Drugs of the Future 1998, 23(8): 897-942

CCC: 0377-8282/98

Information Update

Volume 1-22, Number 8

Estimated developmental phase for this month's updated products:

Preclinical

23(*S*),25(*R*)-1α,24-$(OH)_2D_3$-26,23-Lactone (vitamin D analog, treatment of bone diseases; Okayama Univ., Roche)
IZP-94005 (antiallergic/antiasthmatic; InflaZyme)
Ro-32-0432 (antiarthritic, protein kinase C inhibitor; Roche)

Phase I

SNAC (absorption promoter; Emisphere Technol.)

Phase II

524W91 (anti-HIV, anti-HBV; Emory Univ., Triangle Pharm., Glaxo Wellcome)
ABT-431 (antiparkinsonian, dopamine D_1 agonist; Abbott)
Adozelesin (antineoplastic; Pharmacia & Upjohn, Yakult Honsha)
APC-366 (antiallergic/antiasthmatic, tryptase inhibitor; Arris, Bayer, AxyS)
DA-125 (antineoplastic; Dong-A Pharm.)
Dauricine (cardiovascular agent; Wuhan Med. Coll. Pharm.)
E-1101 (cephalosporin; Eisai)
FK-960 (cognition enhancer; Fujisawa)
L-651582 (antineoplastic; Merck & Co., Natl. Cancer Inst.)
Lenapenem hydrochloride hydrate (carbapenem; Banyu, Merck & Co.)
ONO-4007 (antineoplastic, biological response modifier; Ono)
OPC-14117 (cerebroprotectant; Otsuka)
Piclamilast (antiinflammatory, phosphodiesterase IV inhibitor; Rhône-Poulenc Rorer)
S-9788 (multidrug resistance modifier; Servier)
T-614 (antiinflammatory, treatment of osteoporosis; Toyama)
TCV-309 (PAF antagonist, antipsoriatic, treatment of septic shock; Takeda)

Phase III

Adefovir dipivoxil (anti-HIV, anti-HBV; Bristol-Myers Squibb, Gilead)
Alosetron hydrochloride (5-HT_3 antagonist, treatment of irritable bowel syndrome; Glaxo Wellcome)
AR-121 (antifungal, antiviral; Aronex, M.D. Anderson Cancer Center, Ferrer)
Bropirimine (immunomodulator, antiviral, antineoplastic; Pharmacia & Upjohn, Yakult Honsha)
Etanidazole (radiosensitizer; Natl. Cancer Inst., SRI Int., Roberts, Taisho, Nycomed Pharma, DuPont Merck)
Losoxantrone hydrochloride (antineoplastic; Warner-Lambert, DuPont Merck)
Methylprednisolone suleptanate (corticosteroid; Pharmacia & Upjohn)
Pazufloxacin (fluoroquinolone antibacterial; Toyama, Yoshitomi, HanAll)
Pimagedine (symptomatic antidiabetic; Alteon, Yamanouchi, Gamida, Genentech)
Prulifloxacin (fluoroquinolone antibacterial; Nippon Shinyaku, Meiji Seika)
Ramatroban (antiallergic/antiasthmatic, thromboxane A_2 antagonist; Bayer, Esteve)
Tasosartan (antihypertensive, angiotensin AT_1 antagonist; American Home Products, Wyeth-Ayerst)
Temozolomide (antineoplastic; CRC Technol., Schering-Plough, Natl. Cancer Inst.)
Zatebradine hydrochloride (antianginal; Boehringer Ingelheim)

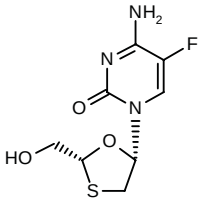
Launched/Year

Cefcapene pivoxil hydrochloride (cephalosporin; Shionogi)/1997
Gemcitabine (antineoplastic; Lilly)/1995
Latanoprost (antiglaucoma; Pharmacia & Upjohn, Chinoin)/1996
Lepirudin (anticoagulant; Hoechst Marion Roussel, Behringwerke)/1997
Lornoxicam (antiinflammatory; Nycomed Pharma, Taisho, Merckle, Ivax, Zeneca)/1997
Mizolastine (antihistaminic; Synthélabo, Mitsubishi Chem., Ferrer, Schwarz)/1998
Nefazodone hydrochloride (antidepressant; Bristol-Myers Squibb, Mead Johnson, Lipha, Cephalon)/1994
Ropinirole (antiparkinsonian, dopamine D_2 agonist; SmithKline Beecham, Recordati)/1996
Ropivacaine hydrochloride (local anesthetic; Astra)/1996
Samarium (^{153}Sm) lexidronam (analgesic; Hoechst Marion Roussel, Cytogen, CIS Bio Int., Syncor, DuPont Merck)/1997
Seratrodast (antiallergic/antiasthmatic, thromboxane A_2 antagonist; Takeda, Grelan, TAP, Astra)/1995
Sibutramine hydrochloride monohydrate (antiobesity, norepinephrine reuptake inhibitor, 5-HT reuptake inhibitor; Knoll, Esai, Hokuriku Seiyaku)/1998
Tacrolimus (immunosuppressant; Fujisawa, Johnson & Johnson)/1993
Tolcapone (antiparkinsonian, COMT inhibitor; Roche, Nippon Roche)/1997

524W91
(–)-FTC

Anti-HIV
Anti-HBV

EN: 190016



$C_8H_{10}FN_3O_3S$ **Emory Univ. (US); Triangle Pharm.; Glaxo Wellcome**

A phase I/II clinical trial has demonstrated the potent antiretroviral effects of (–)-FTC (25 mg b.i.d. or 200 mg/day for 14 days) in 10 HIV-1 infected patients. Preliminary results showed that both doses of the drug were well tolerated. On day 14, plasma HIV RNA was markedly decreased to an average $\log_{10}$ change from basal of 1.4 and 2.1 for the 25-mg and 200-mg doses, respectively (1).

Treatment of woodchucks infected with woodchuck hepatitis virus (WHV) with (–)-FTC (3-30 mg/kg/day p.o. for 4 weeks) resulted in a dose-dependent reduction in virus production in serum as compared to untreated animals. Virus depletion was rapid, occurring at day 7 with 30 mg/kg, with a $t_{1/2}$ of approximately 0.73 days. Virus production increased to initial levels following cessation of drug treatment (2).

A phase I/II clinical trial of FTC was conducted in 10 HIV-infected volunteers to assess pharmacokinetics, safety and antiviral efficacy over a 14-day period. The preliminary results indicated that FTC significantly reduced plasma HIV-1 RNA viral load at the first two dose levels of 25 mg twice daily and 200 mg once daily. At the dose of 25 mg twice daily, HIV-1 RNA in plasma in all 5 patients was reduced from baseline (4.2 $\log_{10}$) by an average of 1.4 $\log_{10}$ or 96% at day 14. At the higher dose of 200 mg once daily, HIV-1 RNA in plasma from all 5 patients was reduced from baseline (4.7 $\log_{10}$) by an average of 2.03 $\log_{10}$ or 99% at day 14. The degree of viral suppression was very consistent among patients within a given dose level. FTC was well tolerated in these 10 patients (3).

1. Pottage, J., Thompson, M., Kahn, J., Delehanty, J., McCreedy, B., Rousseau, F. *Potent antiretroviral efficacy of low dose FTC, initial result from a phase I/II clinical trial*. 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst LB9.

2. Schinazi, R.F., Liotta, D.C., Hurwitz, S.J., Painter, G., Furman, P., Barry, D., Korba, B.E., Tennant, B.C. *Effect of oral (-)-beta-2', 3'-dideoxy-5-fluoro-3'-thiacytidine [(–)-FTC] in carriers of infected woodchuck hepatitis virus (WHV)*. Antivir Res 1998, 37(3): Abst 19.

3. *Triangle reports results from phase I/II FTC trial*. Daily Essentials Jan 29, 1998.

Original monograph - Drugs Fut 1995, 20: 761.

