Drugs of the Future 1999, 24(8): 899-948

CCC: 0377-8282/99

Information Update

Volume 1-23, Number 8

Estimated developmental phase for this month's updated products:

Preclinical

L-Histidinol (antineoplastic; Univ. Saskatchewan)
L-FMAU (anti-HBV; Bukwang, Triangle, Abbott)
LU-25-109T (treatment of urinary incontinence, muscarinic M_1 agonist, muscarinic M_2 antagonist)
SPA-S-753 (antifungal; SPA, Kaken, IntraBiotics)

Phase II

ABT-431 (antiparkinsonian, dopamine D_1 agonist; Abbott)
Adozelesin (antineoplastic; Pharmacia & Upjohn, Yakult Honsha)
APC-366 (antiallergic/antiasthmatic; AxyS, Bayer)
DA-125 (antineoplastic antibiotic; Dong-A)
Ensaculin hydrochloride (cognition enhancer; Schwabe)
FK-960 (cognition enhancer; Fujisawa)
L-651582 (antineoplastic; Merck & Co., Natl. Cancer Inst.)
Liposomal NDDP (antineoplastic, platinum complex; Aronex, M.D. Anderson Cancer Center)
ONO-4007 (antineoplastic, immunomodulator; Ono)
Oral heparin/SNAC (anticoagulant/absorption promoter; Emisphere, Elan)
Piclamilast (antiarthritic, phosphodiesterase IV inhibitor; Rhône-Poulenc Rorer)

Phase III

524W91 (anti-HIV, anti-HBV; Emory Univ., Triangle, Abbott)
Eberconazole nitrate (antifungal; Salvat, Soc. Española Especialidades Farmaco-Terapeuticas, Wassermann)
NK-104 (hypolipidemic, HMG-CoA reductase inhibitor; Kowa, Nissan Chem., Sankyo)
Pimagedine (treatment of diabetic nephropathy; Alteon, Yamanouchi)
T-614 (antiarthritic; Toyama, Eisai)

Preregistered

Adefovir dipivoxil (anti-HIV, anti-HBV; Gilead)
Alosetron hydrochloride (treatment of IBS, 5-HT_3 antagonist; Glaxo Wellcome)
AR-121 (antifungal; Aronex, Ferrer, Abbott, M.D. Anderson Cancer Center)
Bropirimine (antineoplastic; Pharmacia & Upjohn, Yakult Honsha)
Delmopinol hydrochloride (dental agent; Biosurface Pharma)
Pazufloxacin (quinolone antibacterial; Toyama, Yoshitomi)
Prulifloxacin (quinolone antibacterial; Nippon Shinyaku, Meiji Seika)
Tasosartan (antihypertensive, angiotensin AT_1 antagonist; American Home Products, Wyeth-Ayerst)

Registered/Year

Levobupivacaine hydrochloride (local anesthetic; Chiroscience, Maruishi, Purdue Pharma, Abbott)/1998

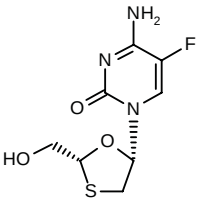
Launched/Year

Budipine hydrochloride (antiparkinsonian, NMDA antagonist; Lundbeck, Byk Gulden)/1997
Cefditoren pivoxil (cephalosporin; Meimi Seika, Abbott, Grünenthal, TAP)/1994
Latanoprost (antiglaucoma; Pharmacia & Upjohn)/1996
Leflunomide (antiarthritic, antineoplastic; Hoechst Marion Roussel, Sugen, Kyorin)/1998
Lepirudin (anticoagulant; Hoechst Marion Roussel)/1997
Lornoxicam (antiinflammatory; Nycomed Amersham, Andrómaco, Merckle, Taisho)/1997
Mizolastine (treatment of allergic rhinitis, histamine H_1 antagonist; Sanofi-Synthélabo, Mitsubishi Chem.)/1998
Pantoprazole sodium (treatment of GERD, H^+/K^+-ATPase inhibitor; American Home Products)/1994
Ropinirole hydrochloride (antiparkinsonian, dopamine D_2 agonist; SmithKline Beecham, Recordati)/1996
Rosaprostol sodium (antiulcer; Ist. Biochim. Ital. Giovanni Lorenzini)/1985
Samarium (^{153}Sm) lexidronam (analgesic; Cytogen, Berlex, DuPont Pharm.)/1997
Sibutramine hydrochloride monohydrate (antiobesity; Knoll, Eisai, Hokuriku)/1998
Tacrolimus (treatment of transplant rejection, antiarthritic, treatment of atopic dermatitis; Fujisawa, Johnson & Johnson)/1993
Temozolomide (antineoplastic; Schering-Plough, Natl. Cancer Inst., Cancer Res. Campaign)/1999
Tolcapone (antiparkinsonian, COMT inhibitor; Roche)/1997 (withdrawn)
Trandolapril (antihypertensive, ACE inhibitor; Kos Pharm., Hoechst Marion Roussel, Knoll, Chugai)/1993

524W91
(–)-FTC
Emtricitabine
Coviracil®

Anti-HIV
Anti-HBV

EN: 190016



$C_8H_1FN_3O_3S$ **Emory Univ.; Triangle; Abbott**

A method has been developed for determining the intracellular levels of FTC-TP in human peripheral blood mononuclear cells from HIV-infected patients. Findings indicated a significant correlation between viral load decline and intracellular levels of FTC-TP (1).

A phase I/II randomized, 12-day study examined the antiviral activity of FTC (25, 100 or 200 mg/day) as compared to 3TC (150 mg b.i.d.) in 81 antiretroviral naive HIV-infected patients. Significantly greater antiviral activity was noted in patients receiving 200 mg FTC as compared to 3TC-treated patients while no differences were observed between 3TC and 25 and 100 mg FTC. Plasma HIV RNA decreases from baseline were 1.45, 1.48, 1.60 and 1.70 $\log_{10}$ for 3TC and 25, 100 and 200 mg FTC, respectively. All regimens were concluded to be well tolerated with 2 patients receiving 200 mg FTC developing asymptomatic CPK elevations (2).

Forty HIV-infected volunteers received FTC in an escalating-dose fashion (25, 100 or 200 mg b.i.d. and 100 or 200 mg/day). Plasma FTC levels were much greater than the mean *in vitro* anti-HIV-IC_{90} (0.012 μg/ml) for at least 24 h. Mean plasma half-life was 7 h. Median suppression of HIV-1 RNA was 2 $\log_{10}$ at doses > 200 mg/day and 1.4 $\log_{10}$ at lower doses. The potent suppression of HIV-1 RNA viremia by FTC can be attributed to its intrinsic activity, plasma kinetics and intracellular TP levels (3).

Preliminary data from a completed, nonrandomized phase I/II study evaluating various doses of emtricitabine (25, 50, 100, 200 or 300 mg/day) indicate that viral DNA levels decreased in all patients after 56 days of drug therapy. PCR analysis revealed that the median reduction in viral load after treatment with emtricitabine ranged from 2.0 $\log_{10}$ at 25 mg/day to 4.3 $\log_{10}$ at 200 mg/day. The agent was well tolerated, with no drug-related toxicities reported (4).

A phase I/II randomized, 12-day study examined the antiviral activity of FTC (25 mg b.i.d. or 100 or 200 mg/day or b.i.d.) in 5 cohorts of 8 HIV-1 infected volunteers. Plasma FTC levels were greater for 24 h than the *in vitro* anti-HIV IC_{90} value of 0.012 μg/ml; plasma half-life was 7 h. PBMCs isolated on days 1 and 12 had dose-dependent increases in FTC-triphosphate levels peaking with > 200 mg/day. Dose-dependent suppression of HIV-1 RNA was observed with reductions of 1.72-1.92 $\log_{10}$ with > 200 mg/day and 1.3-1.48 $\log_{10}$ at the lower doses (5).

Emtricitabine is the new proposed international nonproprietary name for 524W91 (6).

Preliminary clinical data has been presented from 17 hepatitis B (HBV)-infected patients in an ongoing phase I/II study of the anti-HBV activity of FTC, an antiviral nucleoside analogue with potent activity against HIV *in vivo*. Patients in the ongoing phase I/II study are given FTC at doses ranging from 25-200 mg once daily. The median reduction in viral load during the first 14 days of treatment with FTC was 1.9 $\log_{10}$ at 25 mg once daily in 8 patients and 2.8 $\log_{10}$ (99.8%) at 200 mg once daily in 9 patients (7).

The nucleoside analogue FTC has progressed to phase II/III testing for the treatment of HIV infection, AIDS and HBV infection, according to a recent survey of new drugs in development for the treatment of AIDS and related conditions (8).

The results of a phase I/II study evaluating the antiviral activity and safety of emtricitabine in HIV-infected patients have been reported. In this abbreviated monotherapy study, designed to determine the optimum dose of emtricitabine for use in pivotal combination therapy studies, 80 patients were randomized to receive one of three doses of the study drug (25, 100 or 200 mg once daily) or the standard dose of lamivudine (150 mg b.i.d.). Patients were treated for 10 days and followed for an additional 2 days after completion of dosing. All regimens were active, but the highest dose showed the most potent antiviral activity, as determined by a number of variables. Eleven of the 19 patients (58%) receiving the 200-mg dose of emtricitabine had either a 2 $\log_{10}$ decrease in viral load or a reduction in virus to below limits of detection at the end of the treatment period, and 4 of 19 patients (21%) had both. Even 2 days after completion of this short course of therapy, viral load showed an absolute decrease of 43-fold in this cohort of patients (9).

Glaxo Wellcome and Glaxo Group Ltd. have granted a worldwide, exclusive license to Emory University and Triangle Pharmaceuticals giving them access to development and clinical data, drug substance and patent property associated with emtricitabine (10).

Abbott and Triangle Pharmaceuticals have entered into a worldwide strategic alliance for six antiviral products, one of which is emtricitabine in phase III for the treatment of HIV and phase I/II for HBV (11).

1. Valette, G. et al. *Quantitation of intracellular triphosphate of β-L-2',3'-dideoxy-5'-fluoro-3'-thiacytidine (FTC) in peripheral blood mononuclear cells from HIV-infected patients.* 100th Annu Meet Amer Soc Clin Pharmacol Ther (March 18-20, San Antonio) 1999, Abst PII-61.

2. Delehanty, J. et al. *A phase I/II randomized, controlled study of FTC versus 3TC in HIV-infected patients.* 6th Conf Retroviruses Opportunistic Infect (Jan 31-Feb 4, Chicago) 1999, Abst 16.

3. Rousseau, F. et al. *Intracellular FTC-triphosphate levels correlate with the clinical antiviral activity of FTC.* AIDS 1998, 12(Suppl. 4): Abst OP7.5.

4. Gish, R.G. et al. *Anti-hepatitis B virus (HBV) activity and pharmacokinetics of FTC in a 2-month trial in HBV-infected patients.* Dig Dis Week (May 16-19, Orlando) 1999, Abst 2216.

5. Wang, L.H. et al. *High levels of intracellular FTC-triphosphate correlate with the potent antiviral activity of FTC in vivo.* 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst LB-2.

6. *Proposed international nonproprietary names (Prop. INN): List 80.* WHO Drug Inf 1998, 12(4): 260.

7. *Triangle Pharmaceuticals presents preliminary data on FTC in HBV patients.* DailyDrugNews.com (Daily Essentials) Nov 18, 1998.

8. *Triangle initiates phase II/III testing of FTC in HIV and HBV infections.* DailyDrugNews.com (Daily Essentials) Jan 4, 1999.

9. *Excellent anti-HIV activity seen with once-daily emtricitabine in phase I/II study.* DailyDrugNews.com (Daily Essentials) Jan 27, 1999.

10. *Triangle, Glaxo Wellcome and Emory University resolve emtricitabine dispute.* DailyDrugNews.com (Daily Essentials) May 13, 1999.

11. *Abbott and Triangle enter worldwide marketing alliance for antiviral products.* DailyDrugNew.com (Daily Essentials) June 8, 1999.

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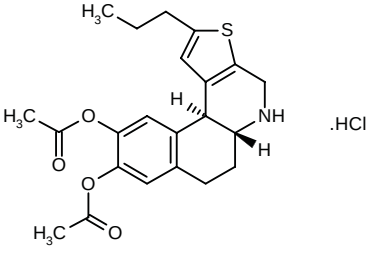
Chu, D.C.K. et al. *Synthesis, chiral separation and anti-HIV activity of enantiomeric oxaselenolane nucleosides.* 12th World AIDS Conf (June 28-July 3, Geneva) 1998, Abst 41200.

Furman, P. *FTC, DAPD and L-FMAU: Three novel nucleoside analogues currently in development for the treatment of HBV infections.* 5th Annu Conf Hepat (Jan 25-26, St. Pete Beach) 1999.

ABT-431

Antiparkinsonian
Dopamine D_1 Agonist

EN: 222577



.HCl

$C_{22}H_{25}NO_4S.HCl$ **Abbott**

In a small study in 14 patients with levodopa-responsive PD, subjects received five doses of ABT-431 (5, 10, 20, 30 and 40 mg) and one dose of placebo following a 12-h period of levodopa withdrawal. At doses of 10 mg and higher, ABT-431 was significantly more effective than placebo as measured by the Unified Parkinson's Disease Rating Scale. Dyskinesia decreased in several patients taking the study drug. The most frequently reported side effects were nausea and emesis, dizziness and hypotension; there were no serious drug-related side effects. ABT-431 is the first dopamine D_1 agonist to demonstrate full antiparkinsonian efficacy in patients with PD (1).

Results from a 15-day study involving 9 experienced cocaine smokers showed that ABT-431 may be a potential treatment for cocaine abuse. ABT-431 (0, 2 and 4 mg i.v. over 1 h) was given prior to 0, 12 or 50 mg of smoked cocaine for a total of 9 sessions. A 6-trial choice (cocaine *vs.* $5 merchandise voucher) procedure was used which involved one sample trial where subjects were given a cocaine dose and 5 choice trials where patients chose between the available cocaine doses and a voucher. ABT-431 had no effect on the number of times subjects chose to smoke each dose of cocaine although dose-dependent decreases in the subjective effects of cocaine (*e.g.*, high and stimulated ratings, dose liking, dose quality) were observed. ABT-431 (4 mg) tended to decrease cocaine craving and increase heart rate, while decreasing systolic and diastolic pressure at each cocaine dose (2).

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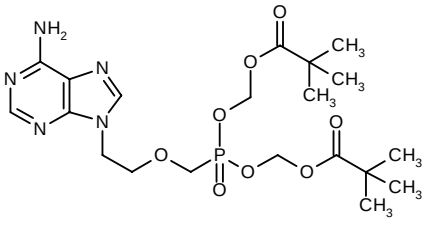
Adefovir Dipivoxil
Preveon™

Anti-HIV
Anti-HBV

EN: 196738



$C_{20}H_{32}N_5O_8P$ **Gilead**

In order to determine cross-resistance of adefovir, an *in vitro* study examined the K_i constants of adefovir diphosphate for recombinant wild-type and mutant human hepatitis B virus (HBV) DNA polymerases (L528M, V521L, P525L, V555l) which are detected in patients and associated with reduced famciclovir sensitivity. Results suggested that adefovir may be useful in HBV-infected patients who failed famciclovir therapy due to resistance or in combination with famciclovir. Preliminary results indicated that L528M, V521L, P525L and V555l mutant HBV polymerases remained sensitive to adefovir with K_i values increasing only 2.3-, 1.5-, 2.3- and 1.9-fold, respectively, compared to the wild-type (1).

The safety of addition of adefovir dipivoxil (120 mg) to background antiretroviral therapy was evaluated in a randomized, multicenter, placebo-controlled trial in 505 patients with advanced HIV disease. No differences were observed in survival, progression of disease or viral load although clinical events rates were low. Grade 4 adverse events were similar in both groups with higher incidence of proximal renal tubule disorder observed in the adefovir-treated group (2).

A phase III randomized study has examined the safety and efficacy of adefovir dipivoxil as part of antiretroviral treatment in therapy naive HIV-infected patients. Results showed that adefovir-treated patients had similar reductions in viral load and HIV genotypes as compared to patients receiving the control therapy. Patients were administered indinavir and either adefovir with AZT/3TC, AZT, 3TC or d4T; the control group received indinavir and AZT/3TC. Out of 98 patients completing 20 weeks of therapy, 79-83% had reduced plasma HIV RNA levels to < 400 copies/ml; 18% had detectable levels (> 400 copies/ml) at several time points including 20 weeks. One patient developed indinavir-associated V82A protease resistance mutation and 2 patients, 1 receiving indinavir/adefovir/3TC and 1 control, developed the 3TC-associated M184V reverse transcriptase mutation (3).

In a phase III placebo-controlled study, 142 HIV-infected individuals treated with adefovir dipivoxil showed a significant 0.53 $\log_{10}$ decrease in plasma HIV RNA after 24 weeks as compared to only 0.01 $\log_{10}$ in the placebo group; antiviral responses were maintained for 48 weeks. High-level, low-level or no AZT-resistance were observed in 53, 8 and 15%, of the patients carrying the M184V 3TC resistance mutation, respectively, and 14, 4 and 6%, respectively, in patients without the mutation. At week 24, plasma HIV RNA decreases of 0.51, 0.75 and 0.65 $\log_{10}$, for the respective resistance groups, were observed in patients carrying the mutation and decreases of 0.05, 0.65 and 0.65 $\log_{10}$, respectively, were observed in those without the mutation. Recombinant viruses from responsive patients had adefovir IC_{50} values similar to or within 3-fold of the wild-type while viruses from nonresponsive patients were > 5-fold above the wild-type (4).

The safety, tolerability and antiviral activity of adefovir dipivoxil (120 mg/day) in combination with indinavir plus AZT, 3TC or d4T were assessed in a randomized, open-label study with 164 antiretroviral naive HIV-infected patients. Preliminary results after 20 weeks from 85 patients indicated grade 3/4 adverse effects of elevations in liver transaminases (8% *vs.* 5% in controls). Of the 17 patients who discontinued treatment, 9 were due to gastrointestinal-related adverse effects; discontinuation rates were the same for all groups. Reductions in plasma HIV RNA and increases in $CD4^+$ cell counts were similar in all groups, indicating that adefovir was well tolerated and effective (5).

After analyzing the incidence of the grade 3 or 4 adverse events associated with adefovir dipivoxil treatment of HIV-infected patients from phase II/III trials, a study has concluded that incidence was uncommon and most side effects were asymptomatic laboratory abnormalities. Of 1300 patients enrolled, grade 3 and 4 serious adverse events were reported in only 154 patients (12%) with 68% being asymptomatic laboratory abnormalities. Adefovir was concluded to be safe and well tolerated (6).

Adefovir was found to be well tolerated in antiretroviral therapy in a study involving 4519 therapy experienced patients with advanced HIV. Patients were administered adefovir (120 mg) and L-carnitine (500 mg) daily in addition to background antiretroviral treatment for at least 24 weeks; adefovir doses were reduced to 60 mg in patients experiencing changes in renal function. Nine percent of the patients discontinued the study due to adverse effects, disease progression, voluntary withdrawal, death or intercurrent illness. Adverse events resulting in discontinuation included gastrointestinal and creatinine elevation and/or proteinuria. A total of 420 serious adverse effects were seen in 5% of the patients. Those adverse effects experienced by 20 or more patients included pneumonia, fever, pancreatitis, infection and pain; renal side effects and all others were reported in < 1% of the patients (7).

In a randomized, placebo-controlled, multicenter trial, the addition of adefovir dipivoxil (120 mg) to background antiretroviral therapy was found to increase the incidence of proximal renal tubule disorder in 505 patients with advanced HIV disease. Significantly more adefovir-treated patients had resolved proximal renal tubule disorder at 12 months as compared to placebo (22% *vs.* 0.5%, respectively) with the earliest incidence occurring at 4 months. At 5 months, the mean serum creatinine level of adefovir-treated patients was 0.1-0.2 mg/dl greater than in patients receiving placebo. Significantly greater weight loss was also noted in adefovir-treated patients as compared to the placebo group at 6 months (mean 2.5 lbs. *vs.* 0.1 lb). Incidence of other adverse effects was similar in both treatment groups (8).

A phase III trial in which 142 HIV-infected patients were grouped according to 3TC- or AZT-resistant mutations showed that both phenotypic and genotypic testing can predict response to adefovir dipivoxil. Patients on stable therapy given adefovir dipivoxil showed a significant mean reduction (0.53 $\log_{10}$) in plasma HIV-1 as compared to placebo (0.01 $\log_{10}$) at 24 weeks which lasted up to 48 weeks. RT mutations occurring during treatment were not resistant to adefovir dipivoxil and did not increase HIV

RNA. Analysis of recombinant viruses from 28 responsive patients showed IC_{50} values similar to or within 3-fold of those obtained for the wild-type while values were > 5-fold above wild-type in 5 unresponsive patients (9).

ALT flares in 7 chronic HBV patients given adefovir (60 or 120 mg once daily) were shown to be due to activation of the immune response to HBV and were more frequent in patients with significant virus-specific T-cell reactivity before treatment (10).

Results from an ongoing study evaluating extended treatment with adefovir dipivoxil in chronic HBV patients were described. Fifteen patients who had previously been treated with adefovir or placebo for 4 weeks were randomized double-blind to receive placebo or doses of adefovir of 60 or 120 mg/day for 24 weeks. Fourteen patients completed the treatment period. A median reduction in HBV DNA of 4.18 $\log_{10}$ was obtained in the 60-mg group and 4.68 $\log_{10}$ in the 120-mg group, as measured by the DNA assay (11).

The dynamics of virus clearance during adefovir dipivoxil treatment in 15 chronic HBV-infected patients receiving 30 mg/day were analyzed and it was concluded that rapid viral clearance observed during treatment was due to nearly complete inhibition of HBV replication rather than to accelerated viral clearance (12).

Two randomized, placebo-controlled phase II studies in 67 $HBeAg^+$ chronic hepatitis patients with normal or high ALT levels showed that adefovir dipivoxil treatment (5, 30 or 60 mg/day) for 12 weeks significantly reduced serum HBV DNA and HBeAg. Treatment was well tolerated and maximum reductions in HBV DNA occurred at the end of 12 weeks and were similar in patients receiving 30 and 60 mg. HBeAg loss and seroconversion rates were higher in patients given 30 (27% and 20%, respectively) and 60 mg (20% for both) as compared to placebo (0%) at follow-up (up to 36 weeks). HBeAg seroconversion was not observed in any patients with normal ALT levels and 4/6 seroconversions were seen during adefovir treatment, in which 3/4 cases occurred following increases in ALT. One patient in the 30 mg group had loss of HBeAg (13).

Gilead has commenced randomization of patients in a multinational phase III clinical trial of adefovir dipivoxil for the treatment of chronic HBV infection. The study is designed to enroll a total of 500 patients at nearly 100 sites in the U.S., Canada, Europe, Australia and Southeast Asia. This trial is the first in a series of pivotal studies Gilead intends to sponsor to further define the role of adefovir dipivoxil in the management of HBV. Study 437 is a 2-year randomized, double-blind, placebo-controlled phase III trial that will evaluate the safety and efficacy of adefovir dipivoxil at two active doses – 10 mg and 30 mg administered once daily. The study is designed to evaluate the treatment effect of the drug compared to placebo in terms of improvements in liver histology, changes in viral load, rates of seroconversion and other important markers of liver disease. Data from this phase III study will be analyzed after the first year of treatment and at trial completion. During the second year of the study, researchers will evaluate the long-term safety and resistance profile. The potential effect of 1 *versus* 2 consecutive years of treatment with adefovir dipivoxil will be studied to determine whether withdrawal of active therapy after 1 year of treatment may increase rates of seroconversion (14).

