of pramipexole, in a dose-escalation study from 0.125 mg q8h to 1.5 mg q8h in 16 healthy volunteers (8 male, 8 female), were shown to be linear to the maximum dose studied in both sexes. Clearance was calculated to be 419 ml/min and elimination half-life was 12.9 ± 3.27 h. Renal clearance accounted for 80% of total clearance. While AUC was greater in females, this was due to reduced creatinine clearance due to increased age of the females in the study (3).

The effect of renal function on pramipexole pharmacokinetics was studied in 26 volunteers with varying levels of renal function. All patients received 0.25 mg of pramipexole, with the end stage renal disease patients receiving another dose before hemodialysis. Following 3 h of hemodialysis, < 9% of the oral dose was cleared. Individual pramipexole clearance was highly correlated with creatinine clearance ($p = 0.0001$) (4).

Data from two new open-label extension studies indicate that pramipexole hydrochloride (Mirapex®) tablets remained effective, without the administration of concomitant levodopa, for periods ranging from 15 to 24 months in patients with early-stage Parkinson's disease (5).

A double-blind, placebo-controlled, randomized trial was conducted in 246 advanced Parkinson's disease patients with wearing off, comparing pramipexole (up to 4.5 mg/day), placebo and bromocriptine (30 mg). UPDRS II and III showed improvement for both treatment groups (more for pramipexole) with a trend by pramipexole for improvement in global clinical assessment. Safety data showed no significant differences (6).

In 15 schizophrenic patients treated with haloperidol, addition of pramipexole decreased the PANSS scores by more than 20% (range 22-62%) in 9 patients. The most common side effect reported was insomnia (4 patients). No significant electrocardiographic or laboratory changes were observed (7).

A multicenter, multidosage, parallel-group, double-blind, placebo-controlled, randomized clinical trial of pramipexole (1.5, 3.0, 4.5 and 6.0 mg/day) was conducted in 264 patients with early Parkinson's disease. Dosage escalation occurred over 6 weeks with a 4-week maintenance period, followed by withdrawal of treatment over 1 week. Pramipexole was well tolerated, with a trend to more adverse events with the highest dosage. Using the UPDRS scale, patients on pramipexole showed a significant improvement ($p < 0.005$), with a 20% increase in scores. Improvement was more marked in patients with worse baseline UPDRS scores (8).

An escalating dose-tolerance study of pramipexole was conducted in 26 severely depressed hospitalized patients. A 14-day dose escalation scheme was used, starting at 1.75 mg/day, increasing to the maximum tolerated dose of 6.25 mg/day. Pramipexole resulted in 35% improvements in the HAMD-17, the MADRS and the BMRES scales in about half of the patients, with significant improvements (50%) in about a quarter of the patients. Little or no improvements were seen in 20% of patients; 5 of these failed to complete treatment either from lack of benefit or side effects (9).

The FDA has approved Pharmacia & Upjohn's Mirapex® (pramipexole dihydrochloride) tablets, a dopamine agonist discovered by and codeveloped with Boehringer Ingelheim, for the treatment of Parkinson's disease. The drug can be used with and without levodopa for the treatment of advanced and early stages of the disease, respectively (10).

Pramipexole dihydrochloride (Mirapex®) has been launched in the U.S. by Pharmacia & Upjohn and Boehringer Ingelheim for the treatment of Parkinson's disease. The product is available as tablets of 0.125, 0.25, 1.0 and 1.5 mg (11).

Boehringer Ingelheim's Mirapex® (pramipexole dihydrochloride) has been cleared for marketing in Canada (12).