Additional References

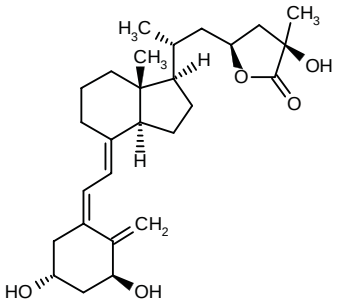
Ussery, M.A. et al. *Anti-HIV activity of the HuPBMC SCID mouse model of six novel nucleoside analogs: (–)-FTC, (±)-FTC, D-DAPD, D-D4FC, CS-92 and CS-87*. Antivir Res 1998, 37(3): Abst 33.

New AIDS drugs in development at Triangle. Daily Essentials July 3, 1998

23(*S*),25(*R*)-1α,25-$(OH)_2D_3$-26,23-Lactone

Vitamin D Analog
Treatment of Bone Diseases

EN: 178334



$C_{27}H_{40}O_5$ **Okayama Univ. (JP); Roche**

In *in vitro* studies using chondrocytes from rabbit costal growth cartilage, 23(*S*)25(*R*)-1α,25-dihydroxyvitamin D_3-26,23-lactone stimulated proteoglycan and collagen synthesis and prevented abnormal morphological changes, indicating that it may have a role in regulating the physiological processes involved in the maintenance of normal extracellular matrix structure in growth cartilage (1).

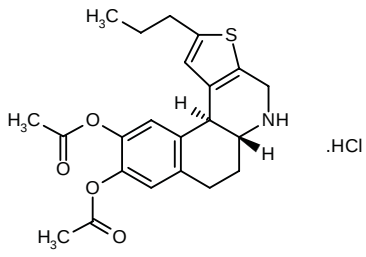
1. Ishizuka, S., Mimura, H., Hayashi, T., Oshida, J., Ishizeki, K., Takigawa, M., Norman, A.W. *23(S)25(R)-1α,25-Dihydroxyvitamin D_3-26,23-lactone stimulates matrix synthesis in chondrocytes from rabbit costal growth cartilage*. 10th Workshop Vitamin D (May 24-29, Strasbourg) 1997, 158.

Original monograph - Drugs Fut 1992, 17: 655.

ABT-431

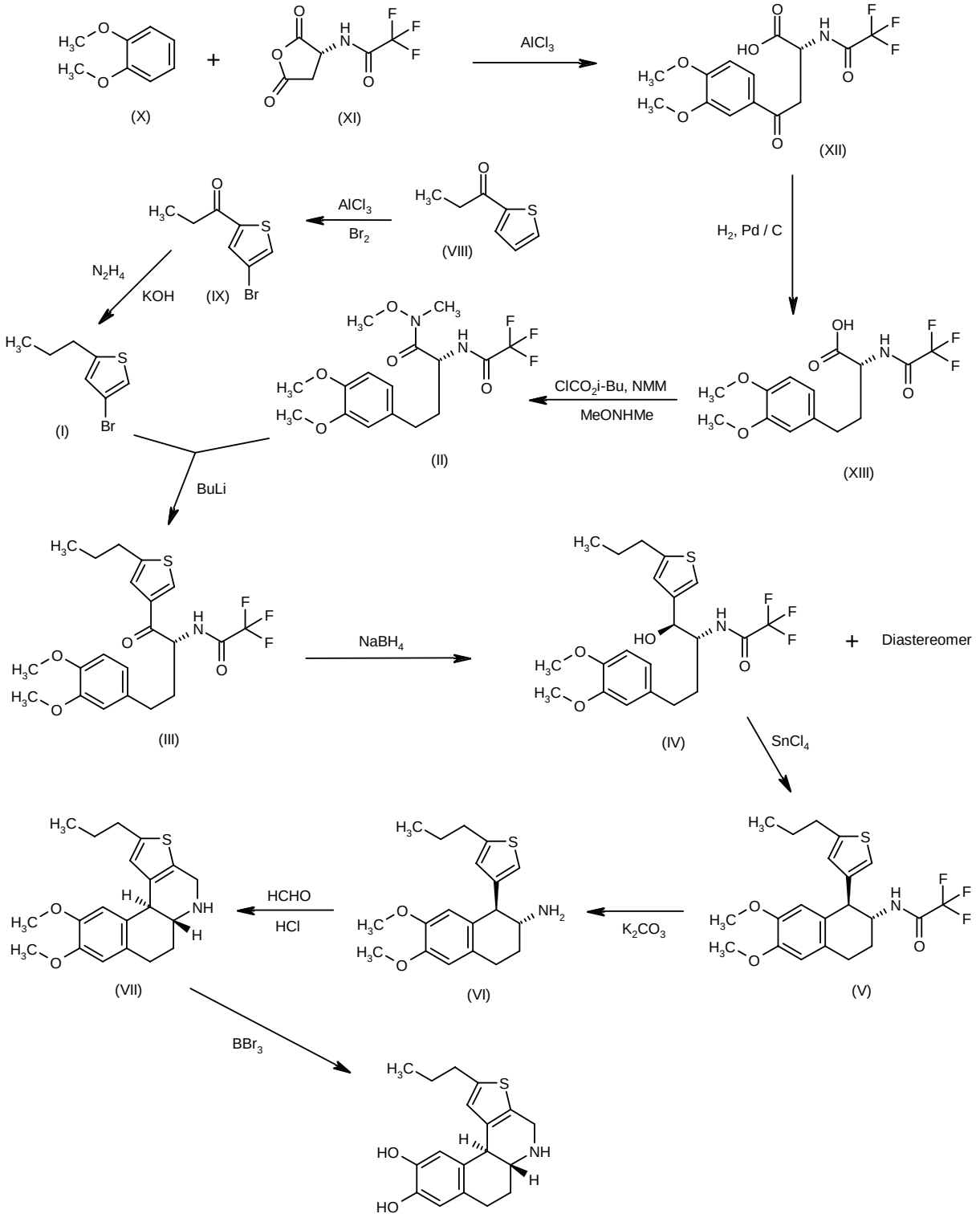
Antiparkinsonian
Dopamine D_1 Agonist

EN: 222577



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

Scheme 1: Synthesis of A-86929



A new enantioselective synthesis of A-86929, the active form of the diacetyl prodrug ABT-431 has been published: The condensation of 4-bromo-2-propylthiophene (I) with 4-(3,4-dimethoxyphenyl)-*N*-methoxy-*N*-

methyl-2(*R*)-(trifluoroacetamido)butyramide (II) by means of butyl lithium in ethyl ether gives 4-(3,4-dimethoxyphenyl)-1-(5-propyl-3-thienyl)-2(*R*)-(trifluoroacetamido)-1-butanone (III), which is reduced with $NaBH_4$ in ethanol yielding 4-(3,4-dimethoxyphenyl)-1-(5-propyl-3-thienyl)-2(*R*)-(trifluoroacetamido-1(*S*)-butanol (IV) in a 4:1 ratio with its diastereomeric alcohol. The cyclization of (IV) with $SnCl_4$ in dichloromethane affords the substituted tetraline (V), which is treated with K_2CO_3 in methanol/water to give (1*S*,2*R*)-6,7-dimethoxy-1-(5-propyl-3-thienyl)-1,2,3,4-tetrahydro-2-naphthylamine (VI). The cyclization of (VI) with formaldehyde and HCl in refluxing ethanol yields the tetracyclic intermediate (VII), which is finally demethylated with BBr_3 in dichloromethane. The two starting compounds (I) and (II) have been obtained as follows:

1) The bromination of 1-(2-thienyl)-1-propanone (VIII) with $Br_2/AlCl_3$ in chloroform gives 1-(4-bromo-2-thienyl)-1-propanone (IX), which is then reduced to (I) with hydrazine and KOH in ethyleneglycol at 160 °C.

2) The Friedel Craft's condensation of 1,2-dimethoxybenzene (X) with 2(*R*)-(trifluoroacetamido)succinic anhydride (XI) by means of $AlCl_3$ gives 4-(3,4-dimethoxyphenyl)-4-oxo-2(*R*)-(trifluoroacetamido)butyric acid (XII), which is reduced with H_2 over Pd/C in HCl/isopropanol yielding 4-(3,4-dimethoxyphenyl)-2(*R*)-(trifluoroacetamido)butyric acid (XIII). Finally, this compound is condensed with *N,O*-dimethylhydroxylamine by means of isobutyl chloroformate and *N*-methylmorpholine (NMM) in THF affording amide (II) (1). Scheme 1.