Preliminary results from two studies comparing two doses of adefovir dipivoxil for the treatment of HIV-infected patients revealed that the dose of 60 mg once daily was similar in efficacy to the 120-mg dose, but with significantly less nephrotoxicity. In a 4-week, double-blind study in treatment-naive patients, 60-mg adefovir dipivoxil monotherapy offered significant anti-HIV activity as compared to placebo. In a 48-week, double-blind, dose-comparison trial in treatment-experienced patients on combination therapy, the 60-mg and 120-mg doses of the drug showed comparable antiviral effects in patients on triple-dose regimens. Moreover, the 60-mg dose was associated with an approximately 30-50% reduction in the incidence of drug-related nephrotoxicity (15).

Gilead has extended its U.S. expanded access program for adefovir dipivoxil to Europe, Canada and Australia. The program will make adefovir dipivoxil available free of charge to HIV-positive patients at least 13 years of age who have failed treatment with at least 2 nucleoside reverse transcriptase inhibitors and 1 protease inhibitor, regardless of their HIV RNA plasma level or CD4 cell count. A 60-mg dose of adefovir dipivoxil will be administered to patients once a day together with the nutritional supplement L-carnitine. In addition to adefovir dipivoxil, Gilead advises physicians participating in the expanded access program to add at least one new antiretroviral agent to their patients' regimens. Enrollment in the expanded access program has begun in France and will commence in additional European countries, Canada and Australia as regulatory approvals are obtained. NeXstar, which reached a definitive merger agreement with Gilead on March 1, 1999, will provide Gilead with support for the international components of the adefovir dipivoxil expanded access program (16).

Gilead has submitted an NDA to the FDA for adefovir dipivoxil 60 mg for the treatment of HIV-infected patients with clinical, immunologic or virologic progression despite prior RTI therapy. Adefovir dipivoxil received fast track designation from the FDA and is expected to receive a 6-month priority review for accelerated approval. Gilead intends to submit an application to market adefovir dipivoxil in the E.U. later this year. The NDA contains safety results compiled from clinical studies in more than 7000 patients and efficacy data from more than 1000 patients treated with adefovir dipivoxil-containing regimens. These data suggest that therapy with adefovir dipivoxil results in antiviral activity in treatment-experienced patients who have developed resistance to commonly used antiretroviral medications. Adefovir dpipvoxil is dosed as a single daily 60-mg oral tablet taken with or without food. It is coadministered with 500 mg of the oral nutrient L-carnitine to replenish body carnitine levels that may be reduced by its administration (17).

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Adozelesin
U-73975
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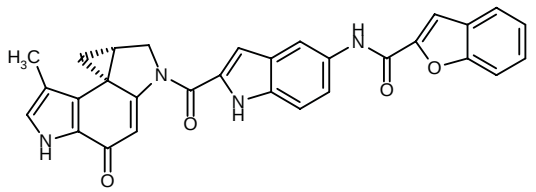
EN: 126014



$C_{30}H_{22}N_4O_4$ **Pharmacia & Upjohn; Yakult Honsha**

A broad spectrum of activity at low concentrations was reported for adozelesin, bizelesin and carzelesin against human tumor colony-forming units. Treatment of colon and kidney carcinoma and melanoma colony-forming units continuously for 14 days (0.02, 0.1 and 0.5 ng/ml) or for 1 h (0.2, 1.0 and 5.0 ng/ml) resulted in similar antitumor activity of all agents. Positive concentration-activity relationships were noted with responses of < 15% with the low dose increasing to > 45% with the highest dose. Adozelesin and carzelesin also showed activity against breast and nonsmall cell lung carcinoma and ovarian carcinoma colony-forming units, respectively. Although adozelesin (58 and 67%) and bizelesin (44 and 49%) had similar response rates with both regimens, the overall response rate for carzelesin was significantly higher with continuous (71%) as opposed to 1 h exposure (46%) (1).

In a multicenter phase II trial, adozelesin was administered initially at a dose of 150 μg/m^2 by 10-min infusion every 4 weeks for up to 1 year in chemotherapy-naive patients with metastatic breast carcinoma. The trial was stopped early due to slow accrual and lack of efficacy and only 17 of a planned 25 or more patients were enrolled; only 14 of these were evaluable for efficacy. One patient had a partial response, 3 had stable disease and 10 showed progressive disease. The most common side effect was myelosuppression, which was reported in 14 patients and consisted mainly of thrombocytopenia and neutropenia. The investigators concluded that adozelesin at this dose and schedule has marginal efficacy in metastatic breast cancer and does not merit further investigation (2).

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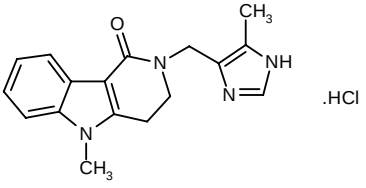
Alosetron Hydrochloride
Lotronex™

Treatment of IBS
5-HT$_3$ Antagonist

EN: 185981



$C_{18}H_{19}N_3O.HCl$ **Glaxo Wellcome**

The application of alosetron to neuronal surfaces inhibited both fast and slow excitatory postsynaptic potentials produced by mucosal stimulation in second-order submucosal neurons, an effect that was not seen with other 5-HT$_3$ antagonists (granisetron, ondansetron). At high concentrations, the compound also inhibited 5-HT$_{1P}$-mediated slow responses and interfered with the activation of submucosal intrinsic primary afferent neurons, an effect that may stem from 5-HT$_{1P}$ antagonism (1).

Results from a study in dogs has shown that alosetron may modulate the visceral nociceptive effect of rectal distension indicating a possible treatment for irritable bowel syndrome (IBS). Anesthetized and awake dogs were administered the agent as an i.v. or i.c.v. bolus and 30 min later a rectal balloon was inflated and blood pressure responses monitored. Significant inhibition of the

vasoactive reflex was observed in anesthetized and awake animals with a high potency observed with i.c.v. administration of the agent (2).

The results from two phase III studies evaluating alosetron hydrochloride in the treatment of IBS have been presented. The results demonstrate that alosetron delivers statistically significant and sustained pain relief and improved bowel function. In one of the largest clinical trials ever conducted in IBS, 647 nonconstipated female patients were treated for 12 weeks with alosetron (1 mg b.i.d.) or placebo. Patients recorded symptoms of pain and bowel function each day during the 12-week treatment period and for 4 weeks thereafter; patients also made weekly reports of IBS pain relief and discomfort over the previous 7 days. Alosetron provided significantly better relief of pain and discomfort than placebo, as well as improving 3 relevant measures of bowel function (urgency, consistency and frequency). Adequate pain relief was greater with active drug than with placebo as soon as 1 week after beginning treatment, reaching a level of significance after the second week and lasting throughout the study period. In a similar fashion, improvement in the 3 measures of bowel function was noted after the first week of treatment and persisted throughout the entire 12 weeks (3).

Glaxo Wellcome has filed an NDA with the FDA for alosetron hydrochloride for the treatment of multiple symptoms of IBS, including abdominal pain. IBS affects as many as 20% of all adults in the U.S., and of those individuals, nearly 70% are females. Two large phase III trials involving more than 1250 nonconstipated female patients with IBS have demonstrated the efficacy and good tolerability of alosetron. Improvements in bowel function (urgency, frequency and consistency) were obtained in patients in both studies after 1 week on alosetron, and continued throughout the 12-week treatment periods. While the effectiveness of alosetron in male patients has yet to be determined (although a major study in men with IBS will begin soon), the company decided to initially advance the development of the drug for female patients as IBS represents a major unmet medical need among women (4).

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2. Miura, M. et al. *Central modulation of rectal distension-induced blood pressure changes by alosetron, a 5-HT$_3$ receptor antagonist.* Dig Dis Sci 1999, 44(1): 20.

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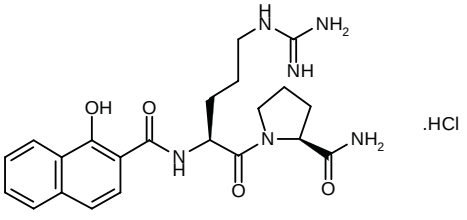
APC-366

Antiallergic/Antiasthmatic

EN: 203911



$C_{22}H_{28}N_6O_4$.HCl **AxyS; Bayer**

AxyS Pharmaceuticals is discontinuing clinical studies of the tryptase inhibitor APC-366, which was in phase II as a dry powder inhaler (DPI) formulation for the treatment of asthma. Phase I results have demonstrated that, at certain dose levels, some study participants given the DPI formulation of APC-366 exhibited signs of bronchospasm as compared to placebo alone. Rather than reformulating the compound, AxyS and partner Bayer have decided to refocus their efforts on the preclinical development of a different tryptase inhibitor for oral use in the treatment of asthma (1).

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AR-121
Nystatin LF
Nyotran™

Antifungal

EN: 211301

Aronex; Ferrer; Abbott;
M.D. Anderson Cancer Center

Liposomal nystatin (2 or 4 mg/kg/day i.v.) was shown to increase survival and reduce fungus-mediated tissue injury in the experimental model of pulmonary aspergillosis in persistently neutropenic rabbits in a manner similar to amphotericin B deoxycholate (1 mg/kg/day i.v.); 1 mg/kg/day liposomal nystatin was ineffective. Although amphotericin B was more effective, both treatments decreased pulmonary fungal tissue burden. Liposomal nystatin was well tolerated with only mild increases in blood urea nitrogen and serum creatinine. Pharmacokinetic studies using noninfected animals demonstrated linear drug disposition in plasma after multiple dosing for 7 days and peak plasma levels greater than MIC for the test strain (1).

The activity of liposomal nystatin was compared to that of free nystatin, amphotericin B, liposomal amphotericin B, amphotericin B lipid complex, amphotericin B cholesteryl sulfate complex, fluconazole and itraconazole against 100 isolates of clinically important filamentous fungi and dermatophytes. The overall geometric mean MIC value for liposomal nystatin was 4.09 μg/ml; geometric mean MIC values for the reference antifungal agents ranged from 1.03 μg/ml (itraconazole) to 201 μg/ml (fluconazole). The antifungal activity of liposomal nystatin was especially pronounced against *Fusarium* strains and was superior to that of the various amphotericin B formulations against *Aspergillus fumigatus* and *A. flavus* (2).

An *in vitro* study examined the activity of liposomal nystatin and other antifungal agents against 60 *Aspergillus* isolates of which 12 were itraconazole resistant. Geometric mean MICs against all isolates were 2.3, 9.51, 0.58, 0.86, 2.07, 2.57 and 0.86 μg/ml for liposomal nystatin, nystatin, itraconazole, amphotericin B deoxycholate and liposomal, lipid complex and colloidal dispersion amphotericin B, respectively. The agents were significantly less effective (geometric mean MIC = 8.72 μg/ml) against *A. terreus* as compared to all other species (3).

Liposomal formulation of nystatin was compared to free nystatin and amphotericin B in terms of their *in vitro* activity against isolates of *Aspergillus* spp., *Candida* spp. and *Cryptococcus neoformans*. Nystatin in both formulations demonstrated fungistatic and fungicidal activities against the 10 species tested, and both formulations were more effective than liposomal amphotericin B. However, amphotericin B deoxycholate and amphotericin B lipid complex demonstrated superior activity as compared to either nystatin formulation (4).

Pharmacokinetic evaluation of liposomal nystatin in normal catheterized rabbits receiving intravenous doses of 2, 4 and 6 mg/kg revealed nonlinear plasma pharmacokinetics with C_{max} values of 14.27, 23.58 and 56.02 μg/ml, respectively, well above MICs for most pathogenic fungi. No significant tissue accumulation was observed, with highest drug concentrations observed in lung, liver, spleen and kidney (5).

Salvage therapy with liposomal nystatin for invasive pulmonary aspergillosis was demonstrated in an immunosuppressed cardiac transplant recipient. The patient was administered nystatin (2 mg test dose followed by 4 daily doses of 4 mg/kg i.v. and 42 doses of 570 mg) after amphotericin B treatment resulted in azotemia, chills, hypotension and hypoxemia. Resolution of azotemia, DIC and hypoxemia was observed upon treatment and bronchoscopy was normal. No recurrence was seen up to 6 months following therapy. Therapy was well tolerated with few intermittent fevers and a manageable transient rise in creatinine at 4 weeks (6).

The efficacy and tolerability of liposomal nystatin (2 or 4 mg/kg/day) were demonstrated in an open-label study in which 75 patients with refractory candidemia were administered the agent within 96 h of obtaining positive blood cultures for *Candida albicans*, *C. tropicalis*, *C. glabrata* or a combination of *C. albicans* and *C. parapsilosis*. Clinical improvement and mycological success were observed in 60% of the patients and treatment was well tolerated with little incidence of adverse effects (7).

Aronex signed a license agreement granting worldwide marketing rights to liposomal nystatin (Nyotran™) to Abbott. Under terms of the agreement, Abbott will provide funding for the continuing clinical development program and will be responsible for marketing the product upon receipt of regulatory approval. Aronex retains rights to copromote the drug within the U.S. and Canada for a period of at least 2 years. Abbott will be responsible for registration of Nyotran™ in countries outside the U.S. and has the right, but not the obligation, to manufacture the product (8, 9).

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2. Carrillo-Muñoz, A.J. et al. *In vitro antifungal activity of Nyotran (liposomal nystatin) against opportunistic filamentous fungi.* Clin Microbiol Infect 1999, 5(Suppl. 3): Abst P1177.

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Bropirimine
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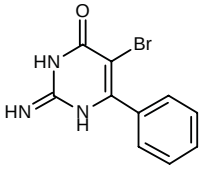

$C_{10}H_8BrN_3O$ **Pharmacia & Upjohn; Yakult Honsha**

Bropirimine (750 mg p.o. t.i.d.) was administered to 20 patients with recurrent superficial transitional cell carcinoma of the bladder at 2-h intervals on 3 consecutive days for 12 weeks. Complete and partial responses were seen in 2 and 3 patients, respectively; the objective response rate was 31.3% for 16 patients who completed the treatment. The most commonly reported adverse events were malaise (23.5%), headache (23.5), fever (11.8%) and loss of appetite (23.5%). Overall, oral bropirimine was effective against marker tumors with a good safety profile (1).

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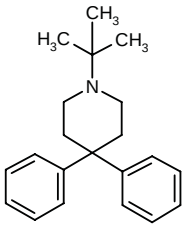
Budipine Hydrochoride
Parkinsan®

Antiparkinsonian
NMDA Antagonist

EN: 090469



.HCl

$C_{21}H_{27}N.HCl$ **Lundbeck; Byk Gulden**

Budipine has been shown to exert neuroprotective and symptomatic antiparkinsonian effects. In 2 randomized, double-blind, placebo-controlled studies, the drug's effects were seen in *de novo* Parkinson's patients and in those with progressed disease. With an efficacy profile similar to that of levodopa, budipine significantly reduced akinesia, rigidity and tremor, and reduced main symptoms by about 40%. Effects were evident by 4-6 weeks (1).

Lundbeck has acquired exclusive European marketing rights to budipine hydrochloride, Byk Gulden's treatment for Parkinson's disease (2).

1. Przuntek, H. *Budipine a new drug in treatment of Parkinson's disease.* Mov Disord 1998, 13(Suppl. 2): Abst P1.254.

2. *Lundbeck licenses European rights to antiparkisonian compound.* DailyDrugNews.com (Daily Essentials) May 21, 1999.

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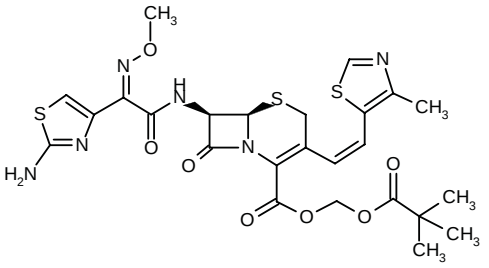
Cefditoren Pivoxil *Cephalosporin*
Meiact®

EN: 112175



$C_{25}H_{28}N_6O_7S_3$ **Meiji Seika; Abbott; Grüenenthal; TAP**

Abbott has aquired rights from Meiji Seika to market cefditoren pivoxil in several major international markets. Under terms of the agreement, Abbott has rights to comarket cefditoren in Europe and exclusive rights to market the compound throughout Latin America. The companies have also signed a binding letter of intent that will allow Abbott to market cefditoren throughout most of Asia, with the exception of Japan and Korea, following execution of a definitive agreement (1).

1. *Abbott obtains marketing rights to Meiji cephalosporin in several major markets.* DailyDrugNews.com (Daily Essentials) April 23, 1999.

Original monograph - Drugs Fut 1992, 17: 665.

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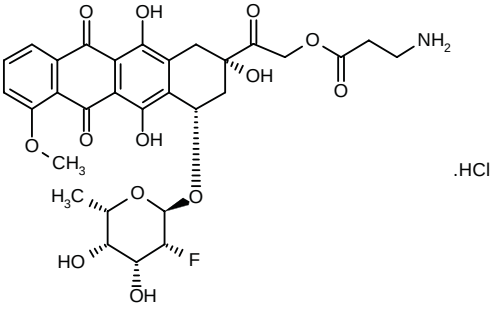
DA-125 *Antineoplastic Antibiotic*
Galarubicin Hydrochloride *Anthracycline*

EN: 198263



$C_{30}H_{32}FNO_{13}$.HCl **Dong-A**

The safety and pharmacokinetics of single dose DA-125 (20, 40, 60, 80 or 100 mg/m^2 i.v. for 5 min) were examined in a phase I clinical trial in 21 patients with various types of cancer. The maximum tolerated dose was concluded to be 100 mg/m^2 with bone marrow suppression the dose-limiting factor. The most common adverse effects which increased with DA-125 dose included nausea, vomiting, leukopenia and thrombocytopenia; no cardiotoxicity, fever, stomatitis, diarrhea, renal or nervous system toxicity, abnormal blood coagulation or deaths were observed. No adverse effects equal to or greater than grade III were observed with doses up to 60 mg/m^2. A dose of 80 mg/m^2 was recommended for phase II studies. Six progressive disease, 14 stable disease and 1 partial response were observed. The AUC, $t_{1/2}$, CL, V_{ss} and MRT of M1 of DA-125 were independent of 20-100 mg/m^2 doses and < 0.75% of M1 was excreted in urine at 96 h. M2 was the main metabolite with 10.1-22.3% excreted in urine at 96 h. Biliary excretion was negligible when examined in 1 patient receiving the 100 mg/m^2 dose (1).

Galarubicin hydrochloride is the new proposed international nonproprietary name for DA-125 (2).

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2. *Proposed international nonproprietary names (Prop. INN): List 80.* WHO Drug Inf 1998, 12(4): 263.

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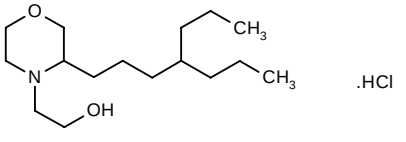
Delmopinol Hydrochloride *Dental Agent*
M-1650
Decapinol®

EN: 100315



$C_{16}H_{33}NO_2$.HCl **Biosurface Pharma**

The efficacy and safety of delmopinol hydrochloride (2 mg/ml, 0.2% Decapinol mouthwash) were evaluated in a 6-month, parallel-group, randomized, double-blind clinical trial involving 149 patients with gingivitis. Chlorhexidine digluconate (2 mg/ml, 0.2% Hibitane Dental) and placebo were used as references; all subjects practiced normal oral hygiene. Plaque index scores were 22% and 13% lower with delmopinol than with placebo after 3 and 6 months, respectively, while bleeding on probing (BOP) decreased by 11% and 18%, respectively, as compared to placebo at the same time

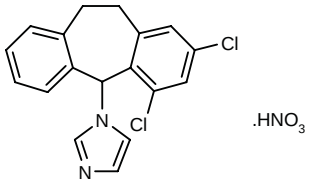
points. Reductions in plaque index scores were 38% and 38%, respectively, for chlorhexidine, while BOP decreased by 18% and 22%, respectively. Plaque reduction was greater with chlorhexidine than delmopinol, but no significant differences were seen between the two active drugs with respect to BOP. Significantly more dental calculus was seen in patients in both active treatment groups as compared to placebo. The most common adverse effects of both active treatments were a transient sensation of anesthesia in the oral mucosa and affected taste; adverse events or lack of cooperation led to 7, 4 and 1 withdrawals in the chlorhexidine, placebo and delmopinol groups, respectively (1).

1. Hase, J.C. et al. *6-Month use of 0.2% delmopinol hydrochloride in comparison with 0.2% chlorhexidine digluconate and placebo (I). Effect on plaque formation and gingivitis.* J Clin Periodontol 1998, 25(9): 746.

Original monograph - Drugs Fut 1996, 21: 787.

Eberconazole Nitrate *Antifungal*
WAS-2160

EN: 166574



$C_{18}H_{14}Cl_2N_2.HNO_3$ **Salvat; Wassermann; Soc. Española Especialidades Fármaco Terapéuticas**

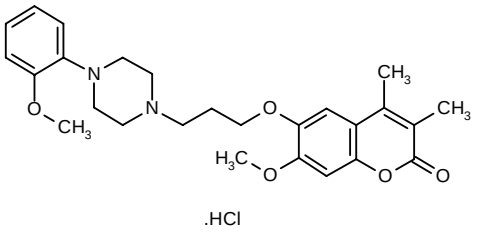
A process useful for the industrial preparation of eberconazole has been reported: The Wittig condensation of 2-(methoxycarbonyl)benzyl(triphenyl)phosphonium bromide (I) with 3,5-dichlorobenzaldehyde (II) by means of NaH in DMF gives 2-[2-(3,5-dichlorophenyl)vinyl]benzoic acid methyl ester (III), which is hydrolyzed with NaOH in methanol to the corresponding free acid (IV). The hydrogenation of (IV) with H_2 over Pd/C in methanol affords 2-[2-(3,5-dichlorophenyl)ethyl]benzoic acid (V), which is cyclized to 2,4-dichloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cyclohepten-5-one (VI) by means of polyphosphoric acid. The reduction of (VI) with $NaBH_4$ yields the corresponding carbinol (VII), which is treated with $SOCl_2$ affording the chloride (VIII). Finally, this compound is condensed with imidazole (IX) in refluxing DMF (1). Scheme 1.

1. Farrerons Gallemi, C, Miquel Bono, I.J., Montserrat Vidal, C. (Laboratorios Salvat SA). *Process for the preparation of eberconazole and intermediates thereof.* WO 9921838.

Original monograph – Drugs Fut 1996, 21: 792.