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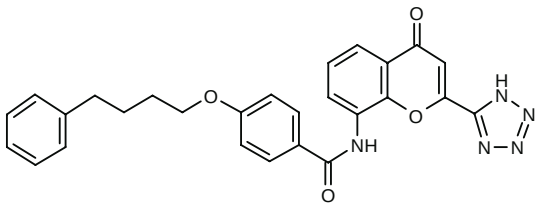

.H_2O

$C_{27}H_{23}N_5O_4.1/2H_2O$ **Ono; SmithKline Beecham**

In a randomized, double-blind, placebo-controlled, crossover study in 8 healthy nonsmoking men, pranlukast (450 mg b.i.d.) given for 5 days significantly increased airways conductance following inhaled leukotriene D_4-induced bronchoconstriction, following a single dose and after prolonged administration. Pranlukast had no effect against histamine challenge (1).

A randomized, double-blind, placebo-controlled, parallel-group, multicenter, 4-week study of pranlukast in the treatment of asthma showed significant increases in morning home PEFR for patients treated with pranlukast 337.5 mg b.i.d. throughout the study, and in week 1 and 2 for a dosage of 225 mg b.i.d. FEV_1 increased significantly 1 h after the first dose and lasted for 8 h. Trough FEV_1 also improved significantly, as well as summary symptom and nighttime asthma scores. No drug-related changes in biochemical or hematological variables were seen, and the drug was well tolerated (2).

The results from the first U.S. clinical trial of pranlukast have been reported. The primary objective of this multicenter, double-blind, randomized, placebo-controlled study was to evaluate the safety and tolerability of doses of 337.5 and 450 mg b.i.d. administered for 4 weeks in 65 patients with mild to moderate asthma. Both doses of pranlukast were well tolerated, no serious side effects or other changes being attributable to the drug. Clinical activity was also observed after both doses of pranlukast at 8 h and over the entire treatment period. Symptom scores and albuterol use were reduced to a greater extent at week 4 in the high-dose pranlukast group compared to the placebo group. Although the results from this trial are consistent with those from Japanese and European trials, longer term studies are in progress to further assess the efficacy and safety of the drug in asthma (3).

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Raltitrexed
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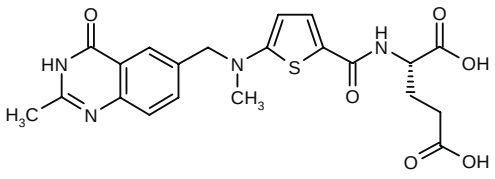

$C_{21}H_{22}N_4O_6S$ **British Technol. Group; Ben Venue Labs.; Zeneca**

A pharmacodynamic study of Tomudex® in 7 patients with advanced colorectal carcinoma showed that, on a dose of 3 mg/m^2 every 3 weeks, drug levels in tumor and bowel on the 5th day showed a 4-fold and 3-fold variation, respectively, and tumor to plasma drug ratios were approximately 90 (1).

Twelve patients with advanced colorectal carcinoma were treated in a phase I study with escalating doses of raltitrexed (0.5-2 mg/m^2) over 15 min followed a day later by 5-FU (900 mg/m^2 bolus). No dose-limiting toxicity was seen and the combination was well tolerated. Two patients showed partial responses and 6 had stable disease (3.7 to > 7.5 months). Pharmacokinetics of 5-FU

were unaffected, suggesting that further dose escalation of both drugs is possible (2).

A randomized, multicenter trial compared raltitrexed (3 and 4 mg/m^2) to 5-FU (425 mg/m^2) plus leucovorin (20 mg/m^2) in 459 patients with advanced colorectal cancer. The raltitrexed 4 mg/m^2 arm was closed after 3 therapy-related deaths. While the response rates were not significantly different between the groups, time to progresion and survival times were significantly shorter for raltitrexed. Overall, raltitrexed showed an acceptable safety profile and a response rate similar to 5-FU plus leucovorin (3).

A study comparing raltitrexed to 5-FU+leucovorin in 495 patients with advanced colorectal cancer showed no differences at 9 month follow-up in median survival rates, objective tumor response rates, hazard ratio and palliative benefits. Raltitrexed-treated patients had significantly lower incidence rates of leukopenia, mucositis (WHO grade 3 or 4) and diarrhea. Dose reduction due to toxicity was required in fewer raltitrexed-treated patients (4).