In animal models of Parkinson's disease, administration of A-86929 to rats (0.11 or 0.22 μmol/kg s.c. t.i.d. for 10 days) and monkeys (0.03, 0.10 or 0.3 μmol/kg i.m.) caused significant dose-dependent levels of contralateral rotation. The magnitude of behavioral response did not change significantly in monkeys during the study, although it did increase in rats following the 0.22 μmol/kg dose. The results indicate that A-86929 may be useful for the treatment of Parkinson's disease due to its full intrinsic activity relative to dopamine (2).

Results of a study in parkinsonian levodopa-primed monkeys showed that acute administration of A-86929 (0.03-1.0 mg/kg) was as effective as levodopa and LY-171555 in relieving MPTP-induced parkinsonism but was less likely to reproduce the dyskinesias observed after levodopa administration (3).

The therapeutic efficacy and potential to induce dyskinesia of ABT-431 were compared to those of levodopa in 2 clinical trials in 8 and 12 patients, respectively, with Parkinson's disease (PD). Subjects in the trials had been diagnosed with idiopathic PD and had been treated for at least 3 years with levodopa; all patients had fluctuating response to levodopa and suffered drug-induced "on" dyskinesias. Following a drug-free overnight period, increasing doses of ABT-431 (5, 10, 20 or 40 mg) were administered by i.v. over 1 h, and effects were compared to the subjects' usual morning oral levodopa/carbidopa or levodopa/benserazide dose. The results obtained in the 2 studies showed that motor improvement obtained with ABT-431 was equivalent to with levodopa, but was associated with significantly less dyskinesia (4).

1. Ehrlich, P.P., Ralston, J.W., Michaelides, M.R. *An efficient enantioselective synthesis of the D_1 agonist (5aR,11bS)-4,5,5a,6,7,11b-hexahydro-2-propyl-3-thia-5-azacyclopenta[c]phenanthrene-9,10-diol (A-86929)*. J Org Chem 1997, 62(9): 2782.

2. Asin, K.E., Domino, E.F., Nikkel, A., Shiosaki, K. *The selective dopamine D_1 receptor agonist A-86929 maintains efficacy with repeated treatment in rodent and primate models of Parkinson's disease*. J Pharmacol Exp Ther 1997, 281(1): 454.

3. Grondin, R., Bedard, P.J., Britton, D.R., Shiosaki, K. *Potential therapeutic use of the selective dopamine D_1 receptor agonist, A-86929: An acute study in parkinsonian levodopa-primed monkeys*. Neurology 1997, 49(2): 421.

4. Rascol, O., Blin, O., Wright, S., et al. *A double blind comparison of ABT-431, a selective, full dopamine D_1 receptor agonist, with levodopa in the treatment of advanced Parkinson's disease*. 50th Annu Meet Amer Assoc Neurol (April 25-May 2, Minneapolis) 1998, Abst S07.001.

Original monograph - Drugs Fut 1997, 22: 821.

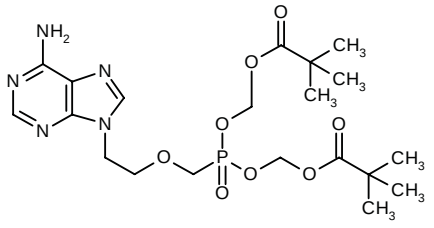
Additional References

Wright, S. *A new selective D_1 agonist, ABT-431, as a candidate for the treatment of Parkinson's disease*. IBC Int Conf Dopaminergic Disord. Nov Approaches Drug Discov Dev (April 28-29, Boston) 1997, 1997.

Wright, S. et al. *Comparison of efficacy and dyskinesia-inducing potential of levodopa and ABT-431, a selective, full dopamine D_1 receptor agonist*. 50th Annu Meet Amer Assoc Neurol (April 25-May 2, Minneapolis) 1998, Abst P03.012.

Adefovir Dipivoxil *Anti-HIV*
Piv2PMEA *Anti-HBV*
Bis(pom)PMEA
GS-840
Preveon™

EN: 196738



$C_{20}H_{32}N_5O_8P$ **Bristol-Myers Squibb; Gilead**

Results of a randomized, double-blind, placebo-controlled, dose-escalation trial of adefovir dipivoxil in 36 patients with HIV infections showed that serum p24 antigen decreased by 31, 25 and 30% in the three drug-treated groups, compared to a 17% increase in the placebo-treated group. Serum HIV RNA decreased by a median of 0.4-0.6 $\log_{10}$ copies/ml in the treatment groups, while no change was observed in the placebo group (1).

The safety and efficacy of oral adefovir dipivoxil (125 and 250 mg/day for 12 weeks) were evaluated in a randomized, double-blind, placebo-controlled study in 72

patients with moderately advanced HIV disease. Changes in CD4 counts and HIV-I RNA levels were significantly greater in drug-treated patients than in those on placebo after 6 weeks of treatment and were maintained through the duration of the study (2).

The bioavailability of adefovir dipivoxil (250 mg suspension or 125 mg b.i.d tablet) was evaluated in fasted, fed and pentagastrin pretreated beagle dogs. The prodrug was completely converted to adefovir following oral administration, while oral bioavailability after administration of the suspension formulation was 35.0%. In the fed, fasted and pentagastrin pretreated dogs, oral bioavailability was 34.7, 37.2 and 44.9%, respectively. Formulation, food and gastrointestinal pH had no effect on oral bioavailability (3).

Results of a phase II study in 29 HIV-infected patients treated with adefovir dipivoxil in combination with other antiretrovirals showed that 8 of the 29 patients developed mutations in reverse transcriptase, although they showed sustained viral load suppression during the 6-12 months of therapy (4).

A phase III study evaluated adefovir dipivoxil coadministered with other antiretrovirals during 48 weeks in 442 patients, the majority of whom had received more than 3 nucleosides previously. Genotypic analyses of HIV isolates from 64 patients demonstrated that baseline samples commonly carried numerous AZT resistance mutations, as well as the 3TC-associated M184V mutation. Nine patients experienced changes in reverse transcriptase after 24 weeks, although it was unclear if they resulted from adefovir dipivoxil administration. After 32 weeks, 6 more patients had changes in reverse transcriptase including AZT resistance mutations, T69S mutations and a double serine insertion between amino acids 69 and 70 in the reverse transcriptase (5).

Gilead has recently broadened the entry criteria of its expanded access program for adefovir dipivoxil in the treatment of HIV infection to include patients in need of new therapeutic options regardless of CD4 cell count or HIV RNA level. The program originally required that patients have HIV RNA $\geq$ 30,000 copies/ml and a CD4 cell count $\leq$ 50 cells/mm^3 to be eligible. The program makes the drug available free of charge to HIV-infected adults in the U.S. who have failed treatment with at least two nucleoside analogue reverse transcriptase inhibitors and one protease inhibitor. In addition to expanding the entry criteria, the protocol has been modified to randomize patients to receive either 60 or 120 mg/day of the drug in combination with other antiretroviral agents. Alternatively, physicians may elect to provide patients with open-label adefovir at the 120 mg/day dose. Two studies are ongoing in patients with advanced HIV disease who have received prior treatment, one in the U.S. and another in Europe and Australia (6).

Data from an international, double-blind, placebo-controlled phase II study demonstrated that treatment with adefovir dipivoxil (30 mg/day) for a period of 12 weeks reduced blood levels of hepatitis B virus to undetectable levels in a majority of chronically infected patients when measured with the branched-chain DNA assay. When assayed with the more sensitive PCR assay, the levels of the virus were reduced by 99.99%. The drug was well tolerated, and the frequency of adverse events reported in the group treated with adefovir dipivoxil was similar to the group receiving placebo (7).