Ensaculin Hydrochloride *Cognition Enhancer*
Anseculin Hydrochloride (former INN)
KA-672.HCl *Acetylcholinesterase Inhibitor*

EN: 215914



$C_{26}H_{32}N_2O_5.HCl$ **Schwabe**

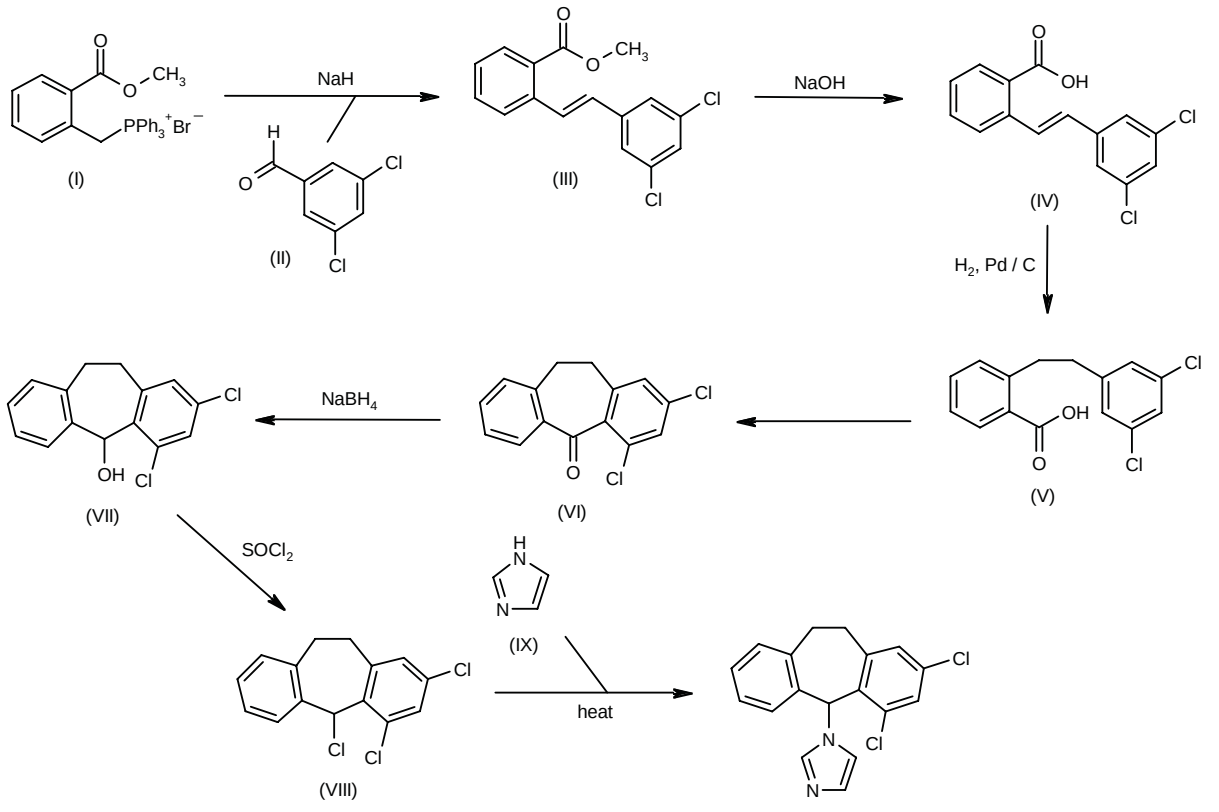
KA-672 was studied for its effects on NMDA receptors by applying patch clamp techniques to acutely isolated hippocampal neurons. KA-672 antagonized NMDA responses in a voltage-dependent manner (1).

A study has reported the design of novel coumarin derivatives with potential activity against NMDA-induced excitatory processes. Structure-activity and pharmacological profiles of the molecules were presented and showed activity against NMDA (i.v.)-induced convulsions and mortality in mice. KA-672.HCl was selected from the series for further development and was shown to be 5 times more potent in antagonizing NMDA-induced mortality than MK-801 (2).

KA-672 has been shown to improve memory and learning in animal models and is in phase II testing for the treatment of Alzheimer's dementia. Several neurotransmitter systems appear to be involved in the action of the compound, including the cholinergic system. Thus, mechanism of action studies were conducted *in vitro* and *in vivo* in order to determine whether the inhibition of acetylcholinesterase (AChE) contributes to the behavioral effects of ensaculin. Although the compound did inhibit AChE *in vitro* in rat brain cortical homogenates, it did not affect acetylcholine release in the rat hippocampus *in vivo*. This may be due to the fact that ensaculin, a lipophilic drug, does not accumulate in the brain in concentrations sufficient for interaction with extracellular AChE. In any case, AChE inhibition has been discarded as a potential mechanism of neuroprotective activity for ensaculin hydrochloride (3, 4).

KA-672.HCl exerts modulatory effects on dopaminergic and serotoninergic neurotransmitter systems and displays NMDA antagonistic qualities. These effects as well as alterations in hydroxyl free radical levels have been studied using microdialysis experiments conducted in freely moving male Wistar rats. Each animal was implanted with a probe and perfused with a calcium reduced Ringer's solution. Upon reaching a stable baseline, KA-672.HCl (1 mg/kg, i.p.) was injected. Findings revealed that the compound's activity may prove therapeutic for Alzheimer's patients (5).

Scheme 1: Synthesis of Eberconazole



The international nonproprietary name for KA-672.HCl has been changed from anseculin hydrochloride to ensaculin hydrochloride (6).

1. Lishko, P.V. et al. *The putative cognitive enhancer KA-672.HCl is an uncompetitive voltage-dependent NMDA receptor antagonist.* NeuroReport 1998, 9(18): 4193.

2. Nöldner, M., Chatterjee, S.S. *Identification of KA-672.HCl as a new functional antagonist of N-methyl-aspartic acid (NMDA) induced convulsions and mortality in mice.* Naunyn-Schmied Arch Pharmacol 1999, 359(3, Suppl.): Abst 368.

3. Hilgert, M., N□ldner, M., Chatterjee, S.S., Klein, J. *KA-672 inhibits rat brain acetylcholinesterase in vitro but not in vivo.* Naunyn-Schmied Arch Pharmacol 1998, 358(4, Suppl. 3): Abst 51.

4. Hilgert, M. et al. *KA-672 inhibits rat brain acetylcholinesterase in vitro but not in vivo.* Neurosci Lett 1999, 263(2-3): 193.

5. Teismann, P., Ferger, B. *Effects of the potential antidementia compound KA-672.HCl on dopamine and hydroxyl free radicals in rats: An in vivo microdialysis study.* Soc Neurosci Abst 1998, 24(Part 1): Abst 286.12.

6. *Proposed international nonproprietary names (Prop. INN): List 78.* WHO Drug Inf 1997, 11(4): 299.

Original monograph - Drugs Fut 1996, 21: 779.

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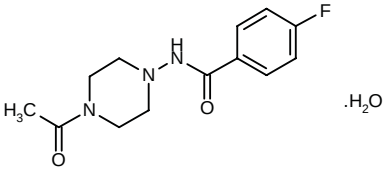
FK-960
FR-59960

Cognition Enhancer

EN: 243654



$C_{13}H_{16}FN_3O_2.H_2O$ **Fujisawa**

The mechanism of action and the effects of FK-960 on long-term potentiation (LTP) as examined in the mossy fiber-CA3 pathway in a guinea pig hippocampal slice

revealed that FK-960 augments the LTP in this pathway by activating the somatostatinergic nervous system in the hippocampus (1).

FK-960 dose-dependently increased the density of axodendritic synapses in the striatum radiatum of the hippocampal CA3 region in aged rats. Changes on the symmetric and asymmetric synapses in the hippocampal CA3 region and lamina I of the parietal cortex were also evaluated whereby the compound exerted different effects on the synaptic density in different classes of synapses and in different regions of the brain of the animal (2).

FK-960's ability to reverse memory deficits was evaluated in a rat model of amnesia using passive avoidance, Morris water maze and 8-arm radial maze test. Its ability to reverse short-term memory deficits was also evaluated in rhesus monkeys. The drug (0.1-10 mg/kg i.p.) reduced memory impairments in rats as observed in all behavioral tasks and significantly restored impaired memory in aged rats. In rhesus monkeys, FK-960 (1-32 μg/kg i.m.) significantly restored scopolamine-induced deficits in short-term memory. Thus, the cognitive enhancing actions of FK-960 appear to be more effective than those produced by cholinesterase inhibitors (3).

Assessment of FK-960's interaction with cholinergic and glutamatergic neuronal systems in nonhuman primates indicated that the drug (1, 10, 100 and 1000 μg/kg i.v.) reverses scopolamine-induced abolishment of regional cerebral blood flow response to somatosensory stimulation through enhancement of cholinergic neurotransmission, and not through the glutamatergic system (4, 5).

1. Inoue, T., Matsuoka, N., Moriguchi, A., Shirakawa, K., Satoh, H., Goto, T., Satoh, M. *FK960, a potential antidementia drug, augments the long-term potentiation in guinea-pig hippocampal slices through the novel mechanism which is mediated by an activation of somatostatinergic nervous system.* Soc Neurosci Abst 1998, 24(Part 1): Abst 286.9.

2. Noda, K. et al. *FK960, a novel antidementia drug, increases symmetrical synapses in the hippocampus of aged rats.* Soc Neurosci Abst 1998, 24(Part 1): Abst 286.10.

3. Yamazaki, M. et al. *FK960, a potential antidementia drug, ameliorates the memory deficits in rats and rhesus monkeys through a novel mechanism of action.* Soc Neurosci Abst 1998, 24(Part 1): Abst 286.8.

4. Tsukada, H. et al. *FK960 [N-(4-acetyl-1-piperazinyl)-p-fluorobenzamide monohydrate], a novel potential antidementia drug, restores the regional cerebral blood flow response abolished by scopolamine but not by HA-966: A positron emission tomography study with unanesthetized rhesus monkeys.* Brain Res 1999, 832(1-2): 118.

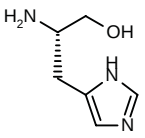
5. Yamazaki, S. et al. *FK960, a novel potential antidementia drug, modulates regional cerebral blood flow response abolished by scopolamine but not by HA-966: PET studies in rhesus monkeys.* Soc Neurosci Abst 1998, 24(Part 1): Abst 286.11.

Original monograph - Drugs Fut 1997, 22: 830.

L-Histidinol

Antineoplastic

EN: 181003



$C_6H_{11}N_3O$ **Univ. Saskatchewan**

The effects of L-histidinol on the antitumor activity and acute cardiotoxicity of doxorubicin were evaluated in mice bearing Ehrlich ascites carcinoma cells. Administration of 5 doses of L-histidinol (250 mg/kg i.p.) prior to administration of doxorubicin (5 mg/kg i.p.) enhanced the antitumor activity of the latter drug. However, in healthy mice, L-histidinol did not affect the acute cardiotoxicity or lethality produced by doxorubicin (1).

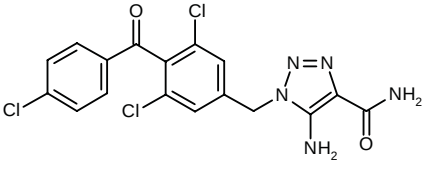
1. Al-Shabanah, O.A., Badary, O.A., Al-Gharably, N.M., Al-Sawaf, H.A. *Effects of L-histidinol on the antitumour activity and acute cardiotoxicity of doxorubicin in mice.* Pharmacol Res 1998, 38(3): 225.

Original monograph - Drugs Fut 1993, 18: 743.

L-651582
CAI

Antineoplastic

EN: 113265



$C_{17}H_{12}Cl_3N_5O_2$ **Merck & Co.; Natl. Cancer Inst. (US)**

CAI was shown to interfere with tumor microvessel formation *in vivo* without affecting normal vasculature in mice injected intraportally with B16F1 cells. The volume of liver metastases in CAI-treated mice was 8 times less than controls although the number of metastases was unaffected. CAI treatment also significantly decreased the percent vascular volume by decreasing the number of microvessels/mm^2 and microvessel cross-sectional area within metastases; no change in percent vascular volume was observed in normal liver surrounding the metastases (1).

A phase I trial of CAI (50, 100 and 150 mg/day gelcaps) with ketoconazole (200 mg/day) in 13 advanced cancer patients showed that the two agents may be administered together for up to 28 days at CAI doses up to 150 mg/day without dose-limiting toxicities. Grade 1 and 2 toxicities included nausea (3 and 4 patients), emesis (1 and 3 patients), anorexia (1 grade 2), fatigue

(3 grade 2), vertigo (1 grade 1) and neurocortical (2 grade 1). Grade 3 neurotoxicities including paresthesia, vertigo and neurocortical toxicity were seen in only 1 patient given 150 mg/day. One patient receiving 100 mg/day showed no toxicities. Stable disease was seen in 1 nonsmall cell lung cancer patient for 6 CAI cycles. Pharmacokinetics from 7 patients given 100 or 150 mg/day CAI alone and with ketoconazole showed that the latter decreased the clearance (2.1 ± 0.8 *vs.* 3.9 ± 1.9) and variability of the former although C_{max} was unaffected (2).

1. Chambers, A.F. et al. *Inhibition of angiogenesis in B16F1 liver metastases by carboxyamidotriazole (CAI).* Proc Amer Assoc Cancer Res 1999, 40: Abst 4093.

2. DeMario, M.D. et al. *A phase I trial of carboxyamido-triazole (CAI) modulated with ketoconazole (K) in patients with advanced malignancies.* Proc Amer Soc Clin Oncol 1999, 18: Abst 607.

Original monograph - Drugs Fut 1991, 16: 717.

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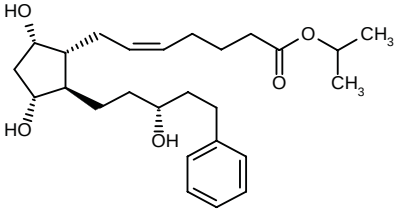
Dixon, S.C. et al. *Down regulation of the nitric oxide-VEGF pathway by carboxy-amido-triazole leads to inhibition of angiogenesis.* Proc Amer Assoc Cancer Res 1999, 40: Abst 459.

Franklin, A.J. et al. *Carboxyamido-triazole is a potent inhibitor of retinal neovascularization.* Invest Ophthalmol Visual Sci 1999, 40(4): Abst 3723.

Latanoprost
Xalatan®

Antiglaucoma

EN: 183029



$C_{26}H_{40}O_5$ **Pharmacia & Upjohn**

The records of 36 patients (56 eyes) treated with latanoprost at a single center were studied in order to evaluate long-term compliance, intraocular pressure (IOP) reduction from baseline and average number of antiglaucoma drugs. IOP decreased by an average of 3.5 mmHg, and an average of 2.2 glaucoma medications were administered during the study period. Latanoprost treatment was continued in 53 of 56 eyes (95%) for an average of 19 months. Latanoprost was considered to be a good adjunctive treatment for the majority of the glaucoma patients included in this study (1).

Latanoprost was added to the maximum tolerated antiglaucoma treatment regimen of 10 uveitis patients who developed intractable glaucoma following either ocular inflammation or chronic steroid use. When added to the treatment regimen upon achieving control of uveitis, latanoprost lowered IOP by at least 4 mmHg in all patients, without any apparent adverse effects on long-term control of intraocular inflammation. Furthermore, no loss of visual acuity secondary to development of cystoid macular edema was associated with latanoprost administration (2).

The results of a prospective, randomized, 3-month clinical study in 70 patients (100 treated eyes) with uncontrolled open-angle glaucoma indicate that substituting latanoprost (0.005% once daily) for preexisting therapy (a topical beta-blocker plus at least one other topical medication) is as effective as adding latanoprost to existing therapy. IOP decreased significantly in patients receiving either latanoprost monotherapy or latanoprost plus preexisting therapy, but in eyes with IOP of > 21 mmHg, latanoprost alone was as effective as latanoprost plus baseline therapy in terms of IOP-reducing effects (3).

A new study conducted in Germany on open-angle glaucoma indicates that patients switched to monotherapy with latanoprost ophthalmic solution experienced the same reduction in IOP as patients taking a combination product incorporating dorzolamide and timolol. The results of the open-label study demonstrate that a switch to latanoprost monotherapy after 2-4 weeks on timolol is an effective alternative to combination therapy with two aqueous flow suppressors. The 3-month, randomized, open-label, multicenter study enrolled 183 patients with open-angle glaucoma, capsular glaucoma or ocular hypertension. IOP reduction was achieved in patients not adequately controlled on timolol alone (5 mg/ml b.i.d.) following a switch to latanoprost (50 mcg/ml once daily) or by the addition of dorzolamide (20 mg/ml b.i.d.) to timolol. Mean diurnal IOP in the latanoprost group decreased by 4.5 ± 0.2 mmHg, while in the combination group it decreased by 4.4 ± 0.2 mmHg. Both treatment groups showed mean reductions in diurnal IOP of 20% at the end of the 3-month treatment period. No serious side effects were seen with either treatment (4).

Xalatan™ Sterile Ophthalmic Solution has been approved by Japan's Ministry of Health & Welfare for the treatment of glaucoma and ocular hypertension (5).

1. FIscella, R.G. et al. *Clinical experience with latanoprost (Xalatan) as adjunctive therapy.* Invest Ophthalmol Visual Sci 1999, 40(4): Abst 4374.

2. Dillon, H.D. et al. *Latanoprost use in patients with uveitic glaucoma.* Invest Ophthalmol Visual Sci 1999, 40(4): Abst 4375.

3. Maraini, G. et al. *Substitution with latanoprost compared with addition of latanoprost to maximally tolerated medical therapy in uncontrolled human glaucoma.* Invest Ophthalmol Visual Sci 1999, 40(4): Abst 4376.

4. *Latanoprost monotherapy is as effective as combination therapy in lowering IOP.* DailyDrugNews.com (Daily Essentials) Nov 20, 1998.

5. *Xalatan approved in Japan for glaucoma and ocular hypertension.* DailyDrugNews.com (Daily Essentials) March 16, 1999.

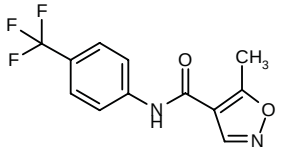
Original monograph - Drugs Fut 1992, 17: 691.

Leflunomide

SU-101
RS-34821
HWA-486
Arava™

Antiarthritic
Antineoplastic

EN: 116061



$C_{12}H_9F_3N_2O_2$

Hoechst Marion Roussel; Sugen; Kyorin

Leflunomide (1 mg/kg/day) was shown to be potentially therapeutic against type 1 allergic diseases in a study demonstrating that formation of ovalbumin-specific IgE was potently suppressed, thus preventing plasma histamine elevation and anaphylactic shock following i.v. ovalbumin administration to rats. Leflunomide given during the primary immune response decreased secondary immune responses (except IgM) and total IgE and ovalbumin-specific IgE serum levels decreased rapidly almost to baseline when given during the secondary response after rechallenge. Although primary responses of ovalbumin-specific IgG_1, IgG_{2a} and IgM were unaffected by leflunomide, secondary responses were potently suppressed by treatment. The active metabolite of leflunomide, A-771726, was shown to inhibit proliferation and antibody production from Brown Norway rats; proliferation was completely restored and antibody formation partially restored with the addition of uridine, indicating that leflunomide inhibits dihydroorotate dehydrogenase (1).

Studies determined that leflunomide's primary mechanism of action in rheumatoid arthritis (RA) is the inhibition of *de novo* pyrimidine synthesis, an effect that is produced by the compound's active metabolite A-771726 (2).

At drug levels achieved in RA patients, the active metabolite of leflunomide inhibited the upregulation of *de novo* uridine synthesis and caused arrest of activated lymphocytes in the G_1 phase. This inhibition of uridine synthesis results in immunomodulation, rather than immunosuppression, leaving other lymphocytes free to fulfill nucleotide requirements via salvage pathways (3).

The ability of long-term treatment with leflunomide to prevent allergic sensitization was investigated in a rat model based on findings demonstrating suppression of antigen-specific antibody production and allergen-induced bronchoconstriction with short-term treatment. Daily treatment with leflunomide for up to 30 days after ovalbumin sensitization resulted in reductions in antigen-specific IgE and IgG compared with controls; immunoglobulin levels increased following cessation of treatment. Decreases in antigen-specific T-cell proliferation and numbers of eosinophils and neutrophils in bronchoalveolar lavage fluid 24 h after challenge were also observed (4).

In a double-blind, phase III study, 358 patients with RA were randomized to leflunomide (100 mg once daily on days 1-3 + 20 mg/day), sulfasalazine (0.5 g/day titrated to 2.0 g/day) or placebo. Leflunomide and sulfasalazine showed statistically equivalent changes in disease progression. One-year data indicate that leflunomide, in addition to other DMARDs, is highly effective in the treatment of RA (5).

A comparison of the renal effects of leflunomide, methotrexate and sulfasalazine during phase III clinical trials indicated that, in contrast to methotrexate, leflunomide and sulfasalazine had no detectable effects on renal function. In addition, the reduction in plasma uric acid observed on leflunomide may represent a beneficial pharmacological effect in patients with abnormally high plasma uric acid levels (6).

Leflunomide (20 mg once daily), methotrexate (7.5-15 mg/week) or placebo were administered to 482 patients with RA to assess the drugs' effects on the slowing of disease progression. Results from this multicenter, double-blind study indicate that treatment with leflunomide for a 12-month period retards disease progression as revealed by x-rays (7).

A phase III, multinational, double-blind study was conducted to assess the impact of leflunomide, sulfasalazine and placebo on the functional ability of 358 patients with RA. Patients were administered leflunomide (100 mg once daily on days 1-3 + 20 mg/day), sulfasalazine (0.5 g/day titrated to 2.0 g/day) or placebo. Leflunomide had a significantly greater impact on health-related quality of life than placebo or sulfasalazine in the treatment of RA (8).

The effects of the duration of RA on the efficacy and safety of leflunomide and methotrexate were assessed in a double-blind, multicenter study in which 479 patients were randomized to leflunomide (20 mg once daily), methotrexate (7.5-15 mg/week) or placebo. Leflunomide and methotrexate demonstrated equivalent efficacies on which disease duration had no effect. In addition, both agents were well tolerated (9).

In all, 358 patients with RA were randomized to leflunomide (100 mg once daily on days 1-3 + 20 mg/day), sulfasalazine (0.5 g/day titrated to 2.0 g/day) or placebo in a 6-month, phase III double-blind study. At 24 weeks, leflunomide was associated with significant reductions in tender and swollen joint counts and increases in ACR response rates as compared to placebo or sulfasalazine. One-year data indicate that leflunomide is safe and highly effective in this patient population (10).

A 12-month, multicenter, randomized trial assessing the safety and efficacy of leflunomide (20 mg/day) demonstrated that the drug was more effective than methotrexate in slowing the progression of RA, as measured by X-ray analysis of the hands and feet. This was accompanied by significant improvements in health-related qualty of life and physical functioning in the leflunomide treatment group. Leflunomide is the first and only drug to be indicated to retard structural joint damage caused by RA (11).

In a multicenter European phase III trial, the efficacy of leflunomide was compared to that of placebo and sulfasalazine in patients with early- and late-stage RA. Over 350 patients were grouped by duration of disease (less than or greater than 2 years) and randomized to receive treatment with leflunomide (100 mg once daily on days 1-3 + 200 mg/day), placebo or sulfasalazine (0.5 g/day titrated to 2.0 g/day at week 4) for 24 weeks. Patients receiving leflunomide showed significantly greater reductions in tender and swollen joint counts and CRP levels as compared to placebo. The 20% ACR response rate for leflunomide (55%) was superior to placebo (29%) and comparable to sulfasalazine (56%). Fewer patients on leflunomide withdrew due to lack of efficacy (8% *vs.* 32% and 11% for placebo and sulfasalazine, respectively) or to adverse events (14%, 5% and 19%, respectively). Treatment-related adverse events included diarrhea, nausea, alopecia, hypertension, rash and headache. Leflunomide was considered effective in treating both early- and late-stage RA (12).

In a randomized, placebo-controlled, 12-month multicenter study, the efficacy of leflunomide (100 mg/day for 3 days loading) compared to methotrexate (7.5-15 mg/week) was examined in 482 patients with active RA; patients also received folate (1 mg once or twice daily). ACR responder criteria was met by 39%, 20% and 24% of the patients at 4 weeks and 52%, 26% and 46% of patients at 52 weeks in the leflunomide, placebo and methotrexate groups, respectively. Leflunomide-treated patients had more sustained responses of longer durations as compared to the placebo and methotrexate groups. AUC analysis of ACR responses showed significantly better values for leflunomide and methotrexate than the placebo (23.7 and 22.6 *vs.* 12.6 weeks) (13).

A phase III, randomized, double-blind, placebo-controlled, multicenter study showed the efficacy of leflunomide (100 mg/day on days 1-3 followed by 20 mg/day) as compared to methotrexate (7.5-15 mg/week) in 479 patients with early or late RA arthritis; patients also received folate (1 mg once or twice daily). Early and late rheumatoid arthritis patients treated with leflunomide both had 20% response rates. Significantly greater decreases in tender and swollen joint counts and improvements in physician and patient global assessments were observed in the leflunomide-treated group as compared to the placebo. Similar efficacy and adverse effects were observed in both leflunomide- and methotrexate-treated patients (14).