Preliminary data from 73 patients with advanced colorectal carcinoma treated with Tomudex® (3 mg/m^2 q3w) showed that the most common NCI grade 3 and 4 toxicities were reversible increases in liver transaminases, leukopenia, granulocytopenia, anemia, diarrhea and neurologic manifestations. Less commonly, thrombocytopenia, nausea, vomiting and fatigue occurred. Tumor blocks showed high thymidylate synthase in 36 patients and low thymidylate synthase in 6. Stratification according to previous therapy showed that Tomudex® may be useful in patients showing progression after a previous nonleucovorin regimen (5).

A study of 7 patients with advanced colorectal carcinoma treated with Tomudex® 3 mg/m^2 every 3 weeks showed that tumor TS/β-actin mRNA ratios ranged from 2-7, while large bowel ratios ranged from 3-11. Tumor FPGS/β-actin ratios were 16-560, while bowel ratios were 26-368. Positive staining for p53 was seen in two-thirds of tumors. Tomudex® levels were approximately 4 times higher in tumor than in bowel and bowel toxicity was higher in patients with higher bowel drug levels. Four patients showed disease response (6).

Raltitrexed has been shown to be best administered at a dose of 3 mg/m^2 as a 15-min infusion every 3 weeks. In a phase II study of 177 patients with advanced colorectal carcinoma, a response rate of 26% was seen, with 11.2 months median survival. The drug has an acceptable safety profile, with myelosuppression, GI toxicity, asthenia and transient elevations of liver transaminases being the main adverse events (7).

Based on an examination of adverse events in studies of approximately 1000 patients with advanced colorectal carcinoma treated with raltitrexed, the dose-limiting toxicities include GI toxicity, hematological suppression and asthenia. Compared to treatment with 5-FU/leucovorin, raltitrexed has some tolerability advantages, primarily in relation to mucositis and leukopenia, and it has less toxicity in early treatment cycles (8).

Phase III trials of raltitrexed (3 mg/m^2 q3w) compared to 5-FU with either low- or high-dose leucovorin in patients with advanced colorectal carcinoma are ongoing. Similar results with the three therapies have been reported in relation to objective tumor response rates, median survival and palliative benefits, but longer median time to progression was evident in the 5-FU plus high-dose leucovorin group. Overall, the treatments are similar, although ralitrexed has a more convenient dosing schedule (9).

Raltitrexed has been established as single-agent therapy for advanced colorectal carcinoma, and it is now appropriate to study its use in early disease and in combination with 5-FU, oxaliplatin and irinotecan for advanced disease, as well as for other tumors (10).

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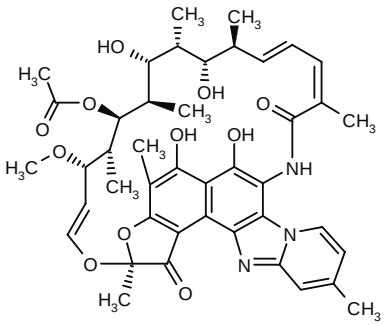
Rifaximin
Normix®

Antibiotic

EN: 090171



$C_{43}H_{51}N_3O_{11}$

Alfa Wassermann; Merckle; Salix; Solochem

Salix has been given FDA clearance to initiate clinical trials with Normix™ for the treatment of antibiotic-associated colitis. The antibiotic was licensed by Salix from Alfa Wasserman (1).

1. *Salix Holdings, Ltd. obtains FDA clearance to start clinical trial with Normix™. Decision follows Investigational New Drug application filed in March.* Salix Holdings, Ltd. Press Release 1997, May 1.