Preliminary results from a multicenter, phase II/III trial in 442 HIV-infected patients on a prior stable regimen for at least 8 weeks demonstrated that treatment with adefovir dipivoxil (120 mg/day p.o.), in addition to other approved HIV therapies, resulted in a significantly reduced mean viral load and reduced mean absolute difference in HIV RNA, as well as a higher CD4 cell count as compared to placebo treatment. Another trial evaluated the effects of adefovir dipivoxil in combination with a protease inhibitor (indinavir) and one or two reverse transcriptase inhibitors (zidovudine, lamivudine and stavudine) in 180 HIV-infected patients who had not previously received antiretroviral therapy. Control subjects received a standard triple combination consisting of zidovudine, lamivudine and indinavir. Preliminary safety and efficacy data obtained from the first 85 patients after 4, 8, 12 and 20 weeks demonstrated a decrease in viral load from 2.1 $\log_{10}$ to 2.5 $\log_{10}$ in patients on triple regimens containing adefovir dipivoxil. After 20 weeks of treatment, 80% of patients on any combination regimen had undectable levels of HIV RNA and increased CD4 cell count as compared to patients in the control group. Laboratory abnormalities included increased liver transaminase levels and increased creatinine kinase, while the most common side effects reported were gastrointestinal effects such as nausea and loss of appetite (8).

1. Barditch Crovo, P., Toole, J., Hendrix, C.W., Cundy, K.C., Ebeling, D., Jaffe, H.S., Lietman, P.S. *Anti-human immunodeficiency virus (HIV) activity, safety, and pharmacokinetics of adefovir dipivoxil (9-[2-(bis-pivaloyloxymethyl)-phophonylmethoxyethyl]adenine) in HIV-infected patients*. J Infect Dis 1997, 176(2): 406.

2. Deeks, S.G., Collier, A., Lalezari, J., et al. *The safety and efficacy of adefovir dipivoxil, a novel anti-human immunodeficiency virus (HIV) therapy, in HIV-infected adults: A randomized, double-blind, placebo-controlled trial*. J Infect Dis 1997, 176(6): 1517.

3. Cundy, K.C., Sue, I.-L., Visor, G.C., Marshburn, J., Nakamura, C., Lee, W.A., Shaw, J.-P. *Oral formulation of adefovir dipivoxil: In vitro dissolution and in vivo bioavailability in dogs*. J Pharm Sci 1997, 86(12): 1334.

4. Miller, M.D., Anton, K.E., Mulato, A.S., Lamy, P.D., Cherrington, J.M. *Antiviral susceptibilities of HIV-1 reverse transcriptase recombinant viruses derived from AIDS patients after extended adefovir dipivoxil therapy*. Antivir Res 1998, 37(3): Abst 74.

5. Cherrington, J.M., Lamy, P.D., Margot, N.A., Mulato, A.S. *Genotypic characterization of HIV-1 isolated from AIDS patients after prolonged therapy with adefovir dipivoxil (Preveon™)) added to existing regimens*. Antivir Res 1998, 37(3): Abst 9.

6. *Gilead broadens HIV expanded access program for Preveon*. Daily Essentials April 8, 1998.

7. *Adefovir dipivoxil shows promise in the treatment of hepatitis B*. Daily Essentials April 14, 1998.

8. *Gilead reports preliminary results from Preveon trials for the treatment of HIV infection*. Daily Essentials April 14, 1998.

Original monograph - Drugs Fut 1997, 22: 825.

Additional References

Locarnini, S.A. *New anti-hepatitis drugs/therapy*. 20th Int Cong Chemother (June 29-July 3, Sydney) 1997, Abst 2138.

Miller, M.D. et al. *Antiviral susceptibilities of HIV-1 RT recombinant viruses derived from AIDS patients after prolonged adefovir dipivoxil therapy*. 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 677.

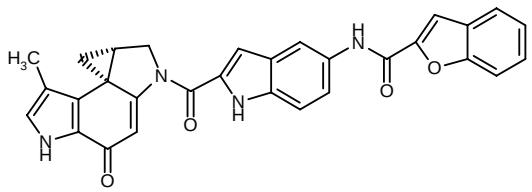
Neyts, J., De Clercq, E. *Antiviral drug susceptibility of human herpesvirus 8*. Antimicrob Agents Chemother 1997, 41(12): 2754.

Adefovir dipivoxil now available in expanded access program. Daily Essentials Dec 9, 1997.

Adozelesin
Adosar®

Antineoplastic

EN: 126014



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

Increasing doses of adozelesin (10-180 μg/m^2 i.v. for 10 weeks) were evaluated in a phase I trial in 47 adult patients with solid malignancies. Myelosuppression was the dose-limiting toxicity and the maximum tolerated dose was determined to be 180 μg/m^2. There was a minor response in 1 previously treated patient with melanoma. Based on these results, 150 μg/m^2 as a 10-min infusion every 4 weeks was the recommended dose for phase II testing (1).

1. Burris, H.A., Dieras, V.C., Tunca, M., et al. *Phase I study with the DNA sequence-specific agent adozelesin*. Anti-Cancer Drugs 1997, 8(6): 588.

Original monograph - Drugs Fut 1991, 16: 741

Additional References

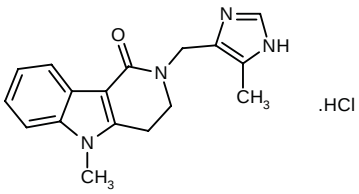
Baraldi, P.G. et al. *Synthesis, cytotoxicity, antitumor activity and sequence selective binding of two pyrazole analogs structurally related to the antitumor agents U-71,184 and adozelesin*. Anti-Cancer Drug Des 1997, 12(7): 555.

Hidalgo, M. et al. *Activity of the cyclo-propapyrroloindole (CPI) compounds bizelesin (B), adozelesin (A), and carzelesin (C) in human tumor colony-forming assay (HTCFA)*. Proc Amer Assoc Cancer Res 1998, Abst 1513.

Alosetron Hydrochloride

5-HT$_3$ Antagonist
Treatment of Irritable Bowel Syndrome

EN: 185981



$C_{17}H_{18}N_4O.HCl$ **Glaxo Wellcome**

In a randomized, double-blind, crossover study, a single oral dose of alosetron (4 mg) was evaluated for its effects on jejunal fluid and electrolyte movement in humans under normal conditions and after cholera toxin-induced secretion. Under normal conditions alosetron treatment increased basal fluid absorption as compared to placebo, while it had no beneficial effect on absorption or secretion following exposure to cholera toxin (1).

A double-blind, randomized, placebo-controlled, crossover study has shown that alosetron treatment (4 mg b.i.d.) in healthy individuals had few side effects and did not influence esophageal motility or lower esophageal sphincter pressure (2).

The efficacy of alosetron to relieve pain and discomfort in female patients with irritable bowel syndrome was examined in a phase II trial involving 370 male and female patients administered either alosetron (1, 2, 4 or 8 mg b.i.d.) or a placebo for 12 weeks. While no significant effects were noted in male patients, 60% of alosetron-treated females receiving1 mg experienced pain relief and significant improvement in stool urgency, consistency and frequency, as compared to 33% of females on placebo. Constipation (20%) was the only observed side effect (3).

1. Bearcroft, C.P., Andre, E.A., Farthing, M.J.G. *In vivo effects of the 5-HT$_3$ antagonist alosetron on basal and cholera toxin-induced secretion in the human jejunum: A segmental perfusion study*. Aliment Pharmacol Ther 1997, 11(6): 1109.

2. Khoury, R., Peghini, P., Katz, P., Castell, D. *Alosetron, a new 5HT$_3$ antagonist has no adverse effects on esophageal motility or lower esophageal sphincter (LES) pressure*. Dig Dis Week (May 17-20, New Orleans) 1998, Abst 730.5.

3. Northcutt, A.R., Camilleri, M., Mayer, E.A., et al. *Alosetron, a 5HT$_3$-receptor antagonist, is effective in the treatment of female irritable bowel syndrome patients*. Dig Dis Week (May 17-20, New Orleans) 1998, Abst 3344.

Original monograph - Drugs Fut 1992, 17: 660.

Additional References

Foster, J.M. et al. *Alosetron slows colonic transit in patients with irritable bowel syndrome (IBS)*. Gut 1997, 40(Suppl. 1): Abst TH175.