A randomized, placebo-controlled, 12-month multicenter study showed the efficacy of leflunomide (20 mg daily) as compared to placebo and methotrexate (7.5-1.5 mg/week) treatment in 482 patients with active RA. Monthly evaluation by the Modified Health Assessment Questionnaire showed significant improvement in function and health status measures in the leflunomide-treated group as compared to placebo. Disability improved in both treatment groups (15, 16).

In a 12-month, placebo-controlled phase III clinical trial, 482 RA patients were given either leflunomide (20 mg/day after a loading dose of 100 mg/day) for 3 days, placebo or the active control drug methotrexate at 7.5 mg/week, with an increase to 15 mg/week in patients with continued active disease. Sixty percent of the methotrexate-treated patients were increased to 15 mg/week during weeks 7-9. Leflunomide was significantly superior to placebo and equipotent to methotrexate in reducing the signs and symptoms of RA, as measured by ACR success rate (defined as completing 12 months of treatment) and ACR response at endpoint. Patients on leflunomide began showing improvements as early as 1 month after treatment, and a greater percentage of leflunomide-treated patients were ACR responders overall compared to patients receiving placebo (52% for leflunomide *vs.* 26% for placebo and 46% for methotrexate). The study drug was well tolerated, with serious treatment-related adverse events occurring in just 1.1% of the leflunomide treatment group (17).

A total of 482 patients with active RA were randomized to leflunomide (20 mg once daily), methotrexate (10-15 mg/week) or placebo in a 12-month, double-blind, multicenter study. Stable doses of prednisone and or NSAIDs were continued; all patients received 1 mg folate once or twice daily. An ACR response (at least 20% improvement) was observed in 52, 26 and 46% of the patients in the leflunomide, placebo and methotrexate groups, respectively. In addition, ACR success rates were observed in 41, 19 and 35% of patients taking leflunomide, placebo and methotrexate, respectively. Adverse event and withdrawal profiles were similar between the leflunomide and methotrexate groups. Thus, leflunomide is as safe and effective as methotrexate in the treatment of active RA (18).

In a double-blind, 12-month, 2-arm study, 1363 patients with RA were randomized to leflunomide (20 mg once daily) or methotrexate (10-15 mg/week). Consistent clinical response was seen in both leflunomide arms (51 and 52%). The ACR 20% response achieved with methotrexate was significantly greater than that with leflunomide (65 *vs.* 51%) in the European arm of the study; however, this difference was statistically equivalent in the U.S. arm (46 *vs.* 52%). AUC analysis *versus* time, changes in x-ray and MHAQ scores were similar between the two groups. As compared to methotrexate, leflunomide improved functional ability and disease progression was significantly slower. Overall, leflunomide and methotrexate demonstrated comparable efficacy and safety profiles (19).

According to DAS28 and ACR responder criteria, leflunomide (20 mg once daily) and methotrexate (7.5-15 mg/week) demonstrated comparable efficacy in a 12-month, multicenter, placebo-controlled trial enrolling 482 patients with active RA. An ACR good response was achieved in 54, 40 and 35% of patients randomized to leflunomide, methotrexate and placebo, respectively. Relatively good agreement was seen between ACR scores and the DAS28 (20).

Analysis of results from three trials assessing the efficacy and safety of leflunomide *versus* placebo and/or sulfasalazine or methotrexate, using both the ACR responder index and the DAS28 EULAR response criteria, again demonstrated equivalent efficacy for the three drugs, providing further support for the use of leflunomide as an efficacious and safe DMARD in the treatment of RA (21).

Following receipt of FDA approval, Hoechst Marion Roussel has officially launched leflunomide in the U.S. under the trade name Arava™. The compound is supplied as 10-, 20- and 100-mg tablets and is indicated for the treatment of active RA in adults (22).

The European Committee for Proprietary Medicinal Products has issued a positive opinion to the European Commission for the approval of leflunomide (Arava™) for the treatment of active RA in adult patients at all stages of the disease. Approximately 2000 patients worldwide have participated in clinical trials of the compound, some of whom have been treated with leflunomide for up to 5 years. Leflunomide was launched in Switzerland in March and has also been approved in Brazil, Argentina, Peru, Guatemala and Mexico (23).

A phase II trial evaluated the activity of SU-101 in the treatment of patients diagnosed with PSA-positive hormone-refractory prostate cancer. The results indicate that the compound, as part of a combination regimen, may contribute significantly to the front-line treatment of these patients. Of the 44 patients in this study, 35 reported bone pain at the outset. Twenty-one of these patients were evaluable for bone pain reduction after 4 weeks, with 9 patients demonstrating significant reductions, for an overall response rate of 26%. Thirteen of 38 patients achieved stable disease or reduced PSA responses (25-100% decrease in PSA in 4 patients), for an overall response rate of 34%. Of 19 patients evaluated for objective response, 2 had tumor regression and 3 stable measurable disease, for an overall response rate of 26%. Side effects were generally mild to moderate and included fatigue and gastrointestinal complaints. Seven patients continue to receive the treatment. The compound appeared to be most active in patients who had received less extensive prior therapy for hormone-refractory disease. Based on these findings and the unique mechanism of action, SU-101 may be effective in combination therapy with mitoxantrone in patients with hormone-refractory prostate cancer. Phase I/II trials evaluating the combination are in progress (24).

In an ongoing phase II study the efficacy and tolerability of SU-101 (400 mg/m^2 i.v. over 4-6 h/week x 11 weeks) were examined in 15 patients with advanced ovarian cancer who failed up to 4 prior chemotherapies. Two patients discontinued for progressive disease, 4 for adverse effects (small bowel obstruction, pulmonary embolism, encephalopathy/death, DIC/death) and 1 for investigator judgement. Of the 8 remaining patients, 1 had significantly decreased CA125 (79.1 to 14.3 at week 6). Increased frequency of adverse effects was noted in this study as compared to others, possibly due to the prior cytotoxic chemotherapy of patients (25).

An ongoing phase I/II pilot study of SU-101 in combination with carmustine was examined as a treatment in 18 patients with newly diagnosed gliomas. Patients were given a 4-day loading dose of SU-101 (200 mg/m^2) followed by carmustine (200 mg/m^2 every 8 weeks) and additional weekly SU-101 infusions. One patient had a partial response on MRI. Discontinuations included 5 patients for progressive disease, 4 for adverse effects (hematological toxicity, acute respiratory distress, diarrhea and seizures) and 2 by request. Cycle 1 toxicities in the remaining 7 patients included grade 3/4 thrombocytopenia (54%) and neutropenia (54%) which appeared to be exacerbations of carmustine effects since nadir was more severe and occurred earlier with carmustine coadministration. The pharmacokinetics of SU-101 or its metabolite were not changed by carmustine. The maximum tolerated dose of carmustine to be given safely with SU-101 was 200 mg/m^2 (26).

A phase II study in 44 patients with PSA-positive prostate cancer demonstrated that SU-101 treatment (4-day induction followed by 10 weekly infusions of 400 mg/m^2) could slow the progression of metastatic prostate cancer and/or ameliorate symptoms of bone pain. Discontinuations were due to death (3), adverse effects (8) and disease progression (24). Out of the 38 evaluable patients, there were 1 complete, 2 partial and 1 minor responses and 9 stable and 31 progressive diseases; an overall response rate of 30% was obtained. An improvement response rate for pain of 26% was achieved, although PSA response did not correlate with pain relief. Improvement and stable disease were seen in 2 and 5, respectively, of the 19 patients with measurable disease. Eighteen of the 28 evaluable patients reported improved or stable quality of life. The most common adverse effects were asthenia (75%), nausea (55%), anorexia (50%) and anemia (41%), with 13/44 patients discontinuing due to side effects (27).

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Hoechst Marion Roussel

Hoechst Marion Roussel has simultaneously filed with U.S. and European regulatory authorities for approval of a new indication for lepirudin for the treatment of acute coronary syndromes. The applications seek approval for the use of lepirudin in the treatment of patients with unstable angina pectoris and/or acute noncomplete myocardial infarction. The efficacy of lepirudin, a genetically engineered hirudin, in this indication was demonstrated in the OASIS-2 study by independent researchers. The double-blind, randomized study compared lepirudin to heparin as an antithrombotic treatment in more than 10,000 patients at 362 hospitals in 15 countries. The results showed that lepirudin treatment was associated with a greater reduction in the combination of cardiac death or new heart attacks and a decreased need for invasive revascularization procedures in patients experiencing unstable angina. Lepirudin is already approved in 19 countries and marketed in 15 countries worldwide for the treatment of heparin-induced thrombocytopenia (1).

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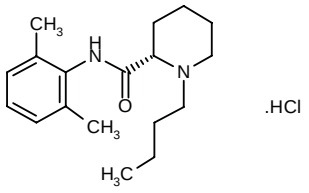

$C_{18}H_{28}N_2O.HCl$

Chiroscience; Maruishi; Purdue Pharma; Abbott

The cardiovascular effects of levobupivacaine were compared with those of racemic-bupivacaine in 14 healthy male volunteers. Both drugs were administered at 10 mg/min i.v. infusion using a randomized, double-blind, complete crossover procedure. Levobupivacaine produced a statistically smaller decrease in mean stroke index, acceleration index and the ejection fraction. Both agents produced small increases in both the PR and the corrected QT interval (1).

In a prospective, randomized, double-blind, sequential allocation study, the minimal local analgesic concentrations (MLACs) of levobupivacaine were compared to those of racemic bupivacaine showing that the latter was 2% more potent than the former. Sixty women in labor received a 20-ml bolus epidural over 5 min of either agent (0.07% w/v) and efficacy was determined using a visual analogue pain score. MLACs were 0.083% (2.85 mM) and 0.081% (2.49 mM) w/v for levobupivacaine and bupivacaine, respectively, with a levobupivacaine:bupivacaine potency ratio of 0.98 (molar ratio: 0.87). It was suggested that toxicity results should be assessed considering the 13% molar potency difference favoring bupivacaine (2).

According to data from recent studies, the risk of arrhythmogenia and other severe cardiac or CNS events may be decreased with levobupivacaine hydrochloride when given as local anesthesia during labor. These findings may translate into an enhanced margin of safety in the obstetric population. A double-blind, randomized, multicenter study comparing 0.25% levobupivacaine and 0.25% racemic bupivacaine for extradural analgesia in labor enrolled 137 women experiencing labor contractions who requested extradural analgesia. Onset, duration and overall quality of analgesia were similar in the two treatment groups, providing satisfactory relief of pain. These clinical findings, together with results obtained previously in animal studies showing that levobupivacaine has a significantly lower potential for cardiovascular toxi-

city, indicate that use of the new local anesthetic may impart greater safety for both mother and child. Another clinical study compared the postoperative analgesic efficacy and safety of epidural infusions of levobupivacaine (0.125%), with or without added clonidine (50 mg/h), to that of clonidine alone in 90 patients undergoing primary hip arthroplasty. Administration of the combination of levobupivacaine and clonidine resulted in a significant increase in time until rescue analgesia (morphine) was requested, as well as a significant decrease in the amount of morphine consumed, as compared to either compound given alone. Furthermore, the combination group experienced fewer adverse effects than the group administered levobupivacaine alone, suggesting that this combination is safe and effective for epidural infusion in the setting of hip arthroplasty (3).

Chiroscience, which has reached an agreement with Zeneca for the return of all rights to Chirocaine[R], has licensed the compound to Purdue Pharma for the U.S. market and to Abbott for all markets outside the U.S. and Japan. In Japan, Chirocaine® is licensed to Maruishi. Chirocaine® was developed by Chiroscience for use in acute pain management following a wide range of surgical procedures, for pain relief during labor and childbirth, and for chronic pain management. Chirocaine® has been approved by regulatory authorities in Sweden and has received an approvable letter from the U.S. FDA. Clinical trials with the compound have been completed in the U.S., Europe, Canada, Australia and New Zealand (4-9).

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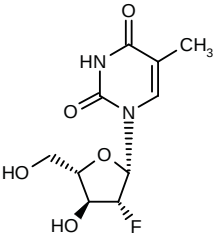

$C_{10}H_{13}FN_2O_5$ **Bukwang; Triangle; Abbott**

The therapeutic potential of L-FMAU was assessed in a woodchuck model of chronic HBV-induced disease. The compound, administered once daily, was effective at doses as low as 0.3 mg/kg p.o. At the higher dose of 10 mg/kg, it suppressed viremia by more than 200-fold over 48 h and by up to 1 billion-fold after 4 weeks. An analysis of viral cccDNA in liver samples indicated that L-FMAU works by inhibiting virus replication to below the level required to maintain cccDNA, leading to a progressive loss of virus-infected cells in the liver and subsequently eliminating the need for lifetime antiviral therapy. As such, L-FMAU appears to have excellent potential in the treatment of chronic HBV infection (1).

Abbott and Triangle Pharmaceuticals have entered into a worldwide strategic alliance for six antiviral products, one of which is L-FMAU. Phase I/II trials with L-FMAU are planned for late 1999 (2).

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The mechanism of action of L-NDDP has been evaluated and its effects compared to those of free NDDP in order to determine whether the liposomes affect the cellular uptake and subcellular distribution of the compound. NDDP was found to be responsible for inducing DNA adduct formation; furthermore, cellular repair of NDDP-induced adducts was significantly less efficient than that of CDDP-induced adducts, a fact that may contribute significantly to the antitumor activity of NDDP in CDDP-resistant cancer cells (1).

The safety and efficacy of i.p. administration of L-NDDP were examined in a phase I study in 24 patients with peritoneal carcinomatosis. The agent (200, 300, 400 and 450 mg/m^2 every 28 days) was given after pretreatment with a serotonin receptor blocker with the first 2 courses administered under laparoscopy and the following courses, if benefit was noted, given via a s.c. port in the peritoneal cavity. Dose-limiting toxicities observed with the highest dose were posttherapeutic adhesions which resulted in discontinuation of treatment in 3 patients. Grade 2 anemia (3), thrombocytopenia (1) and neutropenia (2) were observed with doses of 400 mg/m^2 or more. Toxicities of less than grade 2 were seen with all doses and included nausea/vomiting (8), fatigue (6), abdominal pain (8), back pain (3), constipation (2) and sensory neuropathy (2). All patients with refractory ascites responded and significant antitumor activity was observed in 6/6 mesothelioma patients. An additional cohort will be treated with 350 mg/m^2 (2).

Preliminary results from an ongoing phase II study of L-NDDP (450 mg/m^2) administered intrapleurally to 20 patients with malignant pleural mesothelioma have demonstrated a high rate of pathologic response of the agent. The first course of L-NDDP was given to 8 patients at the time of thoracoscopy with 2 deaths (pneumonia with peritonitis and chest wall cellulitis at the thoracoscopy site) occurring from side effects due to the method of drug infusion. The drug was subsequently administered via a Tenkoff or Denver catheter 1 week after catheter placement and repeated every 3-4 weeks. Only mild to moderate pleuritic chest pain, transient fever, mild nausea/vomiting, fatigue, grade 3 allergic reaction (1), grade 3 thrombocytopenia (1) and grade 3 neutropenia (2) were observed. After 4 courses of therapy, 11/15 patients (73%) had pathologic complete responses (3, 4).

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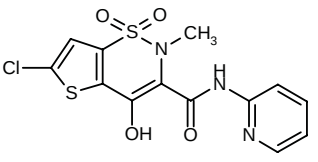

$C_{13}H_{10}ClN_3O_4S_2$ **Nycomed Amersham; Andrómaco; Merckle; Taisho**

The interactions between lornoxicam 0.1, 0.5, 1.0 and 2.0 mg/kg i.v. and morphine were studied in a rat colorectal distension model of acute visceral pain. Monotherapy with morphine was more effective than lornoxicam monotherapy in reducing nociception. However, a potentiation of 36.1% was observed when morphine 3 mg/kg was coadministered with lornoxicam 2 mg/kg, indicating that lornoxicam administered in combination with morphine produces synergistic effects in terms of antinociception (1).

A review of the pharmacokinetics of lornoxicam has been published. The drug demonstrated a relatively short plasma half-life (3-5 h) and its glucuroconjugated metabolites were excreted in urine and feces with an approximate half-life of 11 h. Lornoxicam and its metabolites bound to plasma albumin and high concentrations were found in synovial fluid. Like other compounds of its class, lornoxicam will apparently interact with warfarin, sulfonuyureas, digoxin and furosemide (2).

Lornoxicam has now been introduced in Germany as Telos® by Merckle under license from Nycomed Pharma for the symptomatic treatment of pain and inflammation in rheumatoid arthritis and osteoarthritis. The product is available in tablets of 4 mg and 8 mg. Lornoxicam was launched last year as Xefo® in Austria, Denmark, Sweden, Russia and the Baltic countries, and it is under development in Japan by Taisho (3).

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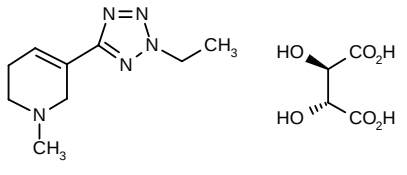
LU-25-109T
Alvameline Tartrate

Treatment of Urinary Incontinence
Muscarinic M_1 Agonist
Muscarinic M_2 Antagonist

EN: 216348



$C_9H_{15}N_5.C_4H_6O_6$ **Lundbeck; Forest**

An *in vitro* study reported that LU-25-109 stimulated amyloid protein precursor (APP) in transfected HEK 293 cells overexpressing human muscarinic m_1 but not m_2 acetylcholine receptors and human hippocampal slices. Rapid (5-35 min) and delayed (55-75 min) secretory responses to the agent were observed with different concentration profiles suggesting involvement of 2 different mechanisms of action. By stimulating APP production and thus inhibiting amyloid beta peptide generation, LU-25-109 may slow amyloid plaque formation in Alzheimer's disease (1).

Although LU-25-109T did not show clinical effectiveness in a phase II/III clinical trial in patients with Alzheimer's disease, Forest Laboratories plans to continue exploring other potential uses for the compound, such as urinary incontinence (2).

Alvameline tartrate is the proposed international nonproprietary name for LU-25-109T (3).

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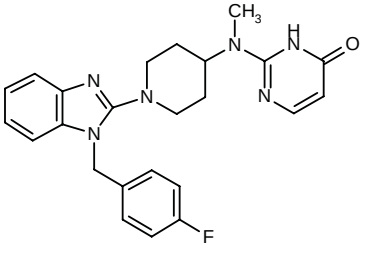
Mizolastine
Mizollen®
Zolim®
Mizolen®

Treatment of Allergic Rhinitis
Histamine H_1 Antagonist

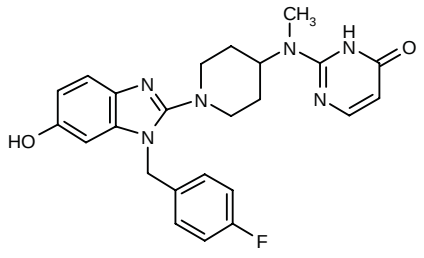
EN: 134006



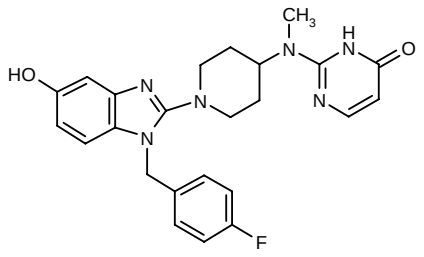
$C_{24}H_{25}FN_6O$ **Sanofi-Synthélabo; Mitsubishi Chem.**

The *in vitro* H_1 receptor affinity and the *in vivo* antihistamine activity of the two major metabolites of mizolastine, M-1 and M-2 have been tested. At nanomolar concentrations (IC_{50} for M-1, 0.095 μM; IC_{50} for M-2, 0.260 μM), both metabolites displaced the binding of ^{3}H-pyrilamine to H_1 receptors. At doses up to 10 mg/kg i.p., neither metabolite antagonized histamine-induced paw edema in rats. Therefore, M-1 and M-2 probably do not contribute to the antihistamine activity of mizolastine (1).

The pharmacological effects of mizolastine metabolites (M-1 and M-2) (Fig. 1) were assessed in experimental



M-1



M-2

Fig. 1.

animals. Neither metabolite affected general activity, behavior or the central nervous system at a dose of 10 mg/kg. Both metabolites caused a brief decrease in mean blood pressure at 10 mg/kg i.v. This hypotensive effect was less than that caused by mizolastine itself, and thus the metabolites may have little negative effect in clincal use (2).

The toxicity of mizolastine was evaluated in rats receiving doses of 3, 4 and 5 g/kg p.o. and 1, 2, 3, 4 and 5 g/kg i.p. and in monkeys (0.5 and 1 g/kg p.o.). No deaths were recorded in the rat treatment groups and the principal clinical sign was redness and swelling of the scrotum. In monkeys treated with the higher dose, vomiting and a slight weight loss were observed on day 2. Lethal doses in rats and monkeys were estimated to be more than 5 and 1 g/kg, respectively (3).

Evaluation of the toxicity of mizolastine 5, 30 and 180 mg/kg administered orally during 6 months in rats showed no treatment-related deaths. Slightly increased blood phosphorus levels were observed, as well as a tendency towards higher urine volumes in females following administration of the highest dose. The highest nontoxic dose was established at 5 mg/kg/day (4).

Oral administration of mizolastine 5, 30 and 180 mg/kg in monkeys during 6 months produced no treatment-related clinical signs at the two lower doses. One animal receiving 30 mg/kg/day displayed cardiac abnormalities. The highest dose produced vomiting, tremor and hypomotility, while gross and histopathological changes observed in the active treatment group were similar to changes observed in control animals. The nontoxic dose in this model was established at 5 mg/kg/day (5).

Administration of mizolastine 1, 5 or 30 mg/kg/day p.o. gavage during 12 months in monkeys produced no notable toxicologic or pathologic effects. The 5-mg dose was considered nontoxic, while the 30-mg dose was established as the limiting dose for the onset of toxic effects in terms of electrocardiographic abnormalities observed in 1/12 animals (6).

Evaluation of mizolastine in terms of its mutagenic and clastogenic potential using *in vitro* bacterial reverse mutation and chromosome aberration tests, and *in vivo* micronucleus test showed that the drug exhibits no mutagenic or clastogenic activity (7).

The effects of oral mizolastine on histamine-induced vascular permeability were evaluated in rats, mice and guinea pigs. Permeability was inhibited by the drug with ED_{50} values of 0.2 and 0.03 mg/kg in rats and mice, respectively, while in guinea pigs the ED_{50} was 0.06 mg/kg. Mizolastine was at least 10 times more potent than terfenadine in terms of antihistamine activity (8).

Mizolastine inhibited IL-4 production in mouse bone marrow-derived mast cells with an IC_{50} of 9.3 μM, while effects on TNF-α production were absent. However, in mouse peritoneal macrophages, TNF-α production was inhibited (IC_{50} = 4.1 μM) (9).

The minimum effective dose of mizolastine for the inhibition of allergic rhinitis in rats was estimated to be 1 mg/kg after oral administration, while astemizole and terfenadine produced minimum effective doses of 1 and 10 mg/kg, respectively (10).

Histamine-induced contractions of isolated guinea pig ileum were dose-dependently and competitively inhibited by mizolastine and terfenadine up to concentrations of 0.1 and 0.3 μM, respectively, with corresponding pA_2 values of 8.46 and 7.17 (11).

Evaluation of mizolastine's effects on 5-lipoxygenase activity in guinea pig peritoneal polymorphonuclear leukocytes showed that the drug inhibits the enzyme's activity with an IC_{50} of 3.7 μM, while terfenadine, ketotifen, astemizole and cetirizine produced weak or no effects at concentrations of 10 μM (12).