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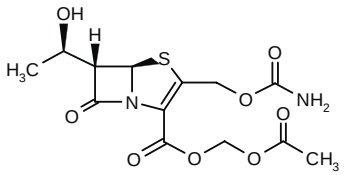
Ritipenem Acoxil
Penemac®

Penem

EN: 159928



$C_{13}H_{16}N_2O_8S$

Pharmacia & Upjohn; Tanabe Seiyaku

An open, noncomparative, pharmacokinetic study of ritipenem acoxil (500 mg t.i.d. for 10 days), conducted in 6 healthy volunteers and using HPLC/UV to measure ritipenem and its open β-lactam ring metabolites, showed that no significant accumulation occurred (half-life of 0.7 h) and the $AUC_{(0\text{-}8h)}$ averaged 10 mg.h/l. Following repeated dosing, ritipenem renal clearance decreased from 132 ml/min to 87 ml/min and urinary excretion of metabolites increased slightly. Time-independent plasma pharmacokinetics were observed for ritipenem and its metabolites (1).

The biliary transfer and clinical efficacy of ritipenem acoxil have been evaluated in patients. In patients undergoing biliary drainage, peak biliary concentrations of ritipenem, the active form, after a single dose of 400 mg were higher than those in plasma. At doses of 150-400 mg t.i.d. for 3-9 days, the drug was associated with excellent, good and fair clinical efficacy in 9, 18 and 4 patients with surgical infections, respectively. Bacteriological eradication rates were 93.8% against Gram-positive bacteria, 80.0% against Gram-negative bacteria and 100% against anaerobic microorganisms (2).

1. Poggesi, I., Spinelli, R., Frigerio, E., Strolin Benedetti, M., Carra, L., Sassella, D., Rimoldi, R. *A study of the pharmacokinetics and tolerability of ritipenem acoxil in healthy volunteers following multiple oral dosing.* J Antimicrob Chemother 1997, 40(2): 291.

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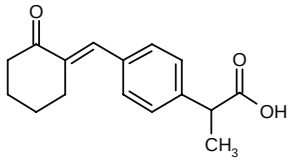
RS-2131
CS-670
Pelubiprofen

Antiinflammatory

EN: 090156



$C_{16}H_{18}O_3$ **Sankyo**

Pelubiprofen has been proposed as the international nonproprietary name for RS-2131 (1).

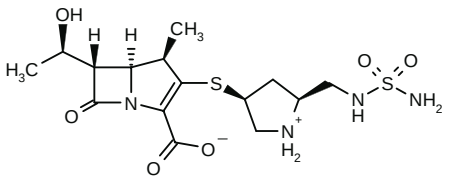
1. *Proposed international nonproprietary names (Prop. INN): List 76.* WHO Drug Inform 1996, 10(4): 214.

Original monograph - Drugs Fut 1984, 9: 275.

S-4661

Carbapenem

EN: 194141



$C_{15}H_{24}N_4O_6S_2$ **Shionogi**

In a comparison of the *in vitro* antibacterial activities of S-4661, imipenem and meropenem, S-4661 showed greater activity against Gram-negative bacteria and equivalent activity against Gram-positive bacteria, based on examination of 1503 isolates (26 species) (1).

A study of the S-4661 influx and efflux routes through the outer membrane of *Pseudomonas aeruginosa* showed that S-4661, like meropenem, uses the OprD channel to enter the outer membrane and exits through the MexAB-OprM efflux system. S-4661 shows stability against the *P. aeruginosa* chromosomal β-lactamase (2).

Carbapenem resistance was induced in 7 susceptible *Pseudomonas aeruginosa* strains and a comparison of MICs between S-4661, meropenem and imipenem showed MICs of 1.6-12.5 μg/ml, 3.2-25 μg/ml and 12.5-25 μg/ml, respectively. Cross-resistance with other β-lactams was not seen. Resistant *P. aeruginosa* showed significant concentration decreases in a particular outer membrane protein (3).

A study of potential synergistic effects of S-4661 and either vancomycin or teicoplanin against MRSA using the checkerboard technique with Mueller-Hinton agar showed synergy was present even though the strains were carbapenem-resistant. Severe infections due to MRSA strains may respond to a combination of S-4661 and either vancomycin or teicoplanin (4).