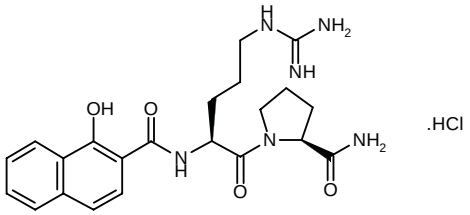
Saslow, S.B. et al. *Medium term effects of a new 5HT$_3$ antagonist, alosetron, in patients with carcinoid diarrhoea*. Gut 1998, 42(5): 628.

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

APC-366

Antiallergic/Antiasthmatic
Tryptase Inhibitor

EN: 203911



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

The effects of inhaled APC-366 (5 mg t.i.d. for 4 days) on antigen-induced early and late asthmatic response and bronchial hyperresponsiveness to histamine were evaluated in 16 mild atopic asthmatics. As compared to placebo, treatment with APC-366 produced a significant reduction in the magnitude of antigen-induced late asthmatic response and a slight, but not statistically significant reduction in early asthmatic response. There were no significant effects on bronchial hyperresponsiveness (1).

Arris has reported preliminary results from a double-blind, crossover U.K. phase IIa trial of APC-366, a tryptase inhibitor for the treatment of asthma, which indicated that the drug reached statistical significance in the achievement of the study's primary endpoint, the late airways response, showing a more than 25% reduction as compared to placebo. In this trial, 16 mild asthmatic patients received either placebo or a nebulized formulation of APC-366 three times daily for four days. An allergen challenge was perfomed after the tenth dose on day four of the study to evaluate the effects of the treatment. Arris is developing APC-366 in collaboration with Bayer. Results from a second phase IIa trial to evaluate the ability of this agent to improve bronchial hyperresponsiveness are expected later this summer and Arris intends to initiate a phase IIb study of the drug in a dry powder inhaler later this year. Bayer is developing a second-generation inhaled tryptase inhibitor and anticipates the initiation of a phase I safety trial of the compound this year (2).

The results of a 4-day, crossover phase IIa trial with APC-366 showed improvement over placebo in two-thirds of the patients, although statistical significance regarding the amount of histamine required to produce a drop of 20% or more in FEV_1 was not found (3).

Results from a double-blind, crossover, placebo-controlled phase IIa trial of APC-366 in 16 mildly asthmatic patients have been reported. Patients were administered either placebo or a nebulized formulation of APC-366, 3 times daily for 4 days. An allergen challenge was performed after the tenth dose on day 4 of the study. APC-366 significantly reduced the severity of allergen-induced late airways response (LAR) in asthmatics. During APC-366 dosing, subjects had a statistically significant improvement in overall mean area under the curve for LAR of 33% and mean maximum fall in FEV_1 of 21% for LAR, as compared to the results with placebo. Short-term repeated administration of the compound significantly reduced the magnitude of the allergen-induced LAR in asthmatics, suggesting that it could be a useful antiinflammatory agent in asthma management and further confirming the role of mast cell tryptase in LAR (4).

AxyS Pharmaceuticals has filed an IND with the FDA for a dry powder inhaler formulation of APC-366 (5).

1. Krishna, M.T., Chauhan, A.J., Little, L., Sampson, K., Mant, T.G.K., Hawksworth, R., Djukanovic, R., Lee, T.H., Holgate, S.T. *Effect of inhaled APC 366 on allergen-induced bronchoconstriction and airway hyperresponsiveness to histamine in atopic asthmatics*. Am J Respir Crit Care Med 1998, 157(3): A456.

2. *Arris reports positive results from phase IIa trial of tryptase inhibitor for asthma*. Daily Essentials June 30, 1997.

3. *Arris reports data from phase IIa asthma trial*. Daily Essentials Sept 26, 1997.

4. *AxyS Pharmaceutical's APC-366 shows good antiasthmatic activity in phase IIa trial*. Daily Essentials May 1, 1998.

5. *AxyS files IND for dry powder inhalation formulation of APC-366*. Daily Essentials June 4, 1998.

Original monograph - Drugs Fut 1996, 21: 811.

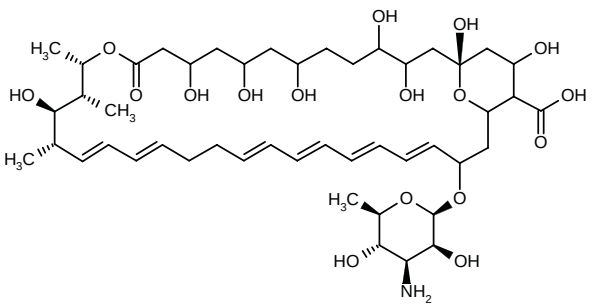
Additional Reference

Moore, W.R. *Low molecular weight tryptase inhibitors: A new therapy for asthma*. NMHCC Protease Inhib Inflamm (Feb 11-12, San Diego) 1997, 1997.

AR-121
Nystatin LF
Nyotran™

Antifungal
Antiviral

EN: 211301



Aronex; M.D. Anderson Cancer Center; Ferrer

In vitro studies evaluating the effect of Nyotran™ against various clinical fungal isolates demonstrated that the drug has potent antifungal activity against *Fusarium*, *Sporothrix* and *Beauvaria* species, as well as *Candida albicans* and *C. tropicalis*, with respective MIC_{80}s of 2.0, 1.0, 2.0, 4.0 and 8.0 μg/ml (1).

Aronex in collaboration with Ferrer has filed an MAA in Spain for Nyotran™ for the treatment of systemic fungal infections (2).

Nyotran™ was evaluated in three clinical trials in the U.K. and U.S. The results, presented at the recent European Congress of Medical Mycology in Glasgow, showed that Nyotran™ possesses broad antifungal activity. The compound was fungicidal for 34% of 60 *Aspergillus* isolates as compared to 7%, 5% and 34% observed with the reference drugs AmBisome, Abelcet and Amphotec, respectively. In addition, Nyotran™ exhibited good *in vitro* activity against a wide range of filamentous fungi, including *Aspergillus*, and was active against 421 yeast isolates from human patients in the U.S. and Europe. *In vitro* and clinical data for Nyotran™ were also presented by Aronex at the American Society of Microbiology meeting in Atlanta. The compound demonstrated efficacy in a cardiac transplant recipient treated for invasive pulmonary aspergillosis, with no signs of recurrence following treatment. The drug also demonstrated good *in vitro* antifungal activity against several *Candida* isolates from human patients, including some amphotericin B-resistant isolates (3).

1. Jessup, C.J., Wallace, T.L., Ghannoum, M.A. *Evaluation of antifungal activity of Nyotran against various pathogenic fungi*. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-88.

2. *Aronex/Ferrer seek approval of Nyotran in Spain*. Daily Essentials Dec 29, 1997.

3. *Nyotran demonstrates broad antifungal activity against multiple fungal species*. Daily Essentials May 26, 1998.

Original monograph - Drugs Fut 1994, 19: 724.

Additional References

Carrabs, M. et al. *Fluconazole vs nystatine in pediatric patients with oropharyngeal candidiasis*. Focus Fungal Infect 8 (March 4-6, Orlando) 1998, Abst 018.

Carrillo-Muñoz, A.J. et al. *In vitro antifungal activity of liposomal nystatin (Nyotran™)*. Trends Invasive Fungal Infect 4 (Nov 5-8, Barcelona) 1997, Abst P-75.

Denning, D.W. *The new generation of antifungals*. Trends Invasive Fungal Infect 4 (Nov 5-8, Barcelona) 1997, Abst O-25.

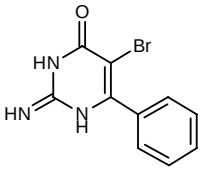
Groll, A.H. et al. *Fluconazole versus nystatin in the prevention of candida infections in children and adolescents undergoing remission induction or consolidation chemotherapy for cancer*. J Antimicrob Chemother 1997, 40(6): 855.

Aronex's Nyotran shown effective against aspergillosis. Daily Essentials Nov 11, 1997.