Mizolastine's effects on ventricular repolarization were evaluated in dogs receiving 3 and 10 mg/kg of the drug alone, or following pretreatment with ketoconazole. Mizolastine prolonged QTc only after administration of the higher dose following pretreatment with ketoconazole. Mizolastine did not produce cardiac arrhythmias (13).

Oral administration of mizolastine 30 mg/kg in intact or pithed normotensive rats did not produce detectable effects on baseline arterial pressure and heart rate. Acetylcholine-induced reductions in blood pressure were not affected, and effects on α- and β_1-adrenoreceptors or 5-HT_2 receptors were absent (14).

Evaluation of the hemodynamic effects of mizolastine (0.3, 1 and 3 mg/kg) in anesthetized dogs showed that administration of the lowest dose produced no statistically significant effects. However, the two higher doses produced short-lasting hypotension with reductions in total peripheral resistance and increased QTc, without increasing QRS (15).

Administration of mizolastine 2 mg/kg i.v. in rats did not alter respiratory rate, tidal volume, resistance and compliance over a 90-min period, as compared to baseline values (16).

The sedative potential of mizolastine 10 mg/kg i.p. was evaluated in rodents using EEG techniques. The drug demonstrated no sedative effects in this model, indicating that administration of therapeutic doses in humans will not induce sedation (17).

Administration of mizolastine 300 mg/kg p.o. in animals affected general activity behavior, spontaneous motor activity, sleeping time, convulsion, intestinal motility, urine and electrolyte excretion and blood coagulation. However, these effects were minimal even at doses 1000 times higher than the effective dose, indicating that mizolastine does not represent major problems in clinical use (18).

ED_{50} values for the antihistamine activity of mizolastine and terfenadine were estimated to be 0.07 and 7.5 mg/kg, respectively, in a canine model of edema. Inhibition was dose-dependent and reached its highest effects 1-2 h after oral administration (19).

Mizolastine attenuated inflammatory edema induced by arachidonic acid injections in the rat paw. The effect was dose-dependent at a concentration range of 0.1-10 mg/kg and was maintained for at least 4 h after treatment. A similar effect was observed with dexamethasone, while terfenadine and loratadine had no effects. The results indicated that the antiinflammatory activity of mizolastine was unrelated to its histamine antagonistic properties (20).

The potential sedative effects of mizolastine have been evaluated in the rat. The drug (3-300 mg/kg p.o.) exerted no effects on spontaneous motor activity, thiopental-induced sleeping time or spontaneous electroencephalogram. At up to 1500 times the effective dose, mizolastine had no influence on the CNS, whereas terfenadine and ketotifen had sedative effects at 143 and 150 times the effective dose, respectively (21).

Evaluation of mizolastine's effects on electrocardiograms in guinea pigs showed that the drug has a safety margin 1667-fold higher than the effective dose in histamine-induced skin edema. In comparison, the safety margins of astemizole and terfenadine were less than 100- and 600-fold, respectively (22).

Radiolabeled mizolastine bound to rat, monkey and human serum protein in a reversible manner with binding rates of 90.7, 96.8 and 98.1%, respectively. Recovery was 97.6 and 94.9% after 0.25 and 3 h, respectively, of administration of a single oral 5-mg/kg dose. In human serum, the drug appeared to bind to albumin and α_1-acid glycoprotein (23).

Evaluation of feto-placental transfer and excretion into milk of mizolastine 5 mg/kg in lactating rats showed that 0.05 and 0.02% of the drug was transferred to the fetus 0.75 and 6 h following dosing on the 18th day of gestation. Drug concentrations in plasma and milk reached maximum levels 0.75 and 2 h following administration, respectively, and the concentration in milk was slightly higher than in plasma (24).

In radioligand binding studies, mizolastine inhibited tridiated pyrilamine binding to histamine H_1 receptor in the guinea pig cerebellum with an IC_{50} of 52.8 nM, while IC_{50} values for the inhibition by astemizole and terfenadine were 14.4 and 130 nM, respectively. Saturation analysis indicated that mizolastine binding at a concentration of 50 nM was competitive with a K_i of 4.36 nM (25).

Antigen-induced infiltration of eosinophils into mouse skin was inhibited by mizolastine with an ED_{50} of 0.3 mg/kg following oral administration of the compound, while infiltration into nasal cavity of guinea pigs was inhibited with an ED_{50} of 0.2 mg/kg after i.p. administration (26).

Mizolastine inhibited histamine release induced by antigen and the calcium ionophore A23187 in rat peritoneal exudate cells with IC_{50}s of 130 and 140 μM, respectively, while LTC_4 production was inhibited with an IC_{50} of 3.8 μM. In bone marrow-derived mast cells from mice, histamine, LTC_4 and LTB_4 production was inhibited with IC_{50}s of 47.3, 3.0 and 6.4 μM, respectively. Antagonistic effects on isolated guinea pig ileum contractions mediated by LTD_4, acetylcholine, substance P and bradykinin were not observed (27).

Evaluation of mizolastine in guinea pig ileum models of type I-IV allergic reactions demonstrated that 10 μM of the drug inhibited the Schultz-Dale reaction. In rats and guinea pigs following oral administration, homologous passive cutaneous anaphylaxis was inhibited with ED_{50}s of 1.0 and 0.02 mg/kg, respectively. The Forssman reaction in guinea pigs and Arthus reaction and delayed-type hypersensitivity in mice were not affected (28).

Sensitization of guinea pigs with mizolastine 0.2 or 2 mg/kg p.o. 5 times per week during 3 weeks, and by subcutaneous injections of 2 mg/kg once weekly during 3 weeks did not produce active systemic anaphylaxis following a challenge with mizolastine 0.16 mg/kg i.v. Antibodies to the drug in sera were not detected, suggesting that mizolastine exhibits no antigenicity (29).

Evaluation of mizolastine's toxicity in rats administered doses of 1, 5, 30 or 180 mg/kg/day during 12 months, with a 1-month recovery period, showed that treatment with 1 and 5 mg/kg/day was well tolerated and nontoxic. Changes associated with the 30 and 180 mg doses were reversible and were restored to some degree after the recovery period (30).

Studies of mizolastine metabolism in rats showed that plasma C_{max} and AUC correlated well following oral administration of 1, 5 and 25 mg/kg, with a t_{max} of 0.5 h after the 5-mg/kg dose. The observed half-life of 1.6-4.5 h indicated gender-based differences in plasma pharmacokinetics, with a bioavailability of 34.1 and 61.1% in males and females, respectively. C_{max} and AUCs decreased by 38 and 80% after administration of the drug with food. Reabsorption from the bile demonstrated enterohepatic circulation of the drug (31).

In rats, oral administration of single doses of mizolastine 5, 25 and 125 mg/kg/day, repeated every 7, 14 and 21 days produced no significant changes in plasma C_{max}, t_{max}, $t_{1/2}$ or AUC. Tissue levels reached steady state after the 7th dosing in lung, liver, spleen and kidney. Excretion

in urine and feces of the total dose was 6.9 and 90.9%, respectively, and the effects on hepatic metabolic enzymes were slight and reversible (32).

Oral administration of single doses of mizolastine 5 mg/kg in male and female monkeys produced plasma C_{max} after 1.0 and 1.4 h, respectively, with respective $t_{1/2}$ values of 8.4 and 8.7 h. Intravenous administration resulted in reduced plasma levels and $t_{1/2}$ values of 11.0 and 6.3 h in males and females, respectively. The drug's absorption rate was considered to be almost 100% when evaluated from urinary excretion rates, while AUCs indicated an absorption rate of 50-64%. Bioavailability was 34-43% (33).

The pharmacokinetics of mizolastine 10 mg once daily was compared in young and elderly subjects. C_{max} was higher in elderly subjects (283 *vs.* 222 ng/ml), as were the AUC values (2308 *vs.* 1527 ng.h/ml), while t_{max} was equal in both groups. Somnolence was reported only in the elderly group (34).

A registration dossier was filed in 1998 in Japan for mizolastine (Mizollen®) for the treatment of seasonal and perennial allergic rhinoconjunctivitis and urticaria; the first product launches took place in other markets. This specific, potent and selective H_1 antagonist is the first antihistamine to obtain registration in all countries of the European Union using the mutual recognition procedure. Mizolastine was launched in 1998 in Belgium, Denmark, Germany, Greece, Italy, Luxembourg, The Netherlands, Spain, Switzerland and the U.K., and launch in France took place in early 1999 (35).

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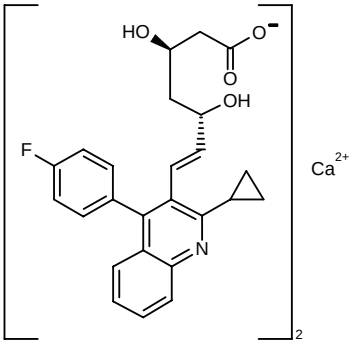
NK-104
Nisvastatin
Itavastatin Calcium

Hypolipidemic
HMG-CoA Reductase Inhibitor

EN: 192009



$C_{50}H_{46}CaF_2N_2O_8$ **Kowa; Nissan Chem.; Sankyo**

A single-dose toxicity study has shown that the lethal dose of oral NK-104 was 500-1000 and 250-500 mg/kg in 6-week-old male and female Wistar rats, respectively, and 100 mg/kg or less in 9-month-old beagle dogs. Adverse effects included death, decreases in body weight, decreases in spontaneous movement, crouching, diarrhea, paralytic gait and hyperkeratosis, ulcer formation and bleeding in the stomach or intestine (1).

In a 3-month, repeated-dose toxicity study, it was concluded that the nontoxic dose of oral NK-104 was 1 mg/kg/day in both male and female beagle dogs. Side effects included opacity of lenses, elevations in GOT and GPT activity, decreases in cholesterol, triglyceride and phospholipid levels, foci of foam cells with inflammatory cell infiltration in the lung and centrilobular dilatation of sinusoids in the liver; all side effects except cataracts were reversed at the end of a 7-week withdrawal period (2).

In a 12-month, repeated-dose toxicity study in beagle dogs, the nontoxic dose of oral NK-104 was determined to be 0.3 mg/kg day. All animals survived with no changes observed in body weight, food or water consumption, urinalysis, hematology or ECG. Side effects included opacity of lenses, elevations in GOT and GPT activity, decreases in cholesterol, triglyceride and phospholipid levels and foci of foam cells with inflammatory cell infiltration in the lung; all side effects except cataracts were reversed at the end of a 2-month recovery period (3).

An embryotoxicity and teratogenicity study of oral NK-104 (on days 7-17 of gestation) in rats has shown that the nontoxic dose for general toxicity in dams was 10 and 30 mg/kg/day for reproduction in dams and fetuses and offspring. Reductions in body weight and food intake were observed in dams receiving 30 mg/kg. No adverse effects on dam pregnancy and nursing or fetal external, visceral or skeletal abnormalities, viability, growth and reproductive performance were observed (4).

An embryotoxicity and teratogenicity study of oral NK-104 (on days 6-18 of gestation) in rabbits has shown that the nontoxic dose for general toxicity in dams was 0.1 mg/kg/day and 1 mg/kg for embryonic and fetal development. At the high doses of 0.3 and 1 mg/kg, death, a decrease in fecal mass and increase in abortions were observed in dams. No fetal external, visceral or skeletal abnormalities were observed in any group (5).

A perinatal and postnatal study has shown that the nontoxic dose of oral NK-104 (0.1-30 mg/kg on days 17 of gestation to 21 of lactation) was 0.3 mg/kg/day for general toxicity and reproduction in pregnant rats and offspring. Side effects in dams with doses of 1 mg/kg or higher included death, decreases in body weight and food intake, reductions in live newborns, increases in stillborns and decreases in viability indices on day 4 after birth. No effects on behavior, reproductive performance or development of second generations were observed (6).

NK-104 (0.1 or 1 mg/kg p.o. plus 1 mg/animal s.c. or i.v.) had no allergenicity in male guinea pigs in a study using active systemic and passive cutaneous anaphylaxis assays (7).

NK-104 at 10 mg/kg/day was determined to be the nontoxic dose in a study examining its effects on rat parental fertility and fetal development in males treated 70 days prior to mating plus 7 days until sacrifice and females treated for 14 days prior to mating plus the first 7 days of gestation, respectively. Side effects in males included decreases in body weight and food consumption and death. No adverse effects were observed on the estrous cycle, copulation or fertility index, number of corpora lutea, implantations, fetal mortality, sex ratio, fetal weight, placental appearance and properties of amniotic fluids (8).

The pharmacokinetics of NK-104 were examined in rats, rabbits, dogs, monkeys and humans with results showing triexponential plasma elimination of the agent after i.v. administration with a half-life of 4-5.3 h in the 4 species of animals. Absorption was rapid after oral administration and high bioavailability (80%) was observed with 1 mg/kg in all animals except monkeys. Dose and AUC relationships were linear at the high dose range in animals and, in humans, the correlation line fell between dog and rats. NK-104 was shown to be excreted mainly in feces by the biliary route. Although renal excretion was minimal in rats, dogs and humans, NK-104 was excreted mainly in the urine of rabbits. Poor excretion in urine and feces was noted for monkeys. The unchanged compound was excreted in rat bile with low levels of the β-oxidation metabolites detected. Unchanged compound in dogs was found in plasma, urine and feces after oral administration with low levels of β-oxidation metabolites (M-5 and M-8). Unchanged NK-104 and its lactone form were found in human plasma after repeated oral administration (2 mg/day for 5 days). Thus, very little metabolism of NK-104 occurs in humans as compared to the animal species studied (9).

Itavastatin calcium is the new proposed international nonproprietary name for NK-104 (10).

With launch of the product in the foreseeable future, Nissan Chemical and Kowa have signed an agreement with Sankyo for comarketing of itavastatin calcium, currently in phase III trials. The product was originally codeveloped by Nissan Chemical and Kowa, with Kowa retaining exclusive marketing rights in Japan. Under terms of the new agreement with Sankyo, the latter will have comarketing rights in Japan, as well as exclusive development and marketing rights in the U.S. (11).

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ONO-4007

Antineoplastic
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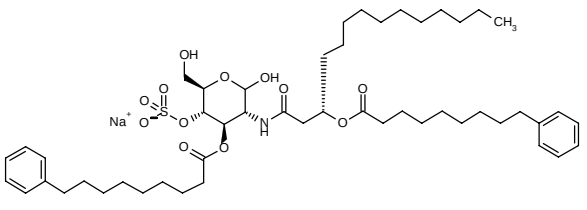
EN: 193855



$C_{50}H_{78}NNaO_{12}S$

Ono

ONO-4007 exhibited TNF-α-mediated antitumor effects against cultured cells from surgically removed glioblastoma tissue. TNF-α production was not elevated in ONO-4007 treated (30, 100 and 300 μg/ml) cells as compared to untreated cells. TNF-α levels were elevated in 3/5 cases of cells exposed to 300 μg/ml ONO-4007 (1).

ONO-4007 was administered to rats on days 7, 14 and 21 after transplantation of a rat hepatic cancer cell strain (KDH-8) and following anti-TNF-α antibody treatment. KDH-8 and KEG-1 were retransplanted after ONO-4007 eradication of tumors. Local tumor TNF-α was markedly reduced by anti-TNF-α administration. Retransplanted KDH-8 was rejected although KEG-1 adhered. ONO-4007 treatment induced $CD4^+$ cell-dependent antitumor immune responses (2).

In a phase I study, 24 cancer patients (melanoma, renal, colorectal, miscellaneous) received an initial 30-min infusion of ONO-4007 (74, 100 and 125 mg) on day 1 followed by 3 once-weekly infusions with a 1-week rest period for 4 cycles. The maximum tolerated dose was 125 mg/day; grade 3 CTC toxicity was observed in 2/6 patients at this dose in addition to grade 2 myalgia, nausea and hypotension. C_{max} with the 75 and 100 mg doses was achieved at the end of infusion and concentrations decreased in a multiexponential manner with a mean half-life of 80-90 h. Systemic exposure dose-proportionally increased with multiple administration by 30% (3).

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Anticoagulant

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Oral formulation of heparin using the Complexing Agent Delivery System (CADDSYS™) carrier SNAC

SNAC *Absorption Promoter*
P414

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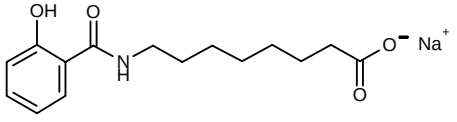

$C_{15}H_{20}NNaO_4$ **Emisphere; Elan**

In a randomized, double-blind study, the safety, tolerability and effects on indexes of anticoagulation of SNAC were assessed with escalating oral doses of heparin. Increases in activated thromboplastin time (aPTT), anti-factors IIa and Xa and tissue factor pathway inhibitor (TFPI) concentrations were observed in normal volunteers who received SNAC 10 g and 20,000 IU heparin. 30,000 IU SNAC and heparin significantly raised TFPI from 74.9 to 254 mg/ml at 1 h after dosing with similar changes taking place in anti-factor IIa and Xa. At 2 h after dosing, aPTT increased from 28 to 42.2 s. Overall, the preparation was well tolerated and established the feasibility of oral delivery of anticoagulant doses of heparin (1).

Emisphere and Elan, who have formed a joint venture to develop and commercialize oral formulations of heparin, have reported that the preliminary results of a phase II study in 127 patients undergoing hip replacement surgery have demonstrated that oral heparin formulations are comparable to injectable heparin in the prevention of deep vein thrombosis (DVT). The comparability of DVTs and side effects in each of the three arms of the trial indicated that phase III studies are warranted, subject to FDA approval (2).

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H^+/K^+-ATPase Inhibitor

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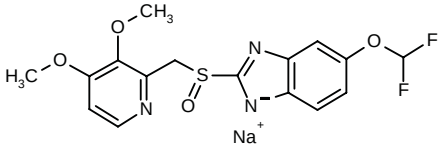

$C_{16}H_{14}NaF_2N_3O_4S$ **American Home Products**

Oral tablet and injectable formulations of pantoprazole sodium (Protonix®) have been approved by the FDA for the treatment of gastroesophageal reflux disease (1).

1. *FDA approves injectable, oral formulations of Wyeth-Ayerst's Protonix.* DailyDrugNews.com (Daily Essentials) Aug 6, 1999.

Original monograph - Drugs Fut 1990, 15: 801.

Pazufloxacin
Pasil®

Quinolone Antibacterial

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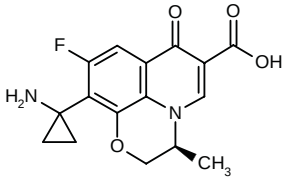

$C_{16}H_{15}FN_2O_4$ **Toyama; Yoshitomi**

A study investigated the metabolism of pazufloxacin mesilate (PZFX; 5 mg/kg i.v.) in urine of mice, rats, rabbits and monkeys and bile from rats. Human urine from a phase I study (400 mg single dose or 300 mg b.i.d. for 5 days) was also examined. Mouse urine radioactivity after administration of [^{14}C]-PZFX was mainly PZFX glucuronide while the unchanged compound was found in rat urine; biliary excretion was minor in rats. The PZFX glucose adduct, PZFXM1, was also detected in urine and PZFXM2 and -3 were found in rabbit and monkey urine. In human urine, 94% of unchanged compound, 5.7% PZFX glucuronide and small amounts of PZFXM2 and -3 were detected after a 400 mg dose and the glucuronidation rate was unchanged with repeated dosing (1).

The broad spectrum antibacterial activity of pazufloxacin mesilate was compared *in vitro* and *in vivo* to other antibiotics including ofloxacin, ciprofloxacin,

imipenem, ceftazidime, gentamicin and minocycline. Potent bactericidal activity in a short period of time was observed with pazufloxacin and longer postantibiotic effects at high concentrations of pazufloxacin were observed as compared to the other agents. The MIC_{90} values for pazufloxacin against Gram-positive *Staphylococcus aureus* and *S. epidermidis* were 0.25-4 μg/ml; pazufloxacin was the most potent agent against methicillin-resistant *S. aureus* (MIC_{90} = 16 μg/ml). Activity against Gram-negative bacteria including *Enterobacteriaceae* and imipenem- and gentamicin-resistant *Pseudomonas aeruginosa* was the same as ciprofloxacin and better than the other agents. Ciprofloxacin but not pazufloxacin uptake was affected by CCCP coadministration. *In vivo* studies showed protective effects of pazufloxacin against systemic Gram-positive and Gram-negative, pulmonary and urinary infections in mice (2).

Pazufloxacin mesilate (i.v.) was less active than imipenem and tosufloxacin and as effective as ciprofloxacin and ceftazidime against anaerobic clinical strains. MIC_{90} values for pazufloxacin were ≥ 1.56 μg/ml with good activity observed against several strains of *Clostridium perfringens*, *Fusobacterium nucleatum*, *Peptostreptococcus*, *Porphyromonas* spp., *Prevotella* and *Propionibacterium acnes*. Less activity was observed against *Bacteroides fragilis* and *Prevotella bivia* with MIC_{50} values of ≥ 6.25 μg/ml (3).

A study reported that pazufloxacin had good activity against several strains of anaerobic bacteria, indicating a potential use of the agent in obstetric and gynecological infections. The MIC_{50} values against clinical isolates of *Streptococcus agalactiae*, *Gardnerella vaginalis*, *Escherichia coli*, *P. aeruginosa*, *Peptostreptococcus magnus*, *B. fragilis* and *P. bivia* were 3.13, 6.25, 0.025, 0.78, 6.25, 6.25 and 12.5 μg/ml, respectively, and the respective MIC_{90} values were 3.13, 6.25, 0.10, 12.5, 25, 12.5 and 25 μg/ml (4).

The broad spectrum antibacterial activity of pazufloxacin mesilate was compared *in vitro* and *in vivo* to other antibiotics including levofloxacin, ciprofloxacin and imipenem. Antibacterial activity of the agent *in vitro* was similar to ciprofloxacin and levofloxacin and no cross-resistance to β-lactam antibiotics (imipenem, flomoxef, ceftazidime) was observed. Pazufloxacin and ciprofloxacin were the most effective against Gram-negative systemic infections in mice with ED_{50} values 4-120 times better than imipenem. The ED_{50} for a single s.c. pazufloxacin injection was 2-4 times better than multiple s.c. injections. Pazufloxacin was as effective as flomoxef and more effective than levofloxacin and ciprofloxacin against 3 strains of *S. aureus*. The *in vitro* postantibiotic effects of pazufloxacin were concentration- and time-dependent against *E. coli* and *P. aeruginosa* (5).

A broader spectrum of antibacterial activity was observed for pazufloxacin mesilate as compared to ceftazidime and gentamicin and similar activity as ciprofloxacin and imipenem was observed against Gram-positive and Gram-negative bacteria *in vitro*. MIC_{90} values for pazufloxacin against streptococci were inferior (3.13 μg/ml) to imipenem and superior (0.2-6.25 μg/ml) to ceftazidime against quinolone-susceptible staphylococci and enterococci. MIC_{90} values for pazufloxacin against Gram-negative bacteria including cephem-resistant *Enterobacteriaceae* and ceftazidime-, imipenem- and gentamicin-resistant *P. aeruginosa* were 0.025-50 μg/ml. Bactericidal activity of pazufloxacin was observed with higher MICs against *S. aureus*, *E. coli* and *P. aeruginosa* and was superior to ceftazidime and imipenem; postantibiotic effects against *P. aeruginosa* were superior to imipenem and ceftazidime. A 1.45- to 496-fold superiority of pazufloxacin over ceftazidime was observed *in vivo* against Gram-positive and Gram-negative systemic infection including MDR strains in mice. Pazufloxacin was superior to ceftazidime against respiratory, urinary tract, s.c. implanted disk and CMC pouch infections (6).