S-4661 has been evaluated *in vitro* and compared to imipenem, meropenem, biapenem, cefpirome and ceftazidime. S-4661 displayed a well-balanced and wide spectrum of activity against Gram-positive and Gram-negative bacteria. It was more active than meropenem against Gram-positive strains and more active than imipenem against Gram-negative microorganisms, and it was particularly active against members of the family *Enterobacteriaceae*, *Haemophilus influenzae* and *Moraxella catarrhalis*. Additionally, it was the most active antibiotic tested against imipenem-resistant *Pseudomonas aeruginosa* and was also active against a number of ceftazidime-, ciprofloxacin- and gentamicin-resistant isolates of *P. aeruginosa*. Its activity was also assessed in murine systemic infection models and respiratory tract infections in mice caused by *Streptococcus pneumoniae*, and compared to that of imipenem/cilastatin, meropenem/cilastatin, vancomycin, ceftazidime and/or cefotaxime. Although the compound showed good protective effects, even in infections caused by resistant strains of *P. aeruginosa* or penicillin-resistant *S. pneumoniae*, its efficacy was less than expected from its *in vitro* activity. Pharmacokinetic studies in mice showed that combination with cilastatin increased the AUC and prolonged the half-life of S-4661, similar to imipenem and meropenem, and it is suggested that future studies should examine the efficacy of the combination. These results indicate that S-4661 is a promising carbapenem for the treatment of infections caused by both Gram-positive and Gram-negative bacteria, including resistant strains (5).

In a comparison of the anticonvulsant activity in mice of S-4661, other carbapenems and cephalosporins, it was seen that S-4661 had the weakest convulsant activity following intraventricular injection, not inducing convulsions up to 500 nmol/head. S-4661 also showed the weakest GABA receptor binding inhibition with an IC_{50} of 50 mM (6).

Following a 30-min i.v. drip infusion of S-4661, concentration levels were 0.14-0.4 μg/g in sputum, < 0.16-15.4 μg/ml in bile, < 0.1-1.87 μg/g in gallbladder tissue and < 0.20-10.6 μg/g in female genital tissue. A maximum serum level of 8.03-15.0 μg/ml was seen, resulting in a serum transfer ratio of 1.03-4.8%. Transfer to retroperitoneal fluid occurred at 3.15-9.82 μg/ml 30-60 min after the infusion, and at the higher dose of 500 mg reached a level of 9.53-13.9 μg/ml. All these levels were equal to or greater than levels reached with other carbapenem antibiotics (7).

The use of S-4661 (250-1000 mg/day b.i.d. or t.i.d. for 3-8 days) in complicated urinary tract infections was studied in 52 patients (20-75 years old) in a phase II trial.

Efficacy (based on 34 patients, 16 with pyelonephritis) was 93.8%, with a bacteriological eradication rate of 98.2%. Adverse events included 1 case of rash and transient elevations of liver function tests, which returned to normal without requiring treatment discontinuation (8).

S-4661 (250-1000 mg/day b.i.d. or t.i.d. for 5-15 days) was studied in 55 patients with chronic respiratory infections in a phase II trial. Overall efficacy (in 42 eligible patients) was 95.2% with a bacterial eradication rate of 87.5%. Only mild adverse events occurred, including tongue numbness, headache, eosinophilia (6 cases) and increased liver enzymes (2 cases); all adverse events disappeared by the end of treatment (9).

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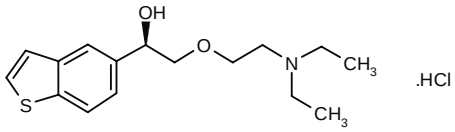
T-588

Cognition Enhancer

EN: 197376



$C_{16}H_{23}NO_2S.HCl$ **Toyama**

An *in vitro* study of T-588-stimulated noradrenaline release in rat cerebral cortical slices demonstrated that the stimulation is not dependent on Ca^{2+} and calmodulin, but may be mediated through *N*-ethylmaleimide-sensitive factors, despite evidence that a different mechanism appears to be at work (1).