Bropirimine
Remisar®

Immunomodulator
Antiviral
Antineoplastic

EN: 090374



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

Bropirimine was compared to the existing standard treatment for carcinoma *in situ* (CIS), BCG (Bacillus Calmette-Guerin), in a phase III clinical trial in 55 BCG-naive patients with newly diagnosed CIS. Patients were randomized to treatment with bropirimine (3 g/day p.o. for 3 days, followed by 4 days without drug) for up to 1 year, or with BCG given as weekly instillations for 6 weeks. The incidence of complete response (mean duration of response), as evidenced by negative biopsy and cytology, was the same in both treatment groups: 96% (11 months) for bropirimine and 100% (12 months) for BCG. The incidence of adverse effects was much lower in the bropirimine group than the BCG group (73% *vs.* 92% for irritative complaints and 27% *vs.* 63% for hematuria), and fewer patients in the former group withdrew from the study due to adverse events (4% *vs.* 14%) (1).

1. Witjes, W.P.J., Hall, R.R., Schulman, C.C., Zurlo, M., Fittipaldo, A., Riggi, M., Debruyne, F.M.J. *Bropirimine versus BCG in BCG-naive patients with carcinoma in situ of the urinary bladder. Preliminary results of a European randomized phase III trial*. J Urol 1998, 159(5, Suppl.): Abst 553.

Original monograph - Drugs Fut 1984, 9: 567.

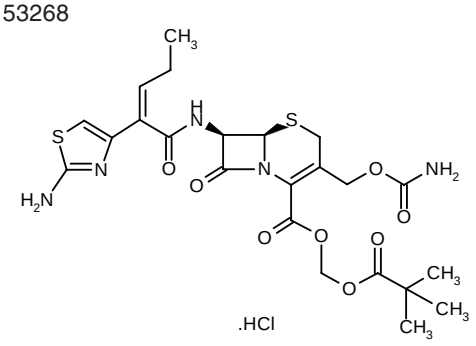
Additional Reference

Witjes, W.P.J. et al. *Bropirimine versus BCG in BCG-naive patients with carcinoma in situ of the urinary bladder. Results of a European randomized phase III trial*. Eur Urol 1998, 33(Suppl. 1): Abst 407.

Cefcapene Pivoxil Hydrochloride
Flomox®

Cephalosporin

EN: 153268



$C_{23}H_{29}N_5O_8S_2.HCl$ **Shionogi**

In studies evaluating the antimicrobial activity of cefcapene against clinical isolates of respiratory tract infections, the drug was found to be as potent as benzylpenicilin, ampicilin and cefditoren, and less potent than cefaclor, cefdinir and erythromycin, against penicillin-susceptible *Streptococcus pneumoniae*. Cefcapene was as potent as cefditoren against penicillin-intermediate *S. pneumoniae*, and also exhibited good antimicrobial activity against beta-lactamase-producing and -nonproducing *Haemophilus influenza* (1).

Shionogi has launched cefcapene pivoxil hydrochloride (Flomox®) for the treatment of several infective conditions, including folliculitis, furuncle, carbuncle and infective impetigo. It is supplied as 75- and 100-mg tablets and as a granule formulation for pediatric use (2).

1. Ishihara, R., Ishii, Y., Suzuki, Y., Nakazawa, A., Deguchi,K., Toyonaga, Y. *Antimicrobial activities of cefcapene against clinical isolates from respiratory tract infections of out patients.* Jpn J Antibiot 1998, 51(1): 1.

2. *Shionogi's β-lactam antibiotic launched in Japan.* Daily Essentials Aug 7, 1997.

Original monograph - Drugs Fut 1992, 17: 687.

Additional References

Nishimura, K., Yoshida, I. *Antibacterial activity of cefcapene against Haemophilus influenzae*. Jpn J Chemother 1998, 46(6): 210.

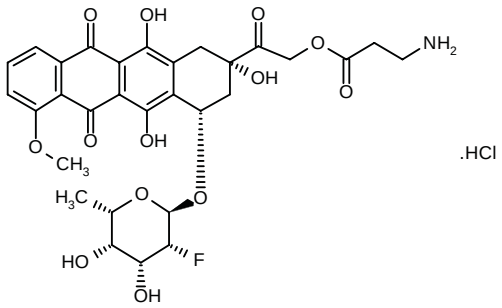
Saito, A. et al. *Recent extrinsic infectious disease and therapy thereof - Cefcapene pivoxil*. Jpn J Antibiot 1997, 50(6): 23.

Saito, A. *Cefcapene pivoxil*. Jpn J Antibiot 1997, 50(6): 1.

DA-125

Antineoplastic

EN: 198263



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

The antitumor activity of DA-125 in human gastric and adenocarcinoma cell lines and their adriamycin- and cisplatin-resistant sublines was comparable to that of adriamycin in terms of both IC_{50} values and relative resistance. IC_{50} values for both compounds were lowest in the parent cell lines, followed by cisplatin- and adriamycin-resistant cell lines. The IC_{50} for DA-125 was significantly lower than that for adriamycin in 4 of the cell lines tested (1).

1. Hong, W.S., Jung, H.Y., Yang, S.K., Kim, H.R., Min, Y.I. *Antitumor activity of DA-125, a novel anthracycline, in human gastric and pulmonary adenocarcinoma cells resistant to adriamycin and cisplatin*. Anticancer Res 1997, 17(5A): 3613.

Original monograph - Drugs Fut 1996, 21: 782.

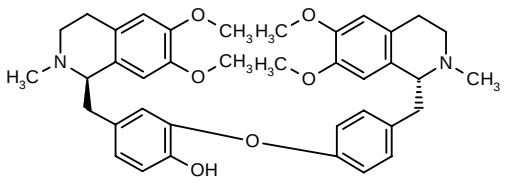
Additional Reference

Choi, Y.J. et al. *Pharmacokinetic changes of M1, M2, M3 and M4 after intravenous administration of a new anthracycline, DA-125, to rats pretreated with phenobarbital, 3-methylcholanthrene, chloramphenicol, or SKF-525A*. Biopharm Drug Dispos 1998, 19(2): 79.

Dauricine

Cardiovascular Agent

EN: 090962



$C_{38}H_{44}N_2O_6$ **Wuhan Med. Coll. Pharm. (CN)**

Results of *in vitro* studies showed that dauricine significantly suppressed L-type calcium current from guinea pig cardiomyocytes. The blocking effect was frequency-independent and partially reversible on washout (1).

Dauricine dose-dependently inhibited $^{45}Ca^{2+}$ uptake from resting and ADP-stimulated rat platelets in an *in vitro* study. Results suggest that the platelet antiaggregation activities of dauricine may be due to inhibition of extracellular Ca^{2+} influx (2).

In vitro studies using papillary muscle demonstrated that dauricine (20 μM) prolonged action potential duration at 90% repolarization and was more effective at short cycle lengths (3).

Dauricine effectively inhibited endothelin-induced arterial smooth muscle cell proliferation *in vitro*, suggesting possible use as an antiatherosclerotic agent (4).

The antioxidative actions of dauricine were demonstrated in hippocampal cortex tissue *in vitro*. Dauricine significantly increased SOD and GSH-PX activities while lowering MDA content, thus increasing SOD/MDA and GSH-PX/MDA ratios (5).

1. Guo, D.L., Zhou, Z.N., Zeng, F.D., Hu, C.J. *Dauricine inhibited L-type calcium current in single cardiomyocyte of guinea pig*. Acta Pharmacol Sin 1997, 18(5): 419.

2. Liu, J.T., Deng, X.L., Qiu, P.L. *Effect of dauricine on $^{45}Ca^{2+}$ uptake into platelets in rats*. Chin Pharmacol Bull 1996, 12(5): 412.

3. *Effects of dauricine, quinidine and sotalol on action potential duration of papillary muscles in vitro*. Acta Pharmacol Sin 1997, 18(4): 348.

4. Luo, X., Zeng, F.D., Hu, C.J. *Effect of dauricine on cultured arterial smooth muscle cell proliferation induced by endothelin*. Chin Circ J 1997, 12(3): 215.

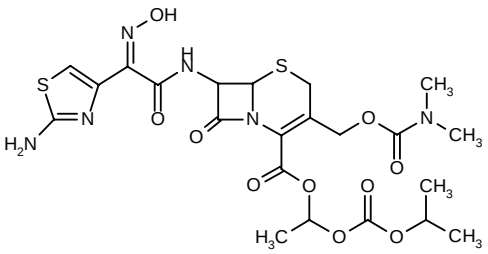
5. He, L.Y., Li, L.Z., Wu, J.L. *Experimental studies on the antioxidation effect of dauricine*. Chin Trad Herb Drugs 1997, 28(8): 479.