The antimicrobial activity, pharmacokinetics and clinical efficacy of pazufloxacin mesilate were demonstrated. The MIC_{90} values of the agent against 155 clinical isolates of *S. aureus*, *Streptococcus pneumoniae*, *E. coli*, *Klebsiella pneumoniae*, *Hemophilus* and *P. aeruginosa* were 25, 3.13, 0.05, 0.05, 0.05 and 6.25 μg/ml, respectively. Serum concentrations of the agent ranged from 3.88-17.04 μg/ml when infused (500 mg b.i.d. i.v.) for 11 days in a patient with diffuse panbronchiolitis. Peak sputum and saliva concentrations were, respectively, 13.5 and 4.88 μg/ml on day 1, 6.70 and 4.14 μg/ml on day 3 and 6.92 and 4.72 μg/ml on day 5 with 64-97% and 16-28% penetration in sputum and saliva, respectively. The efficacy rate was 100% when 11 patients with bacterial pneumonia, pulmonary abscess, secondary infection to chronic respiratory disease, acute bacterial exacerbation of chronic bronchitis, diffuse panbronchiolitis or mycoplasmal pneumonia were treated with the agent, with rapid improvements in body temperature, sputum property and dyspnea observed. No severe adverse effects and only 2 cases of mild eosinophilia were reported (7).

In anesthetized dogs, pazufloxacin (10-100 mg/kg i.v.) transiently decreased blood pressure and increased or decreased femoral blood flow. At doses of 30 mg/kg or more, heart rate decreased, respiratory rate increased and ECG T waves were elevated. Transient increases in blood pressure were observed in anesthetized rabbits (10-100 mg/kg i.v.). Pazufloxacin inhibited acetylcholine-induced contraction and epinephrine-induced relaxation and enhanced epinephrine-induced contraction in guinea pig ileum, trachea and vas deferens, respectively. Epinephrine-induced hypertension was aggravated in dogs given 30 mg/kg and mydriasis was observed in mice receiving 100 mg/kg. Motility of isolated rabbit stomach was inhibited or enhanced by pazufloxacin (100 μg/ml) and ileum and colon motility were inhibited. No effects were noted on gastric secretion or mucosa in rats or on intestinal motility in mice. Urinary potassium and PSP excretion and spontaneous uterine motility were inhibited in rats (100 μg/ml). Platelet aggregation in rabbits was suppressed and vascular permeability-enhancing activity and weak hemolyzing effects were observed in rats (2 mg/ml) and rabbits (3 mg/ml) (8).

Pazufloxacin mesilate (200 mg/kg i.v.) was shown to cause transient depression of the CNS in mice. A dose of 100 mg/kg resulted in antireserpine activity in mice, although 10-100 mg/kg did not affect locomotor activity, motor coordination, pentobarbital-induced hypnosis or convulsions in mice, passive avoidance response in rats, body temperature in rabbits or EEG in cats. The agent (200 mg/kg) did not induce convulsions in mice pretreated with 4-biphenylacetic acid. Pazufloxacin (100 μM) had no effects on gamma-aminobutyric acid receptor binding in rat crude synaptic membranes with or without 4-biphenylacetic acid (9).

The pharmacokinetics of pazufloxacin mesilate (5 mg/kg i.v.) were examined in dogs, rabbits, rats and mice. Serum levels after 5 min were similar in all animals (4.77-6.93 μg/ml) and half-lives of 4.5, 1.0, 0.88 and 0.23 h, respectively, were obtained after single dosing; urinary excretion rates within 24 h were 56.6, 54.9, 74.3 and 44.7% of the dose, respectively. The agent was rapidly distributed to several tissues except brain with high levels found in kidney. In rats (5-100 mg/kg), AUC values were linearly proportional and urinary excretion rates constant; no differences in serum levels of the agent were observed after multiple (b.i.d. for 6 days) as compared to single dosing. Although decreases in serum levels were slightly delayed in rats with D-galactosamine-induced liver dysfunction, serum levels and urinary excretion were similar to normal rats. Rats with $HgCl_2$-induced kidney dysfunction had significantly increased serum levels and decreased urinary excretion (10).

A study in which rats and mice received single or repeated doses of [^{14}C]-pazufloxacin (5 mg/kg i.v.) reported total clearances of 1.03 and 1.21 l/h/kg, respectively, and distribution volumes of 1.25 and 0.99 l/kg, respectively. Elimination half-lives of 1.49 and 1.91 h, respectively, were obtained with biexponential decreases in serum radioactivity. Urinary excretion was the main route of elimination with rates of 77 and 68% obtained in rats and mice, respectively. Radioactivity was higher in kidney and liver with wide tissue distribution observed, including submaxillary glands, spleen, lung, heart, bone marrow, lymph nodes, adrenal, pancreas and muscle but not the CNS. High levels of radioactivity were excreted in milk of lactating rats with decreases paralleling whole blood levels and a delayed transfer to fetuses was observed in pregnant rats with levels slightly decreasing according to maternal plasma levels. Although radioactivity was widely distributed in maternal tissue, none was detected in brain spinal cord and eyes (11).

The pharmacokinetics of pazufloxacin mesilate were examined in 7 elderly patients with renal dysfunction separated into groups according to creatinine clearance values (I: ≥ 60 ml/min; II: 20-60 ml/min; III: ≤ 20 ml/min). After a 30-min i.v. infusion of 300 mg, C_{max} values were reached in all groups. Serum clearance was slower in patients with serious renal dysfunction and the $t_{1/2}$ was longer (2.3-2.4, 4.6-4.7 and 12.1-18.3 h for groups I, II and II, respectively). While AUC values increased (12.3-17.8, 38.5-53.7 and 94.2-148.2 μg.h/ml, respectively) with the severity of dysfunction, urinary recovery rates decreased (80.7-92.8, 60.9-63.6 and 12.2-28.6%, respectively) (12).

Results from a phase I single (50, 100, 200, 400 and 500 mg 30-min drip infusion) and multiple dose (300 and 500 mg b.i.d. and 500 mg t.i.d. for 5 days as 30- or 60-min drip infusion) study on pazufloxacin mesilate in 52 healthy males were reported. Two cases of slightly increased NAG were observed in subjects receiving single or multiple doses of 500 mg. In the single dose study, dose-dependent serum levels were observed peaking at 30 min at the end of infusion and were 1.28, 2.68, 4.61, 9.93 and 11.0 μg/ml for the respective doses; a terminal half-life of 1.74-1.88 h was obtained. Although C_{max} and AUC were dose-proportional, urinary excretion rates (89.5-93.9% at 24 h) were unaltered by dose. When probenecid was added to the multiple dosing regimen, increased half-life and decreased urinary excretion were observed, indicating glomerular filtration and tubular absorption of the agent (13).

The clinical efficacy of pazufloxacin mesilate was shown in a phase II study involving 278 patients with moderate to severe respiratory infections given the agent by i.v. infusion (300 or 500 mg b.i.d. or t.i.d.) for 3-14 days. The overall clinical efficacy rates were 75.1, 76.1/75.7 and 63.3% for chronic respiratory tract infections, pneumonia/lung suppuration and for poor responders to other anitmicrobials, respectively; the overall causative-organism elimination and usefulness rates were 69.2 and 72.9%, respectively. Adverse events observed in 11 cases (4%) included CNS disorders (3), allergic disorders (2), gastrointestinal symptoms (5) and dry mouth (1); 36 (14.3%) cases of abnormal laboratory findings (transaminase elevation and eosinophilia) were reported. The usefulness and clinical efficacy rates according to daily dosing were 71.7 and 74.2% for 600 mg and 72.6 and 74.7% for 1000 mg, respectively (14).

A phase II study has demonstrated the efficacy and safety of pazufloxacin mesilate in 179 patients with urinary infections infused with the agent (300 mg b.i.d or 500 mg b.i.d or t.i.d) for 5 days. The overall clinical efficacy rates were 81.6 and 77.0% for 300 mg b.i.d. and 500 mg b.i.d., respectively. Clinical efficacy rates were 78.7, 75.9 and 80.4% in all 150 evaluable cases, 58 cases with complicated pyelonephritis and 92 cases with complicated cystitis, respectively. Only 2 mild to moderate adverse events (1.1%) were observed and 13 cases of mild to moderate abnormal changes in laboratory findings were reported (8.0%) (15).

The efficacy of pazufloxacin was demonstrated in patients with surgical infections administered the agent (300 or 400 mg b.i.d. or t.i.d. i.v.) for 3-14 days. Clinical efficacy rates were 78.3, 86.7, 73.7, 86.7 and 80% for intraabdominal, biliary tract and wound infections, postoperative pneumonia and against *P. aeruginosa* mixed infection, respectively. No adverse effects were observed although elevated transaminase levels, eosinophilia and/or increased leukocyte counts were observed in

12.5% of the patients. When pazufloxacin (300 or 500 mg i.v.) was administered to 10 patients undergoing cholecystectomy, serum levels of 0.45-11.8 μg/ml were observed and good penetration of the agent was obtained in the gallbladder and bile from the gallbladder and bile duct. Peak bile concentrations (5.17-65.4 μg/ml) were 4 times higher than serum concentrations following PTCD- or T-tube insertion. Peak ascitic fluid, pleural effusion and sputum concentrations were 1.87-2.40 μg/ml, 1.43 μg/ml and 0.87-6.24 μg/g, respectively (16).

Pazufloxacin mesilate at daily doses of 600 or 1000 mg (30 min i.v.) was effective against obstetric and gynecological infections. When a dose of 500 mg (i.v. drip infusion over 30 min) was given to 5 patients undergoing radical hysterectomy, serum (20.98 μg/ml) and retroperitoneal exudate (6.98 μg/ml) levels peaked at 15-30 min and 1.5-2.5 h, respectively. Twice-daily dosing with 600 and 1000 mg showed excellent (1) and good (4) clinical efficacy in 5 patients with pelvic peritonitis. Out of 8 strains of 7 species isolated from these patients, 7 were eradicated. No adverse effects were observed (17).

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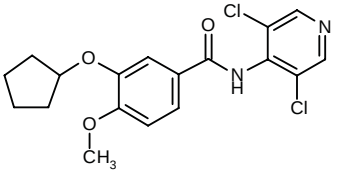

$C_{18}H_{18}Cl_2N_2O_3$ **Rhône-Poulenc Rorer**

It has been demonstrated that RP-73401 acts in two ways to downregulate tumor necrosis factor α (TNF-α).

One is by an IL-10-dependent mechanism that makes up the greater inhibition of TNF-α. The other has yet to be fully identified but is independent of biologically active IL-10 (1).

In an *in vitro* study using a novel human whole blood assay, the biochemical efficacy of RP-73401 was demonstrated with results showing its antiinflammatory properties. RP-73401 inhibited LPS-induced TNF-α production. The effect of RP-73401 was proportionally enhanced by PGE_2 with a peak at 24 h and attenuated by inhibition of PGE_2 production with indomethacin. RP-73401 also inhibited LPS/fMLP- and A23187-stimulated increases in LTB_4 levels with a potency similar to that observed in the TNF-α assay (2).

RPR-73401 was effective in a model of immunological inflammation. Using the mouse ear swelling test in which the ear epidermis of mice was sensitized to dinitrochlorbenzene for 4 days, mice were treated locally on the ear with RPR-73401 (20 µl of 3% solution in acetone/DMSO) or i.p. (1 or 10 mg/kg in 10% PEG200 and 0.45% methyl cellulose). Mice were then topically challenged with 1% allergen (20 µl) twice within 24 h. RPR-73401-treated animals showed 44 responses (54%) 48 h after challenges as compared to 59 responses (89%) in control rats. RPR-73401 decreased challenge-induced increases in ear thickness (3).

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Pimagedine *Treatment of Diabetic Nephropathy*
Aminoguanidine

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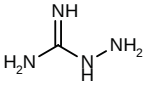

CH_6N_4 **Alteon; Yamanouchi**

Treatment with aminoguanidine (500 mg/kg/day for 12 weeks in the diet) was shown to attenuate serum (23.3 ± 4.1 *vs.* 11.7 ± 1.8 ng/ml in control db/db rats) and pancreatic (64.3 ± 17.9 *vs.* 30.0 ± 2.6 in control db/db rats) reductions in insulin after prolonged hyperglycemia in type II genetically diabetic mice. The extent of pancreatic islet degeneration was also reduced by treatment. Results suggest that advanced glycation end products may be involved in aggravation of type II diabetes and therefore aminoguanidine is a potential treatment (1).

Aminoguanidine's effect on mucosal damage in experimental colitis has been reviewed, whereby it was shown to exert an antiinflammatory effect on the chronic phase of TNB colitis and a proliferative effect on epithelial cells of the colon. Thus, aminoguanidine may be a new therapeutic approach to inflammatory bowel disease (2).

In rats, aminoguanidine dose-dependently reduced ischemic brain damage and improved neurologic recovery. Evaluating the timing of administration of aminoguanidine relative to the induction of cerebral ischemia revealed that delayed treatment may serve as a therapeutic option to selectively target the development of ischemic damage during the postischemic period (3).

Aminoguanidine administered in drinking water at a concentration of 1 g/l was evaluated in terms of its effects on glomerular basement thickness and anionic content, red blood cell anionic charge, urine glycosaminoglycan and albuminuria in a diabetic rat model. The results demonstrated that aminoguanidine reduces anionic charges in glomerular basement membranes and glomerular basement membrane thickening. The described activity can potentially be the mechanism by which aminoguanidine reduces albuminuria in diabetic rats (4).

Alteon announced that Genentech intends to terminate its support covering the development of pimagedine and second-generation AGE inhibitors (5).

Analyses of a pivotal phase III trial of pimagedine in type I diabetic patients with kidney disease show that, although pimagedine reduced the risk of doubling of serum creatinine, it did not reach statistical significance in this primary endpoint. Pimagedine therapy did result in a statistically significant and clinically meaningful reduction in urinary protein excretion. Pimagedine also reduced, to a statistically significant level, LDL cholesterol and triglycerides, as well as the progression of retinopathy. In addition, diastolic blood pressure, not prospectively defined as a clinical endpoint, was reduced in a statistically

significant manner. Patients in the ACTION I trial were exposed to optimal medical therapy, including the use of ACE inhibitors, the only therapy approved for diabetic nephropathy, as well as tight glycemic and blood pressure control. Pimagedine results were over and above this standard treatment. Alteon is broadening active discussions with major pharmaceutical and biotechnology companies worldwide regarding potential partnerships for pimagedine, as well as for its AGE crosslink breaker compounds (6).

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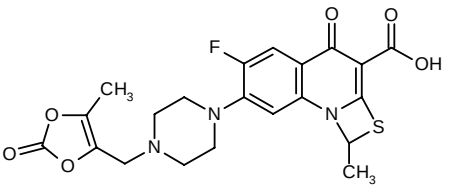

$C_{21}H_{20}FN_3O_6S$ **Nippon Shinyaku; Meiji Seika**

The potential influence of prulifloxacin on the pharmacokinetics of theophylline has been evaluated. Twelve volunteers were given one dose of theophylline (6 mg/kg p.o.) in a control session. On days 1 and 7 of an 8-day regimen, prulifloxacin (600 mg p.o once daily) was administered. Prulifloxacin decreased the elimination of theophylline, which was probably inhibited by cytochrome P450 1A2-mediated drug oxidation. This interaction is not foreseen to have important clinical implications, but mon-

itoring of potential changes in serum theophylline levels is recommended as for all patients taking theophylline in combination with other agents that may affect drug metabolism (1).

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Ropinirole Hydrochloride *Antiparkinsonian*
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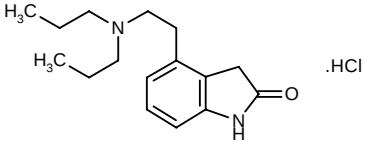

$C_{16}H_{24}N_2O.HCl$ **SmithKline Beecham; Recordati**

Forty-eight elderly patients (60-90 years) with Parkinson's disease received ropinirole to assess its efficacy and tolerability. A mean dose of 0.68 mg was administered in combination with levodopa. Findings indicate that the drug was well tolerated with a good efficacy profile (1).

Ropinirole 0.75-24 mg/day as an adjunct to levodopa was evaluated in 149 patients with Parkinson's disease with motor fluctuations. A $\geq$ 20% reduction in levodopa dose and in time spent off was achieved in more patients receiving ropinirole than in patients receiving placebo. Thus, ropinirole permits reductions in levodopa administration and produces enhanced clinical benefits in patients with Parkinson's disease (2).

The efficacy and adverse effects of treatment with ropinirole in patients with restless legs syndrome (RLS) have been assessed. Ropinirole alleviated the symptoms of both primary and secondary RLS without provoking serious side effects. This open-label clinical trial tested the agent in 16 patients with RLS; 10 of the patients reported marked improvement in symptoms, 3 reported moderate improvement and 3 discontinued the trial due to adverse effects. The compound was generally well tolerated, with adverse effects including generally mild sedation, nausea, fatigue, dyspepsia, shoulder pain, acne and hypomania. However, it is possible that the syncope or hallucinations associated with the use of dopamine agonists such as ropinirole to treat patients with Parkinson's disease may also occur in RLS therapy (3).

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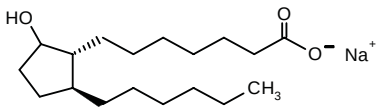

$C_{18}H_{33}NaO_3$ **Ist. Biochim. Ital. Giovanni Lorenzini**

A new synthesis of racemic rosaprostol has been reported: The condensation of methyl decanoate (I) with dimethyl methylphosphonate (II) by means of butyl lithium in THF gives dimethyl 2-oxoundecylphosphonate (III), which is treated with tosyl azide and NaH in benzene/THF, yielding the α-diazo compound (IV). The cyclization of (IV) by means of rhodium acetate in refluxing dichloromethane affords *trans*-2-(dimethoxyphosphoryl)-3-hexylcyclopentanone (V), which is condensed with methyl 6-formylhexanoate (VI) by means of $NaOH/Al_2O_3$ in benzene, giving methyl 6-(2-hexyl-5-oxocyclopentylidene)hexanoate (VII). The selective reduction of (VII) with sodium tellurohydride (NaHTe) in ethanol gives the saturated ester (VIII), which is hydrolyzed with NaOH in hot ethanol, yielding the corresponding free acid (IX). Finally, this compound is reduced to the target compound with $NaBH_4$ in methanol (1). Scheme 2.

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Samarium (^{153}Sm) Lexidronam
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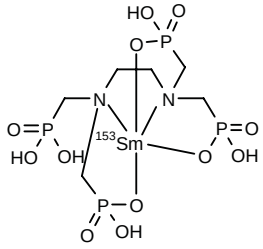
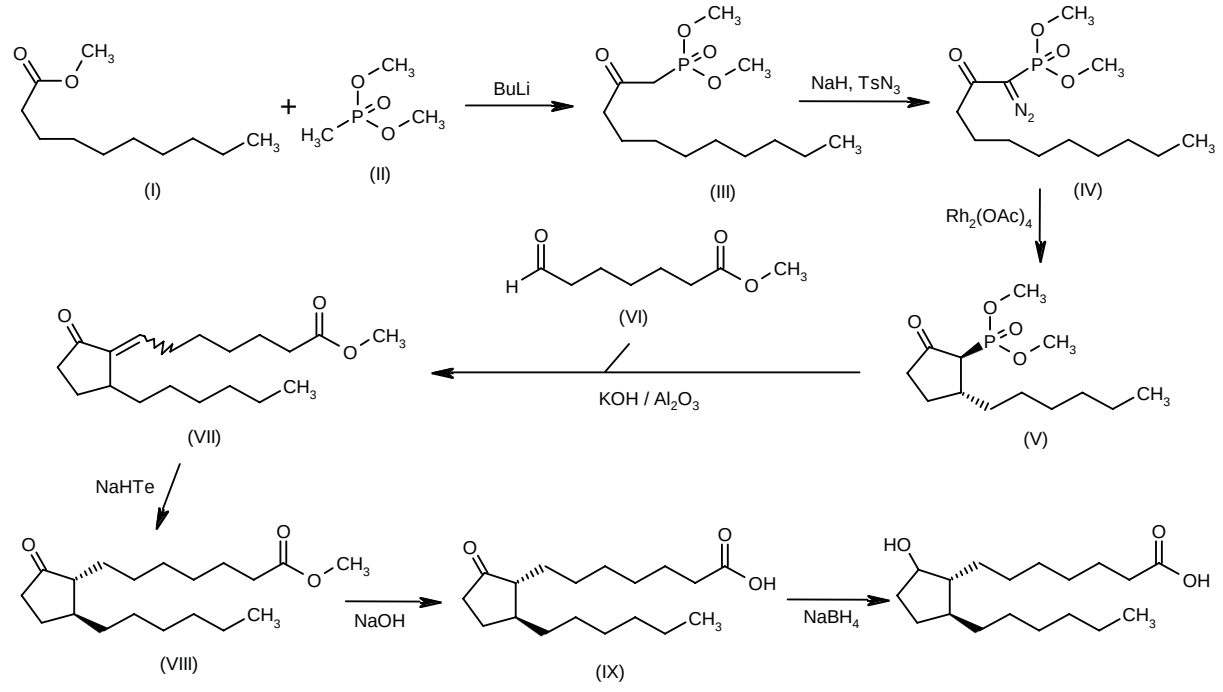


$C_6H_{17}N_2O_{12}P_4{}^{153}Sm$ **Cytogen; Berlex; DuPont Pharm.**

A single dose of samarium-153-EDTMP was shown to be palliative in 83.8% of 105 patients with painful bone metastases in a multicenter trial in China. Changes in daily analgesic consumption, pain score, sum effect product, Physician's Global Assessment, blood counts and organ function were assessed for 16 weeks. Positive responses were observed in 58/70 and 30/35 receiving

Scheme 2: Synthesis of Rosaprostol



37 and 185 mBq/kg, respectively, and 17 patients showed no response; a reduction in analgesic consumption was observed in 63/72 patients. An improved condition with treatment was indicated by an increased Karnofsky score (58.54 ± 25.90 to 71.67 ± 26.53). Although this change was not significant, the subset of patients with breast cancer did exhibit a significant improvement in scores. Side effects included transient myelosuppression with decreases in white blood cells (44/105) and platelet counts (34/105), in addition to 10 patients having abnormal liver function tests; no serious adverse effects were observed (1).

Cytogen Corp. has obtained expanded rights for the use of Quadramet® for the treatment of rheumatoid arthritis from The Dow Chemical Co. Cytogen already held rights for this use in North and Latin America, where it also has rights for the treatment of pain from cancer that has spread to the bone. Berlex Laboratories, Inc., recently given marketing rights to Quadramet®, also holds a license for rheumatoid arthritis applications in these territories (2, 3).

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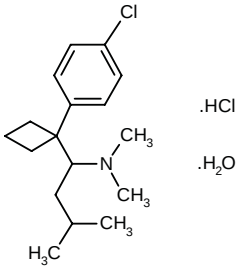
Meridia®

EN: 125655



$C_{17}H_{26}ClN.HCl.H_2O$ **Knoll; Eisai; Hokuriku**

The effects of sibutramine on the function of 5-HT were compared with the effects of fluoxetine, (+)-fenfluramine and (+)-amphetamine. Sibutramine markedly enhanced central 5-HT function through its secondary and primary amine metabolites. The effect was most likely mediated through the inhibition of 5-HT uptake. (+)-Fenfluramine and (+)-amphetamine, however, enhanced 5-HT function mostly by increasing 5-HT release, although the effects exerted by (+)-amphetamine were weaker (1).

The major amine metabolite of sibutramine hydrochloride monohydrate has been shown to improve insulin-mediated glucose uptake *in vitro* and *ex vivo*. The metabolite produced a concentration-dependent increase in 2-deoxyglucose uptake in cultured L6 rat muscle cells (10 nM-1 μM), as well as in soleus muscles from fasted mice pretreated orally with a dose of 10 mg/kg in the presence of insulin (2).