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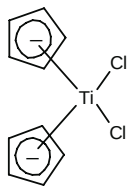
Titanocene Dichloride

Antineoplastic
Titanocene Complex

EN: 121909



$C_{10}H_{10}Cl_2Ti$ **Inst. Anorg. Analyt. Chem. (DE); Medac**

A phase I dose-escalation trial of titanocene dichloride (70-185 mg/m^2/week as a 1-h infusion) was conducted in 20 patients with a range of solid tumors. Various drug-limiting toxicities occurred at 185 mg/m^2, including fatigue, bilirubinemia and hypokalemia. Partially reversible nephrotoxicity was cumulative and dose-dependent. Metallic taste and emesis also occurred. Titanium was detected at doses greater than 140 mg/m^2. Suggested phase II dosage is 140 mg/m^2/week (1).

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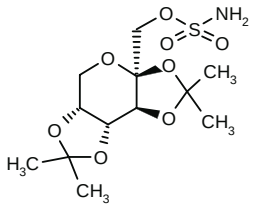
Topiramate *Anticonvulsant*
Topamax®
Topimax®

EN: 105605



$C_{12}H_{21}NO_8S$ **Janssen-Cilag; Kyowa Hakko**

A retrospective review of case records and medical charts of 38 patients with refractory partial-onset seizures who participated in double-blind or open-label studies of topiramate showed a 58% incidence of side effects (psychomotor slowing, mild subjective dysnomia and memory problems). In 10 patients, side effects occurred only with initial use, in 5 they began early and resolved partially, in 5 they began early and resolved but returned at higher doses, and in 2 they appeared only later at higher doses. Seven patients discontinued treatment due to side effects (1).

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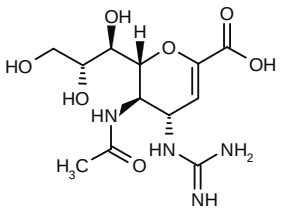
Zanamivir *Antiviral*
Relenza®

EN: 191315



$C_{12}H_{20}N_4O_7$ **Biota Holdings; Glaxo Wellcome**

Analysis of nasal wash samples from patients with influenza treated with zanamivir or placebo by plaque reduction assays in MDCK cells and neuraminidase enzyme assays showed that no resistant strains to zanamivir developed during treatment (1).

A randomized, unblinded, pilot study involving 88 healthy volunteers comparing zanamivir (inhaled 10 mg for 14 days) and standard rimantadine (100 mg) for the prophylaxis of influenza A in a nursing home epidemic showed that both regimens were equally effective in preventing flu-like illness and influenza A isolates (2).

A gamma scintigraphy study of radiolabelled zanamivir administered by Diskhaler dry powder device to 11 healthy subjects showed that, on average,13.2% of the inhaled dose was distributed evenly in the lungs, and 77.6% was left in the oropharynx. Further study of a prototype inhaler showed similar results (12.6% lungs, 81.1% in oropharynx) (3).

Two randomized, double-blind, double-dummy, placebo-controlled trials compared zanamivir (10 mg by inhalation or 6.4 mg by nasal spray with 10 mg by inhalation) for 5 days with placebo for the early treatment of influenza in 417 patients (63% with proven influenza). Duration of illness was shorter in the zanamivir-treated group (mean 1 day less), especially those with fever at onset or duration of illness < 30 h (3 days shorter). Nasal wash viral titers were also decreased by zanamivir (4).

A randomized, blinded, placebo-controlled study of zanamivir (b.i.d. or q.i.d.) for 5 days in influenza-infected patients showed that both regimens improved patient health status and productivity, while decreasing healthcare contacts, based on patient questionnaires and monitoring of healthcare contacts (5).

The effect of zanamavir on influenza-induced middle ear pressure (MEP) abnormalities was studied in randomized, double-blind, placebo-controlled trials with 185 healthy volunteers injected with either influenza A/Texas/36/91(H1N1) or B/Yamagata/88 viruses. Zanamavir given intranasally as prophylaxis and as early treatment significantly reduced MEP abnormalities for both influenza A and B (6).

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