Original monograph - Drugs Fut 1985, 10: 626.

E-1101

Cephalosporin

EN: 185449



$C_{22}H_{28}N_6O_{10}S_2$ **Eisai**

Rats infected with *Escherichia coli* or *Bacteroides fragilis* isolated from patients with uterine endometritis or pyometra, respectively, were administered E-1101 (20 mg/kg p.o. b.i.d.) or cefdinir (20 mg/kg p.o. t.i.d.) for 5 days. Polymicrobial infections and inflammatory changes in the uterus were reduced in both groups of treated animals as compared to untreated controls and the two agents were equally effective (1).

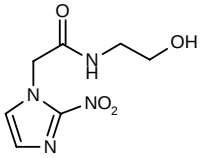
1. Kawazoe, K., Mikamo, H., Sato, Y., Izumi, K., Hachiya, S., Satoh, M., Munakata, K., Tamaya, T. *Comparative study of oral cephalosporins in the uterine pyometra model*. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-187.

Original monograph - Drugs Fut 1995, 20: 766.

Etanidazole
Radinyl®

Radiosensitizer

EN: 090758



$C_7H_{10}N_4O_4$ **Natl. Cancer Inst. (US); SRI Int.; Roberts; Taisho; Nycomed Pharma; DuPont Merck**

In a nonrandomized study in 30 patients with limited stage small cell lung cancer, etanidazole used in combination with thoracic irradiation (500 cGy in 5 weeks) and administered between the first and second cycle of a 6-cycle chemotherapy regimen, was found to improve the thoracic failure rate by almost 50%, with a 30% 5-year crude survival rate (1).

Results from a phase I study in patients with anaplastic astrocytoma (n=19) or glioblastoma multiforme (n=50) treated with etanidazole (2 g/m^2 i.v. x 6 doses) in combination with radiotherapy showed that the median survival for patients with glioblastoma multiform was 1.1 years, while patients with anaplastic astrocytoma survived for an average of 3.1 years (2).

A phase II study in 30 patients with limited stage small-cell lung cancer evaluated the toxicity and survival rates after treatment with etanidazole (2 g/m^2 i.v. 3 times per week) together with radiotherapy and a standard combination chemotherapy regimen. Treatment produced an overall response rate of 96% in terms of primary lesion in the thorax, with a complete response rate of 64%. Crude survival after 2 years was 46%, while the 3- and 5-year survival rates without evidence of disease were 33% and 30%, respectively. There was a moderate increase in transient peripheral neuropathies which was probably related to concomitant use of etanidazole with vincristine and cisplatin (3).

1. Urtasun, R.C., Palmer, M., Kinney, B., Belch, A., Hewitt, J., Hanson, J. *Intervention with the hypoxic tumor cell sensitizer etanidazole in the combined modality treatment of limited stage (LD) small cell lung cancer (SCLC)*. Proc Amer Soc Clin Oncol 1997, Abst 1605.

2. Chang, E.L., Loeffler, J.S., Riese, N.E., Wen, P.Y., Alexander, E., Black, P.M., Coleman, C.N. *Survival results from a phase I study of etanidazole (SR2508) and radiotherapy in patients with malignant glioma*. Int J Radiat Oncol Biol Phys 1998, 40(1): 65.

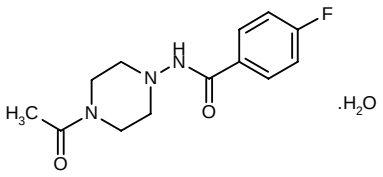
3. Urtasun, R.C., Palmer, M., Kinney, B., Belch, A., Hewitt, J., Hanson, J. *Intervention with the hypoxic tumor cell sensitizer etanidazole in the combined modality treatment of limited stage small-cell lung cancer. A one-institution study*. Int J Radiat Oncol Biol Phys 1998, 40(2): 337.

Original monograph - Drugs Fut 1995, 20: 772.

FK-960
FR-59960

Cognition Enhancer

EN: 243654



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

In a double-blind, placebo-controlled study in 20 healthy young male volunteers, FK-960 (0.2, 2, 20 and 200 mg p.o.) demonstrated significant antagonistic effects on scopolamine-impaired working and episodic memory. The effects were observed on both the accuracy and speed of performance and occurred with all doses studied, although doses in the intermediate range showed greater improvements (1).

1. Wesnes, K.A., Ramezani, E., Oliver, S. *FK960 antagonizes the memory impairments produced by scopolamine in healthy volunteers*. J Psychopharmacol 1997, 11(3, Suppl.): Abst 225.

Original monograph - Drugs Fut 1997, 22: 830.

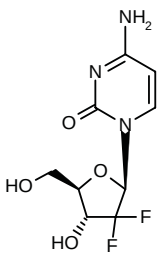
Additional Reference

Ito, M. et al. *Comparison of pharmacokinetics of FK-960, an antidementia agent, in non-elderly and elderly subjects*. Jpn J Clin Pharmacol Ther 1997, 28(1): 263.

Gemcitabine
Gemzar®

Antineoplastic

EN: 102180



$C_9H_{11}F_2N_3O_4$ **Lilly**

Gemcitabine (1250 mg/m^2 as 30-minute i.v. infusion on days 1, 8 and 15 every 28 days) has been compared to the combination of cisplatin (80 mg/m^2 on day 1 every 28 days) + etoposide (80 mg/m^2 on days 1, 2 and 3 every 28 days) in patients with advanced non-small cell lung cancer. Of 26 evaluable patients on gemcitabine, 5(19.2%) has a partial response compared to 5 of 24 (20.8%) on combination therapy. Median survival time was 37 and 49 weeks, respectively, on gemcitabine and cisplatin + etoposide. Toxicity was mainly myelosuppression and vomiting, and gemcitabine was better tolerated than the combination (1).

The FDA's Oncologic Drugs Advisory Committee has recommended that gemcitabine hydrochloride (Gemzar®) be approved for use as a single agent or in combination with cisplatin for the treatment of locally advanced or metastatic non-small cell lung cancer (2).

1. Perng, R.P., Chen, Y.M., Ming Liu, J., Tsai, C.M., Lin, W.C., Yang, K.Y., Whang Peng, J. *Gemcitabine versus the combination of cisplatin and etoposide in patients with inoperable non-small-cell lung cancer in a phase II randomized study*. J Clin Oncol 1997, 15(5): 2097.

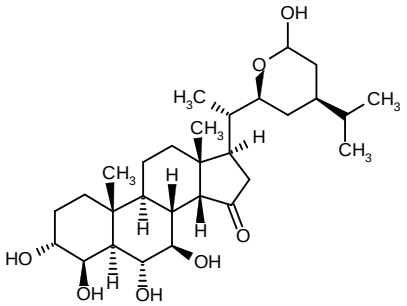
2. *Approval recommended for Gemzar supplemental NDA*. Daily Essentials March 20, 1998.

Original monograph - Drugs Fut 1990, 15: 794.

IZP-94005
Contignasterol
Pneumocort®

Antiallergic/Antiasthmatic

EN: 211497



$C_{29}H_{48}O_7$ **InflaZyme**

The allergen-induced plasma protein exudation in tracheobronchial airways of sensitized guinea pigs was abolished by contignasterol, budesonide and nedocromil (200 μg/kg) when they were administered 30 min prior to ovalbumin. However, when the drugs were administered 5 min before ovalbumin, only nedocromil had this effect (1).

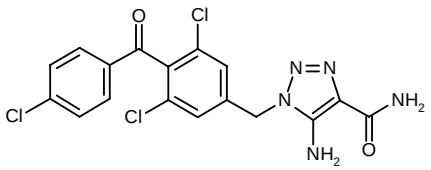
1. O'Donnell, S.R., Coulson, F.R. *Contignasterol inhibition of allergen-induced plasma exudation in airways of sensitised guinea-pigs in vivo*. Am J Respir Crit Care Med 1998, 157(3): A826.

Original monograph - Drugs Fut 1994, 19: 738.