The effects of sibutramine on glucose homeostasis in insulin-resistant mice have been investigated. Young ob/ob mice were treated with sibutramine 5 mg/kg/day orally or placebo for 6 weeks. This dose of sibutramine did not significantly reduce daily food intake, but a significant decrease in weight gain and nonesterified fatty acid levels was observed. Chronic administration of sibutramine also reduced hyperinsulinemia and improved insulin resistance in these animals (3).

In all, 159 patients with a body mass index > 30 kg/m^2 were randomized to sibutramine (10 mg) or placebo for 1 year to determine the effects on long-term maintenance of weight loss after a very-low-calorie diet. The absolute weight change was –5.2 ± 7.5 kg in the active treatment group and +0.5 ± 5.7 kg in the placebo group. A 5% loss of original body weight was reported for 86 and 55% of patients on sibutramine and placebo, respectively. At 1 year, 75 and 42% of the patients in the active and placebo groups, respectively, had maintained 100% of the weight loss (4).

An analysis of 4 long-term, placebo-controlled, double-blind studies has shown that sibutramine (15 mg/day) treatment significantly reduced waist circumference and waist-to-hip ratios. Preliminary results showed that sibutramine-treated patients had decreases of 18, 17 and 22% in total abdominal fat, subcutaneous fat and visceral fat, respectively; a significant increase in subcutaneous-to-visceral fat ratio was also observed. Such changes in fat levels improve risk factors such as fasting glucose and insulin levels and blood pressure (5).

A randomized, placebo-controlled, double-blind, 12-month trial in 236 obese patients showed that sibutramine (15 mg once daily) enhanced weight loss and improved glycemic control and plasma lipid profiles. All patients began the trial with a 2-week placebo run-in where they were started on a 700 kcal deficit diet; 210 patients completed the 12 months. Treatment was well tolerated with no changes in blood pressure although pulse rate was significantly increased by 4 bpm in the sibutramine group. Weight loss was maximal at month 9 in both groups with significantly more sibutramine patients losing 5% or more (65%) and 10% or more (27%) of their body weight as compared to placebo (17 and 5%, respectively). Patients given sibutramine had improvements in glycemic control and lipid parameters which were related to the degree of weight loss (6).

In a double-blind, placebo-controlled study followed by a 12-month open-label extension, 210 obese patients with type II diabetes mellitus were given either sibutramine or placebo for a mean duration of 7.6 ± 3.9 months. No significant differences were found between groups in the incidence of left-sided cardiac valve disease as determined by rates of aortic and mitral valve thickening and regurgitation (7).

Concomitant administration of an ACE inhibitor for up to 24 weeks with sibutramine (20 mg/day) was shown not to affect long-term (8, 28 and 52 weeks) predosing plasma levels of sibutramine active metabolites in a study evaluating the drug's long-term pharmacokinetics in healthy subjects and obese hypertensive and normotensive patients (8).

The efficient weight loss and weight maintenance observed in clinical trials involving obese patients could be due to the dual effects of sibutramine on energy balance. Sibutramine was shown to enhance satiety and stimulate energy expenditure in humans. The agent increases satiety via combined noradrenergic and serotonergic effects and stimulates thermogenesis by activation of the sympathetic nervous system (9).

In a 24-week, randomized, double-blind, placebo-controlled, parallel-group study, 175 obese patients with type II diabetes were given sibutramine (5 mg titrated to 20 mg/day every 2 weeks for 6 weeks followed by 20 mg/day from week 6-24) or placebo. The mean actual and percent changes from baseline weight from the 121 patients completing 24 weeks were –4.3 kg and –4.5% and –0.3 kg and –0.4% for sibutramine-treated and placebo groups, respectively, with 33 and 8.3% of the sibutramine-treated patients reaching at least 5 and 10% weight loss, respectively. Sibutramine-treated patients had significantly larger mean reductions in waist circumference (–3.4 *vs.* –2.0 cm) and mean BMI changes were –1.5 and –0.1 kg/m^2 for sibutramine and placebo groups, respectively. Improvements in glycemic control and general health, social functioning and bodily pain scales assessed by quality of life evaluations were noted in sibutramine-treated patients. The agent was well tolerated with similar incidence and type of adverse effects in both groups (10).

Sibutramine hydrochloride monohydrate (Reductil®) has been approved in Germany, Switzerland and South Africa. Known as Meridia® in North America, the drug is now available in eight countries around the world. The German registration allows Knoll to start the mutual recognition process to obtain other approvals in the E.U. and in those countries which require a European Certificate of Free Sale from Germany. The product is currently under active review by Health Canada (11).

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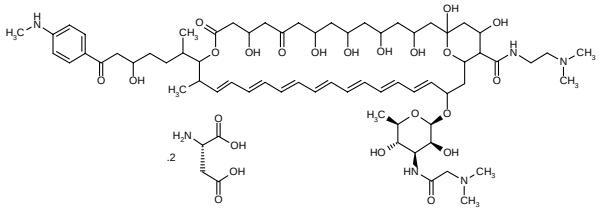
SPA-S-753
IB-643

Antifungal

EN: 211784



$C_{67}H_{103}N_5O_{19}.2C_4H_7NO_4$ **SPA; Kaken; IntraBiotics**

The antifungal activity of IB-643 has been demonstrated in a murine model of systemic candidosis. Beginning 4 days after infection with *Candida albicans*, 10 mice in each group were treated with vehicle, amphotericin B (AmB, 0.3 or 1 mg/kg) or IB-643 (0.3, 1, 3 or 10 mg/kg). All drugs were administered intravenously 3 times weekly for 2 weeks. A control group of uninfected mice was also administered the highest dose of IB-643. Ninety percent of vehicle-treated control mice died as a result of infection, as compared to just 1 and 2 mice in the AmB and IB-643 treatment groups, respectively, and survival time was prolonged significantly in all active treatment groups as compared to vehicle. One uninfected mouse treated with the highest dose of IB-643 died of possible drug-related toxicity after the third dose. AmB reduced *C. albicans* burdens in spleen and kidneys in a dose-dependent fashion; IB-643 also reduced fungal burdens in both organs, but this effect was not strictly dose-related. Overall cure of infection in both spleen and kidneys was achieved in 3/10 and 4/10 mice in the AmB 1 mg/kg and IB-643 10 mg/kg treatment groups, respectively, and this dose of IB-643 was considered to be the most effective treatment (1).

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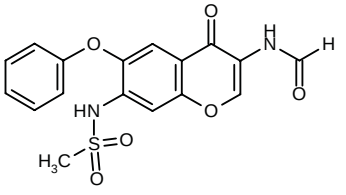
T-614

Antiarthritic

EN: 153332



$C_{17}H_{14}N_2O_6S$ **Toyama; Eisai**

The effects of T-164 on cytokine production and inflammatory cell infiltration have been studied *in vitro*. The compound induced concentration-dependent inhibition of lipopolysaccharide (LPS)-stimulated IL-8 and MCP-1 production in human monocyte-derived cells and inhibited IL-8 mRNA expression. At effective concentrations, it also inhibited the activity of the gene transcription factor NF-κB. Concentration-dependent inhibition of IL-1β-induced neutrophil infiltration into mouse auricle and inhibition of TNF-α-stimulated cytokine production in synovial cells from patients with chronic rheumatoid arthritis were also reported. Thus, it is suggested that the efficacy of T-614 against rheumatoid arthritis may involve inhibition of cell infiltration via inhibition of cytokine production (1).

Evaluation of the therapeutic effects of T-614 showed that the drug dose-dependently suppressed the development of active experimental autoimmune encephalomyelitis (EAE) in rats. T-614 also suppressed the clinical severity of the disease in rats receiving myelin basic protein-sensitized lymphoid cells. Thus, T-614 seems to suppress the development of EAE by inhibiting the proliferation of autoreactive T-cells and proinflammatory cytokine production by T-cells and macrophages and/or microglia (2).

Toyama and Eisai have signed an agreement for the codevelopment and comarketing of Toyama's T-614 in Japan, where it is now in phase III trials (3).

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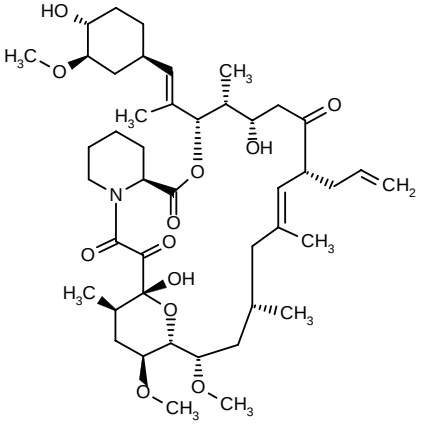
Original monograph - Drugs Fut 1993, 18: 714.

Tacrolimus
Prograf®
Protopic®

Treatment of Transplant Rejection
Antiarthritic
Treatment of Atopic Dermatitis

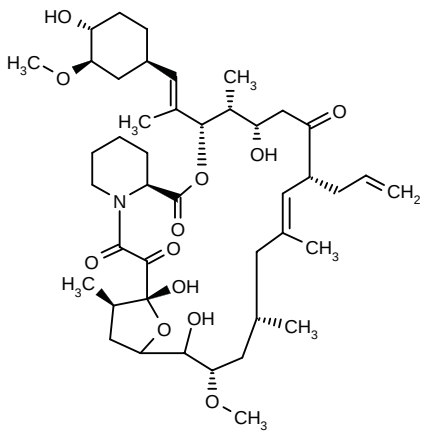
EN: 124071



$C_{44}H_{69}NO_{12}$ **Fujisawa; Johnson & Johnson**

The oxidative metabolism of FK-506 and its *in vitro* major metabolite has been investigated in rat liver microsomes. FK-506 was metabolized to polar metabolites via M-I [I] and the metabolism of M-I was catalyzed by cytochrome P450-3A as seen in the metabolism of FK-506 (1).

FK-506 was examined for potential neuroprotective effects in an experimental stroke model. In this study, rats were subjected to 2 h of middle cerebral artery (MCA) occlusion followed by 22 h of reperfusion and were randomized to receive intravenous FK-506 at doses of 0.3 or 1.0 mg/kg, vehicle or saline given 30 min before MCA occlusion. Treatment with FK-506 at the dose of 0.3 mg/kg significantly reduced infarct volume in both ipsilateral cortex and ipsilateral striatum. The higher dose significantly reduced infarct volume only in the cortex. Microdialysis experiments indicated that the dose- and region-dependent neuroprotective effect of FK-506 in this



[I]

model of transient focal cerebral ischemia was not due to inhibition of ischemia-induced nitric oxide production (2).

A phase III trial has compared the efficacy of tacrolimus and ciclosporin – both in combination with methotrexate – for the prevention of graft-*vs.*-host disease (GvHD) in patients with hematologic malignancies receiving HLA-identical sibling bone marrow transplants. Although a significantly greater proportion of patients with severe GvHD were randomized to the tacrolimus arm of the study, the incidence of grade II-IV acute disease was nonetheless lower (31.9% for tacrolimus *vs.* 44.4% for ciclosporin). The incidence of acute grade III-IV disease was similar in the two groups (13.3% for tacrolimus and 17.1% for ciclosporin), and the incidence of chronic disease was also similar in the two treatment arms of the study (49.4% for tacrolimus and 55.9% for ciclosporin). The incidence of clinical extensive chronic GvHD, however, was significantly greater in the ciclosporin treatment group. Relapse rates were similar with both immunosuppressive regimens, although 2-year disease-free survival was greater in the ciclosporin group and overall survival was greater with tacrolimus. This difference may lie in the fact that patients on tacrolimus had more severe disease, as there was no difference in survival among patients with less advanced disease. Among patients with advanced disease, the incidence of death resulting from treatment-related toxicity was greater on tacrolimus. The toxicity of tacrolimus must be addressed to maximize the therapeutic index of the compound in this indication (3).

Tacrolimus was evaluated in a long-term (1 year) study of patients with atopic dermatitis. An ointment formulation was applied once or twice daily at the maximum dose of 10 mg. Transient symptoms of skin irritation, expressed as itching, tingling and flush, were reported by 79.1% of the 569 patients available for analysis; these symptoms tended to decrease upon improvement of dermatitis eruptions. Other skin symptoms such as acne and skin infections were observed in 10.2% and 20.7% of the patients analyzed. Impaired renal function, an effect occurring with oral and injectable formulations of the drug, was not a problem with the topical formulation.

Tacrolimus-treated patients did not suffer from skin atrophy, a common side effect of long-term treatment with topical steroids. Disease symptoms began to improve as soon as 1 week after beginning treatment, with a rate of improvement at 1 week of 46.8%; the improvement rate at 10 weeks was nearly 90%. These interim results support the safety and efficacy of long-term treatment with tacrolimus ointment in atopic dermatitis (4).

Fujisawa received clearance from the Mexican Secretary of Health for the marketing and distribution of Prograf® in Mexico. The compound is intended to be used as prophylaxis for organ rejection in allogeneic kidney or liver transplants and will be distributed by Cilag de Mexico, a member of the Janssen-Cilag group and a subsidiary of Johnson and Johnson. Prograf® has also been launched in Taiwan as a primary immunosuppressant in liver or kidney allograft recipients and as a treatment of organ rejection resistant to treatment with ciclosporin (5).

The U.S. FDA's Oncologic Drugs Advisory Committee recommended that the FDA not approve Prograf® for the indication of GvHD following allogeneic bone marrow transplant procedures involving either matched sibling donor transplants or unrelated donor transplants. As part of the vote, the Committee recommended that the company conduct an additional study to clarify open questions it had concerning the data submitted. The vote was based primarily upon a review of the results of two pivotal phase III multicenter studies conducted by Fujisawa in the U.S. A company spokesperson said that Fujisawa will work closely with the FDA to resolve outstanding issues concerning the use of tacrolimus in the GvHD indication (6, 7).

The Japanese CPAC's Committee on Drugs has not approved Fujisawa's application for an ointment formulation of tacrolimus hydrate (Protopic®) for the indication of atopic dermatitis in adults. The application has been referred for further consideration of safety, especially in pregnant women and women of child-bearing age. A pediatric formulation of tacrolimus for atopic dermatitis is in phase III trials in Europe and in phase II in Japan, and in the U.S. supplemental NDAs will be filed for both the adult and the pediatric formulations of the drug in the treatment of atopic dermatitis (8).

Prograf® has been launched in China for the indications of primary immunosuppression in liver and kidney allograft transplant recipients and the treatment of organ rejection resistant to treatment with conventional immunosuppressants. The product will be available as 1 mg and 5 mg capsules, as well as a 5 mg/ml infusion. Nearly 150 patients in China have already received the drug on a compassionate-use basis as rescue therapy for rejection resistant to conventional immunosuppressive regimens. Fujisawa Hong Kong, an affiliate of Fujisawa, will be responsible for the drug's launch in China (9).

Patient enrollment has begun in Fujisawa's phase III study of Prograf® in patients with rheumatoid arthritis (RA) who have demonstrated resistance to or intolerance of disease-modifying antirheumatic drugs. About 450 patients 16 years of age or older with a diagnosis of RA of at least 6 months are expected to be recruited at approximately 50 centers in the U.S. (10).

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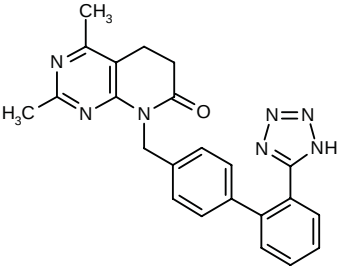
Original monograph - Drugs Fut 1989, 14: 746.

Tasosartan
Verdia®

Antihypertensive
Angiotensin AT_1 Antagonist

EN: 189224

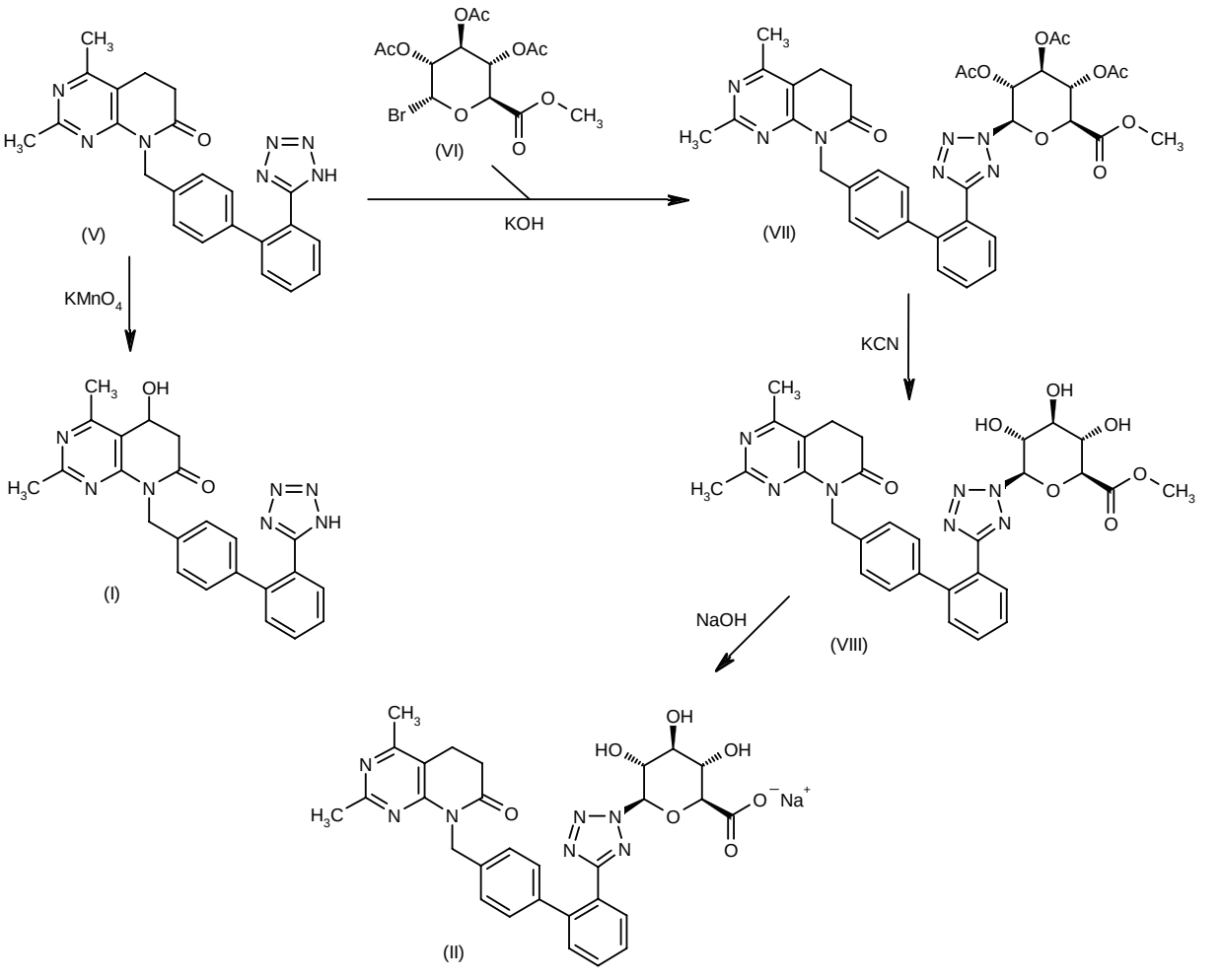


$C_{23}H_{21}N_7O$

American Home Products; Wyeth-Ayerst

The synthesis of the tasosartan metabolites, 5-hydroxy-2,4-dimethyl-8-[2'-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidin-7-one

Scheme 3: Synthesis of Tasosartan Metabolites (I) and (II)



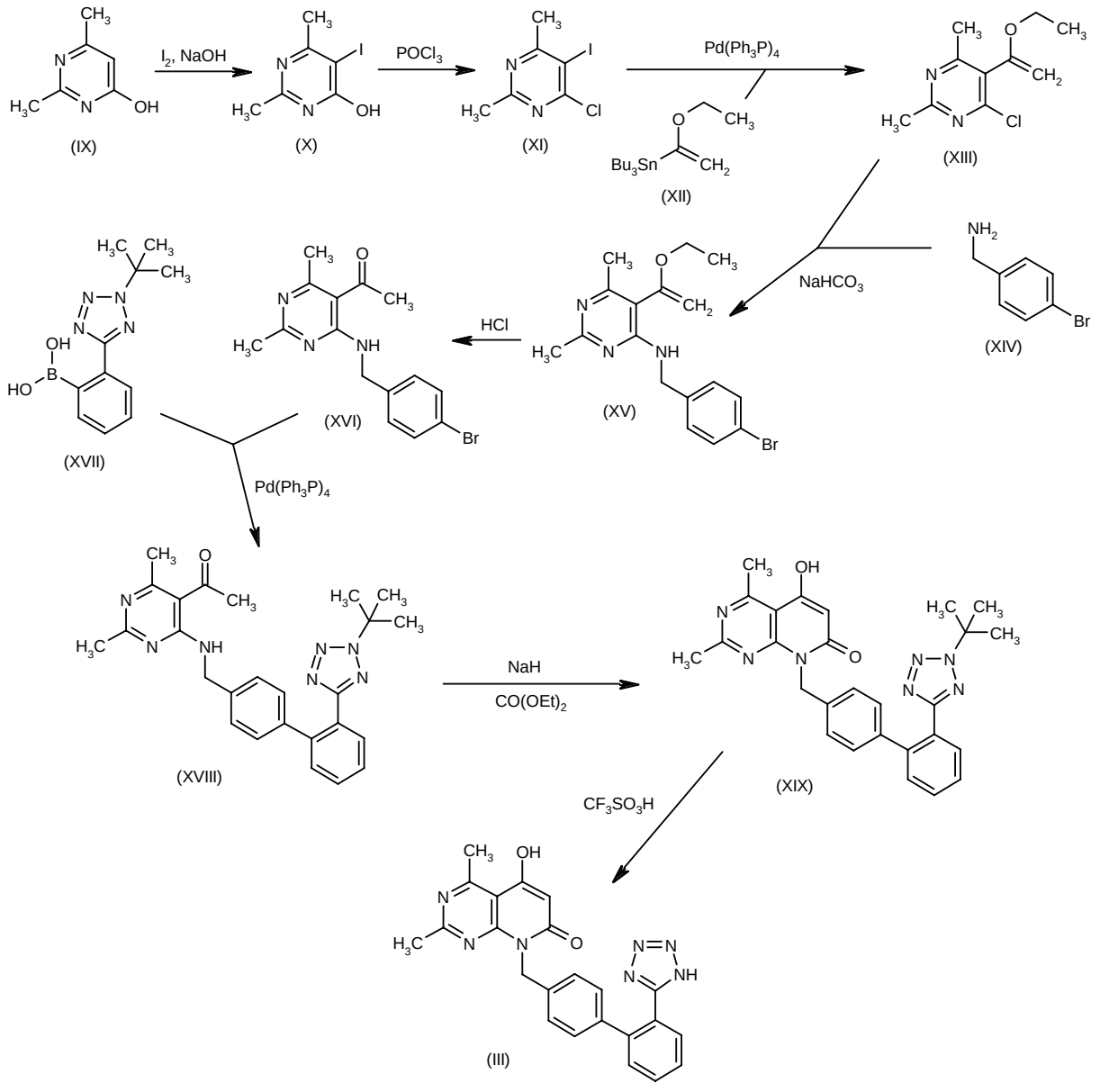
(I), 8-[2'-[2-(β-D-glucopyranos-1-yluronic acid methyl ester)tetrazol-5-yl]biphenyl-4-ylmethyl]-2,4-dimethyl-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidin-7-one (II), 5-hydroxy-2,4-dimethyl-8-[2'-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (III) and 2,4-dimethyl-8-[2'-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (IV) has been described (1):

1) The oxidation of tasosartan (V) with $KMnO_4$ and NaOH in water gives metabolite (I). Scheme 3.

2) The condensation of tasosartan (V) with 2,3,4-tri-*O*-acetyl-1α-bromo-1-deoxy-D-glucopyranosyluronic acid methyl ester (VI) by means of KOH in refluxing acetone gives the acetylated glucuronide methyl ester (VII), which is deacetylated with KCN in methanol yielding glucuronide methyl ester (VIII). Finally, this compound is hydrolized with NaOH in methanol to afford metabolite (II). Scheme 3.

3) The iodination of 2,6-dimethylpyrimidin-4-ol (IX) with I_2/NaOH in refluxing water gives 5-iodo-2,6-dimethylpyrimidin-4-ol (X), which is treated with $POCl_3$ in refluxig toluene yielding 4-chloro-5-iodo-2,6-dimethylpyrimidine (XI). The reaction of (XI) with (1-ethoxyvinyl)-tributyltin (XII) catalyzed by tetrakis(triphenylphosphine)-palladium in refluxing dioxane affords 4-chloro-5-(1-ethoxyvinyl)-2,6-dimethylpyrimidine (XIII), which is condensed with 4-bromobenzylamine (XIV) by means of $NaHCO_3$ in refluxing butanol giving 4-(4-bromobenzylamino)-5-(1-ethoxyvinyl)-2,6-dimethylpyrimidine (XV). The hydrolysis of (XV) with HCl in refluxing acetone yields the corresponding acetyl derivative (XVI), which is condensed with 2-(2-*tert*-butyl-2*H*-tetrazol-5-yl)phenylboronic acid (XVII) by means of tetrakis(triphenylphosphine)palladium to afford the biphenyl derivative (XVIII). The cyclization of (XVIII) with diethyl carbonate and NaH in hot THF gives 8-[2'-(2-*tert*-butyl-2*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-5-hydroxy-2,4-dimethylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (XIX), which is finally deprotected with trifluoromethanesulfonic acid in refluxing toluene to give metabolite (III). Scheme 4.

Scheme 4: Synthesis of Tasosartan Metabolite (III)

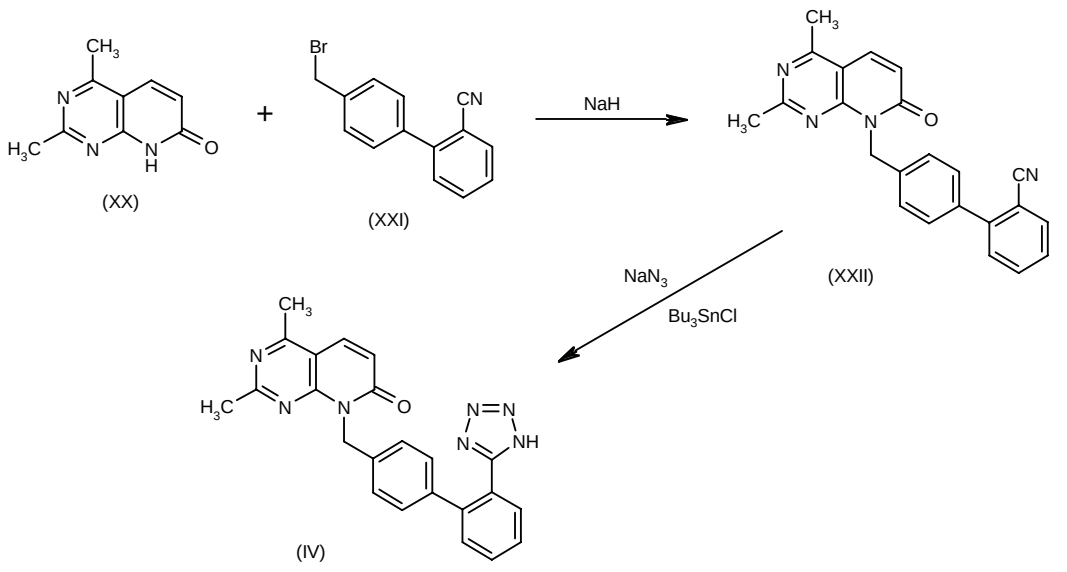


4) The condensation of 2,4-dimethylpyrido[2,3-*d*]-pyrimidin-7(8*H*)-one (XX) with 4'-(bromomethyl)biphenyl-2-carbonitrile (XXI) by means of NaH in DMF gives 8-(2'-cyanobiphenyl-4-ylmethyl)-2,4-dimethylpyrido-[2,3-*d*]pyrimidin-7(8*H*)-one (XIX), which is then cyclized with sodium azide in refluxing xylene to afford metabolite (IV). Scheme 5.

Results of an *in vitro* angiotensin II receptor binding assay suggested that the high protein binding (> 99.9%) of enoltasosartan may partly explain the discrepancy between its pharmacokinetics and pharmacodynamics (2).

The potential for combination therapy with tasosartan and enalapril was shown in a pharmacokinetic trial in which 11 hypertensive adults were administered placebo + enalapril (20 mg/day) on days 1-5, enalapril + tasosartan (50 mg/day) on days 6-19, tasosartan on days 20-24 and placebo on days 25-34. Combination therapy did not alter the pharmacokinetics of enalapril except a small decrease (9%) in AUC_{24h} and an increase (up to 11%) in

Scheme 5: Synthesis of Tasosartan Metabolite (IV)



oral clearance. Enalapril caused small decreases in t_{max} (25%), C_{max} (6%) and AUC_{24h} (7%) for enoltasosartan, the active metabolite of tasosartan. However, combination therapy resulted in significantly greater reductions in systolic and diastolic blood pressure and increases in blood renin activity as compared to either agent alone; the efficacy of combination therapy outweighed the small alterations in pharmacokinetics, suggesting a viable treatment option for some hypertensive patients (3).

The contribution of the metabolite enoltasosartan to the pharmacodynamic activity of tasosartan was evaluated in a double-blind, randomized, crossover study in 12 healthy subjects. Each subject received single doses of 50 mg i.v. tasosartan, 100 mg p.o. tasosartan and 2.5 mg i.v. enoltasosartan with 1-week intervals between doses. Both doses of tasosartan provided a peak reduction in the angiotensin II-induced increase in systolic blood pressure at 1-2 h, with significant blockade still observed at 24 h. In contrast, enoltasosartan showed a delayed effect, with peak inhibition at 3-4 h following injection, in spite of high plasma levels as early as 1 h following administration. These findings indicate that the metabolite is not involved in the early angiotensin II blockade following tasosartan administration. It is suggested that high protein binding, slow dissociation from the carrier or very slow binding to the AT_1 receptor may account for the discrepancy between the high affinity of the metabolite, its high plasma levels and the delayed *in vivo* hypotensive effect (4).

The efficacy and safety of tasosartan have been demonstrated in a double-blind, placebo-controlled, dose-titration study involving 262 patients with stage I or stage II essential hypertension. Following a washout period of 2-4 weeks, patients were randomized to 10 weeks of treatment with tasosartan, beginning at 50 mg and titrated at 3-week intervals to 100 and then 200 mg, or with placebo. A final 2-week washout period followed. The primary endpoint was the effect of tasosartan on the magnitude and duration of blood pressure response; evaluation of safety was a secondary objective. Sitting diastolic blood pressure decreased more in the tasosartan treatment group than in the placebo arm (–9.4 ± 0.7 mmHg *vs.* –2.0 ± 0.7 mmHg, respectively) at the end of the 10-week treatment period. Similar decreases in seated systolic blood pressure were observed in the tasosartan group (–12.2 ± 1.2 mmHg *vs.* +0.4 ± 1.2 mmHg for placebo). At the end of the treatment period, 30 patients continued on the 50-mg dose, while 49 and 53 patients, respectively, were taking the 100 and 200 mg doses. At week 3, when all patients were being treated with the lowest dose of tasosartan, 42% qualified as responders. By week 6, when patients were being treated with doses of 50 or 100 mg, 52% qualified as responders. By week 10, the combined response rate for all three doses was 55%. The placebo response rate was 19% at all three time points. Blood pressure was effectively controlled with once-daily dosing of tasosartan, as seen by assessing blood pressure during the final 4 h of the dosing interval. The peak-to-trough ratio for tasosartan was 66% to 72% (DBP to SBP). Efficacy began to plateau after 4 weeks of active treatment. The safety profile of the study drug was similar to that of placebo, with no significant side effects reported (5).

In a randomized, double-blind, placebo-controlled study, 24 patients with moderate hypertension were given tasosartan (100 mg/day) or placebo for 2 weeks, followed by a 2-week washout and then 2 more weeks of

treatment. Blood pressure was significantly decreased in tasosartan-treated patients (from 147/93 mmHg to 135/87 mmHg) as compared to controls, although total peripheral resistance, cardiac output and stroke volume were unaffected. Both blood pressure and total peripheral resistance were significantly decreased during submaximal exercise in tasosartan-treated patients; no changes in blood pressure or maximal aerobic capacity were observed at maximum exercise (6).

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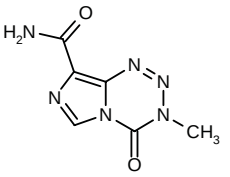
Temozolomide
Temodal®

Antineoplastic

EN: 108485



$C_6H_6N_6O_2$ **Schering-Plough; Natl. Cancer Inst. (US); Cancer Res. Campaign**

Results of *in vivo* studies using MSH2 and PMS2 mouse bone marrow cells demonstrated an increased hematopoietic progenitor resistance to temozolomide + O^6-benzylguanine (1).

In vitro evaluation of the antiproliferative activity of temozolomide against 222 tumors extracted from patients showed that exposure to the drug (0.1, 1.0 and 10 μM) produced responses in 9 out of 101 evaluable tumor specimens. The drug demonstrated activity against a variety of human tumors including breast, ovarian and non-small cell lung cancers, including tumors resistant to chemotherapy with cisplatin, doxorubicin and 5-fluorouracil (2).

A novel microcrystalline formulation of temozolomide with greater solubility was developed and tested in an athymic rat model with Mer^- and Mer^+ human glioma neoplastic meningitis. A significantly increased survival (29 days) of 142% was observed in treated (2.2 μM twice weekly) Mer^- animals although there were no long-term survivors, while animals treated with 6.8 μM had a mean survival of > 56 days (> 367% increase) with 4/8 long-term survivors. In Mer^+ animals, the agent increased mean survival to > 592% at 4 doses tested. Small patchy focal demyelination limited to 5% of spinal cord long tracks was attributed to treatment with the highest dose. A phase I study is being designed (3).

The activity of oral temozolomide (200 mg/m^2/day for 5 days) was assessed in 16 patients with advanced pancreatic adenocarcinoma previously untreated with chemotherapy. Cycles were repeated every 28 days. Fifteen patients were evaluable in whom no response was observed; 14 had progressive disease within 2 months of therapy. Three patients experienced grade 3 or higher neutropenia and thrombocytopenia. Temozolomide at this schedule was inactive against adenocarcinoma of the pancreas (4).

A retrospective, case control study used the results of 3 phase II trials and contemporaneous dacarbazine trials to compare the incidence of CNS relapse in patients with advanced melanoma treated with temozolomide or dacarbazine. Of a total of 40 patients, 7 dacarbazine and 6 temozolomide patients are still alive and 10 patients developed CNS disease. Significantly fewer instances of

relapse were observed in the temozolomide group (2 *vs.* 8 patients) (5).

A randomized phase II study in 225 patients with glioblastoma multiforme has shown that temozolomide (150-200 mg/m^2/day for 5 days every 28 days) at first relapse was well tolerated with better progression-free survival as compared to procarbazine (125-150 mg/m^2/day for 28 days every 56 days). Progression-free survival and overall survival rates at 6 months were significantly higher in the temozolomide-treated group (21 and 60%, respectively) as compared to the procarbazine group (8 and 44%, respectively); median progression-free survival was also significantly longer in the temozolomide group (2.89 *vs.* 1.88 months). At 3 and 6 months, more temozolomide-treated patients had improved or had stable health-related quality of life as compared to procarbazine-treated patients. Nausea, vomiting and constipation were common adverse effects with thrombocytopenia the major hemotoxicity observed (6).

A randomized phase III study in 305 patients with advanced metastatic melanoma has shown that treatment with oral temozolomide (200 mg/m^2/day for 5 days every 28 days) showed better survival and response rates and quality of life benefits as compared to oral dacarbazine (250 mg/m^2/day for 5 days every 21 days). Overall survival and response rates were 7.9 months and 13.5% and 5.7 months and 12.1% in the temozolomide and dacarbazine groups, respectively. Temozolomide treatment was well tolerated with the most common adverse effects being mild to moderate, including nausea (52%), vomiting (34%), pain (34%), constipation (30%), fatigue (20%) and headache (22%). Quality of life was better preserved in the temozolomide group with physical functioning decreasing by only 18% after 3 months as compared to 42% in the dacarbazine group (7).

A multicenter, phase II, single-arm study in 162 patients with recurrent anaplastic astrocytoma has shown that temozolomide (150 and 200 mg/m^2/day p.o. for 5 days every 4 weeks, for patients with and without prior chemotherapy, respectively) at first relapse was well tolerated and produced significant response rates and better progression-free survival. The overall response rate was 35%, of which 8% were complete responses and 27% were partial responses or stable disease. Progression-free survival at 6 and 12 months was 46 and 24%, respectively, and median survival was 13.6 months; median progression-free survival was 5.43 months. Many patients with stable disease also experienced improved quality of life. Grade 3 and 4 myelotoxicity was only seen in 4.9% of the cycles (8).

Preliminary results from a phase II study in 13 patients with newly diagnosed/recurrent anaplastic oligodendroglioma and progressive low-grade glioma have shown the potential efficacy of temozolomide (200 mg/m^2/day p.o. for 5 days every 28 days). No unexpected grade 3 or 4 toxicity was observed. One patient had an allergic reaction to the agent. Out of the 4 evaluable patients with anaplastic oligodendroglioma, 1 partial response and 3 stable diseases were observed. Of the 6 patients with progressive low-grade glioma, 5 stable and 1 progressive disease were reported (9).

The efficacy and tolerability of concomitant daily temozolomide (continuous 75 mg/m^2/day p.o. for 42-45 days) and radiation followed by adjuvant temozolomide (200 mg/m^2/day for 5 days) for 6 cycles was shown in a study involving 19 patients with newly diagnosed glioblastoma multiforme. Of the 13 patients who completed the combination therapy, half had completely resected tumors. No subjective toxicity was seen in most patients. Lymphocytopenia was observed during concomitant therapy and thrombocytopenia after the first cycle of adjuvant therapy. Following radiation, 3 patients progressed or had decreased performance status and were not continued on adjuvant therapy; no patients had died at the time of reporting (10).

A phase II study showed the efficacy and tolerability of temozolomide (300 mg/m^2/day p.o. for 5 days every 28 days for a mean of 4 courses) in 21 patients with recurrent malignant gliomas (anaplastic astrocytoma, glioblastoma multiforme and oligodendroglioma) previously treated with chemoradiotherapy or radiotherapy. Only 1 case of grade 3 thrombocytopenia was noted. Major responses were observed in 19%, including 1 complete response, and stable disease was seen in 48%. Eighteen patients were still alive at the time of reporting (11).

The efficacy and toxicity of temozolomide (150 or 200 mg/m^2/day p.o. every 4 weeks) were evaluated in a phase II trial in 8 patients with relapsing glioblastoma multiform. Out of 4 patients, 2 had stable and 2 others progressive disease with responses lasting 4 months; median survival was 3 months for the 8 patients. Three patients reported reduction in headaches and improved mobility and cognitive status. Hematologic toxicity (grade 2-3) was reported in 1/8 patients and most patients experienced grade 1 transient nausea/vomiting on the first day of treatment (12).

In a phase I pharmacokinetic study, 15 cancer patients were administered 45 courses of temozolomide and cisplatin (4 h later) at the following doses (temozolomide [mg/m^2/day]/cisplatin [mg/m^2]): 100/52, 150/75, 200/75 or 200/100 for 5 days every 4 weeks. Two patients receiving 200/100 developed dose-limiting grade 4 toxicities of thrombocytopenia, neutropenia with fever and vomiting. One patient receiving 200/75 experienced brief grade 4 neutropenia after courses 1 and 3 and grade 4 thrombocytopenia after course 3. Nonhematological toxicities included grade 3 nausea/vomiting in patients treated with 150/75, 200/75, 200/75 and 200/100. Two partial responses were seen in patients with head and neck cancer and leiomyosarcoma given 200/75, the recommended dose for phase II studies. At this dose, C_{max} and AUC values were similar on days 1 and 2 and cisplatin did not affect the pharmacokinetics of temozolomide (13).

A report from a phase I study of temozolomide (100, 150, 180, 215, 245 and 260 mg/m^2/day p.o.) from Children's Cancer Group showed that treatment was well tolerated and the maximum tolerated dose was 180 and 215 mg/m^2/day for 5 days (28-day cycles) for pediatric

recurrent cancer patients with or without prior craniospinal irradiation, respectively. Out of the 27 noncraniospinal irradiation patients, only grade 1 and 2 hematological toxicities were observed with doses of 100, 150 and 180 mg/m^2; only 1 grade 3 hematological toxicity was observed with a dose of 214 mg/m^2 and 3/8 (38%) receiving 245-260 mg/m^2 had dose-limiting toxicity which included neutropenia and thrombocytopenia. Hematological dose-limiting toxicity occurred in 1/6 and 2/4 receiving 100 and 215 mg/m^2, respectively, among the 22 evaluable patients on craniospinal irradiation. Nausea and vomiting was observed in more than half of the patients. After 2 courses of treatment, 10 patients had stable disease and 3 had partial responses, of which 1 developed complete response maintained throughout the 24 month follow-up (14).

A phase I study of oral temozolomide (500-1200 mg/m^2 once daily for 28 days) in children with advanced cancers showed that the maximum tolerated dose and dose recommended for phase II studies was 1000 mg/m^2/cycle. Out of 20 patients not receiving prior craniospinal irradiation or nitrosourea therapy, 16 were evaluable. Grade 4 thrombocytopenia was seen in 1/6 and 2/4 patients given 1000 and 2000 mg/m^2, respectively. The agent was rapidly absorbed and eliminated with dose-dependent linear increases in peak plasma concentrations and systemic exposure. Complete and partial responses were observed in 2/5 patients with high-grade astrocytomas and 1 patient had stable disease. Out of 10 patients with diffuse intrinsic brain stem glioma, 1 long-term partial response and 2 stable diseases were observed (15).

A randomized phase II study in 178 patients with glioblastoma multiforme has shown that treatment with temozolomide (150-200 mg/m^2/day for 5 days every 28 days) resulted in more frequent improvement in health-related quality of life as compared to treatment with procarbazine (125-150 mg/m^2/day for 28 days every 56 days). Significantly higher proportions of temozolomide-treated patients had improvements in social functioning, motor dysfunction and communication deficit with trends for improvement observed in role functioning, global quality of life, visual disorder and drowsiness as compared to procarbazine-treated patients. A higher proportion of temozolomide-treated patients reported improvement in at least 3/7 domains as compared to the procarbazine treatment group (32 *vs.* 19%) (16).

The FDA's Oncologic Drugs Advisory Committee voted not to recommend the approval of temozolomide capsules as first-line treatment for adult patients with recurrent glioblastoma multiforme. However, it has recommended approval of the drug for the treatment of adults with anaplastic astrocytoma who have relapsed followoing treatment with a nitrosourea and procarbazine. Schering Plough has stated its intention to continue working closely with the agency in its review of temozolomide (17-21).

The Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMEA) has issued a positive opinion recommending approval of Temodal[R] capsules for the treatment of patients with anaplastic astrocytoma who show recurrence or progression after standard therapy. Temodal® was launched for the first time in the U.K. for the treatment of patients with glioblastoma mutiforme showing recurrence or progression following standard therapy. An application for Temodal® as a first-line treatment for patients with advanced metastatic melanoma is currently pending regulatory review. Through a licensing agreement with Cancer Research Campaign Technology, Schering-Plough has exclusive worldwide rights to market Temodal® (22-26).

Temodal® has been launched in Germany for the treatment of glioblastoma multiforme, the indication for which it has already received E.U.-wide approval. Temozolomide is supplied as capsules containing 5, 20, 100 or 250 mg and is marketed by the Essex Pharma division of Schering Plough (27).

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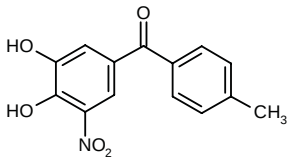

$C_{14}H_{11}NO_5$ **Roche**

A total of 203 patients with Parkinson's disease were randomized to tolcapone or pergolide in a parallel-group study. Relative to baseline, tolcapone and pergolide reduced "off" time by 18 and 16%, respectively. Investigator-rated improvement was observed in 86% of patients on tolcapone and 78% of patients on pergolide. Clinically important adverse events (tolcapone *vs.* pergolide) included hypotension (1 *vs.* 7%) and confusion (4 *vs.* 10%). Other adverse events included dystonia, urine discoloration with tolcapone and nausea, constipation, abdominal discomfort and dyspepsia with pergolide (1).

The FDA and Roche are advising doctors about reports of a new finding of fatal liver injury associated with the use of tolcapone (Tasmar®), which has led Roche to revise the labeling. These changes reflect additional information obtained through postmarketing experience in approximately 100,000 patients worldwide. Rare and unexpected adverse events, including 3 fatal cases of unpredictable, fulminant hepatitis, have been reported. In consultation with the FDA, Roche is issuing a revised label in the U.S. indicating that the drug should be reserved for use only in patients who do not respond to or who are not appropriate candidates for other available therapies. In the E.U., authorities have initiated the procedure of asking member states to suspend the use of Tasmar® as of November 17, 1998. Roche and regulatory authorities in other countries are working closely to ensure that the revised recommendations for the appropriate use of the drug are implemented (2).

The Therapeutic Products Directorate (TPD) of Health Canada began the suspension of sale of tolcapone (Tasmar®) in Canada. The decision was based on reports of rare hepatocellular injury, including 3 cases of fatal fulminant hepatic failure around the world. Roche, after a careful assessment of all available information and in consultation with outside medical experts, is of the opinion that for a restricted group of patients with Parkinson's disease, especially those with motor fluctuations that are not adequately controlled by alternative medications or in whom alternative drugs are contraindicated, the addition of tolcapone to standard therapy provides significant benefits that outweigh the risks. In agreement with the TPD, Roche will continue to supply tolcapone to these patients in Canada through a special access program while working to resolve pending questions (3).

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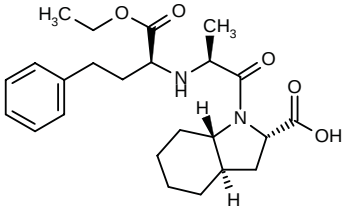

$C_{24}H_{34}N_2O_5$ **Kos Pharm.; Hoechst Marion Roussel; Knoll; Chugai**

Kos Pharmaceuticals has announced a definitive agreement with Knoll to copromote Mavik® (trandolapril) and Tarka® (trandolapril/extended-release verapamil hydrochloride), Knoll's antihypertensive drugs. These products are once-daily antihypertensive medications containing the ACE inhibitor trandolapril. Tarka® also contains the calcium channel blocker verapamil, providing additional benefit in patients not adequately controlled with monotherapy (1, 2).

1. *Kos to copromote two cardiovascular drugs with Knoll.* DailyDrugNews.com (Daily Essentials) June 16, 1999.

2. *Kos and Knoll reach definitive agreement for promotion of antihypertensive drugs.* DailyDrugNews.com (Daily Essentials) July 28, 1999.

Original monograph - Drugs Fut 1989, 14: 778.