L-651582
CAI

Antineoplastic

EN: 113265



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

CAI (0.1, 1.0, 10 μM) dose-dependently inhibited serum-induced retinal pigment epithelial (RPE) cell proliferation (0, 15 and 30%, respectively) and bFGF-induced proliferation. Fibronectin-stimulated migration was also inhibited with the 1.0- and 10-μM doses (24 and 60%,

respectively). Although RPE attachment to laminin was unaffected, it was inhibited on extracellular matrix components such as collagen (48%) and fibronectin (55%) (1).

Mononuclear cell isolates from 12 patients with B-cell chronic lymphocytic leukemia were exposed to varying concentrations of CAI (0.01-100 μM) for 4 h to 4 days. The LC_{50} for CAI at 4 days was 53.5 μM. Cytotoxicity at a concentration of 10 μM was noted in cells from 6 patients, with a 27% mean decline in viability at 4 days (2).

The effects of food on steady-state plasma levels of CAI were evaluated in 17 patients. Therapy consisted of CAI (150 mg/m^2) taken for 1 month with a bedtime snack and for 1 month without a snack. CAI steady-state plasma levels were 128.2% higher in patients in the snack group than in patients in the no snack group. There was no significant difference in toxicity between groups; neurotoxicity was observed in 3 patients in the snack group and 1 patient in the no snack group (3).

1. Ehren, M., Hoffmann, S., Jin, M.L., Kohn, E., Hinton, D.R., Ryan, S.J. *Inhibition of RPE proliferation, attachment and migration by carboxyamido-triazole (CAI), a drug which acts by modifying calcium mediated signal transduction*. Invest Ophthalmol Visual Sci 1997, 38(4, Part 2): Abst 3486.

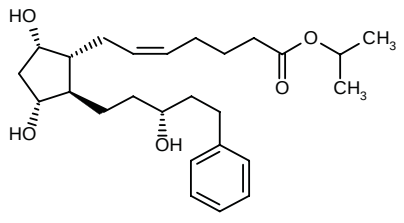
2. Waselenko, J.K., Byrd, J.C., Shinn, C.A., Flinn, I.W., Diehl, L.F., Sausville, E., Grever, M.R. *Carboxyamido-triazole (CAI), a signal transduction inhibitor, demonstrates marginal activity against human B-cell chronic lymphocytic leukemia in vitro*. Blood 1997, 90(10, Suppl. 1, Part 2): Abst 4147.

3. Berlin, J., Tutsch, K.D., Alberti, D., Arzoomanian, R.Z., Feierabend, C., Morgan, K., Simon, K., Wahamaki, A., Wilding, G. *Effects of food on the pharmacokinetics (pk) and toxicities of oral carboxyamidotriazole (CAI)*. Proc Amer Assoc Cancer Res 1998, Abst 3557.

Original monograph - Drugs Fut 1991, 16: 717.

Latanoprost *Antiglaucoma*
Xalatan®

EN: 183029



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

The ocular hypotensive effects of latanoprost and unoprostone have been compared in cynomolgus monkeys with glaucoma and their mechanism of action characterized in normal monkey eyes. After the first application of latanoprost (0.005%) and unoprostone (0.12%), IOP was significantly reduced for 4 and 2 h, respectively, with maximum decreases of 5.4 ± 0.8 mmHg and 3.8 ± 0.5 mmHg, respectively. The prostanoids were administered twice daily in the morning and afternoon for 5 days and, in contrast to unoprostone, IOP was significantly reduced for at least 18 h following each afternoon dose of latanoprost. The ocular hypotensive effect was enhanced with repeated doses in both cases, but latanoprost was associated with superior efficacy and a longer duration of action than unoprostone after each application. Studies in normal monkeys showed that the compounds did not affect outflow facility or aqueous humor flow rates and it was concluded that both compounds reduce IOP in monkeys by enhancing uveoscleral outflow (1).

The effects of latanoprost in combination with cholinergic agents were evaluated in 17 patients with open angle glaucoma on multiple medications including cholinergics. Patients were administered latanoprost (0.005%) to one eye while the fellow eye served as control. The cholinergic agent was then discontinued and intraocular pressure was evaluated. Intraocular pressure was reduced by 3.04 mmHg when latanoprost was added to cholinergics and was increased by 0.08 mmHg when latanoprost was used instead of cholinergics (2).

Administration of latanoprost as an adjunctive agent in 28 patients with glaucoma produced a 4.1% reduction in intraocular pressure following 2 weeks of treatment. Patients being treated with pilocarpine or a similar type of drug had a 4.5% reduction in IOP, while 5 of 15 eyes being treated with a miotic had an average increase in IOP of 4 mmHg. Thus, the efficacy of latanaprost in combination with other drugs appears to be questionable (3).

The efficacy of latanoprost was evaluated in 74 eyes of 46 patients with uncontrolled glaucoma. Intraocular pressure was reduced by 3 mmHg or more in 61% of the eyes following latanoprost therapy. Of 36 eyes being treated with a miotic, 47% responded to latanaprost, indicating that it may not be as effective in the presence of a miotic (4).

The effects of latanaprost (0.005% one drop daily) in addition to other regimens was evaluated in 148 eyes of 89 glaucoma patients nonresponsive to previous therapy. Mean intraocular pressure decreased from a baseline of 22 mmHg by 5, 4.5, 3.5 and 4 mmHg at 1, 3, 6 and 9 months, respectively. The reduction in intraocular pressure was significantly greater in eyes not receiving miotic therapy when measured at 1 month (5).

In a study in 41 patients with medically resistant glaucoma, latanaprost was shown to have significant additive effects in reducing intraocular pressure which were directly proportional to pretreatment intraocular pressure values; the effects were more pronounced in patients with pigmentary glaucoma. Four patients discontinued therapy due to systemic side effects (6).

In a pilot study in 10 eyes from 10 patients with a history of acute angle closure attacks, latanoprost (0.005%) successfully reduced intraocular pressure in some patients and apparently did not cause uveitis. However, a rapid tachyphylactic effect was observed in a significant

  CCC: 0377-8282/98

percentage of the eyes, suggesting that further study is needed before widespread use of the compound in patients with narrow angle glaucoma (7).

Results of a prospective study in 21 patients undergoing argon laser trabeculoplasty indicated that pretreatment with latanoprost (0.005%) was as successful as apraclonidine (0.5%) in preventing postoperative intraocular pressure spikes and also had an equally acceptable effect in lowering IOP at 6 weeks (8).

In a multicenter, randomized, double-masked study in 115 patients with primary open angle glaucoma, the fixed-ratio combination of latanoprost 0.005% and timolol 0.5% was significantly more effective in reducing intraocular pressure than the latanoprost 0.001% and timolol 0.5% fixed-ratio combination (9).

In a pilot study in 18 patients with open angle glaucoma, the addition of latanoprost to beta-blockers and topical carbonic anhydrase inhibitors produced a significant reduction in intraocular pressure (10).

The effect of substituting latanoprost for pilocarpine was studied in 18 patients with chronic glaucoma. All patients were on multiple medications which were continued throughout the study. Mean intraocular pressure was 21.0 mmHg before substitution and 21.2 mmHg afterwards. Most patients did not experience changes in their intraocular pressure, indicating that latanoprost may serve as a substitute for pilocarpine, although the exchange should be monitored carefully (11).

Latanaprost (50 μg/ml) as a second or third topical medication applied once daily in 21 patients with advanced open angle glaucoma produced mean reductions in intraocular pressure of 21% and 28%, respectively, after 1 and 2 months. There were no changes in visual acuity or iris color, and no side effects were reported (12).

In a double-blind study in 10 healthy volunteers, a single topical instillation of latanaprost lowered intraocular pressure without affecting ocular blood flow, velocity or volume (13).

The efficacy and safety of long-term treatment with latanoprost (0.005% once daily) was evaluated in 277 patients with open-angle glaucoma or ocular hypertension. Latanoprost reduced intraocular pressure by approximately 8 mmHg from baseline values, which was maintained during the 2-year treatment period. No systemic side effects were observed (14).

The additive effect of latanoprost, with or without miotic therapy, was evaluated in 54 chronic glaucoma patients in need of surgical intervention. Mean intraocular pressure, which was uncontrolled on maximum tolerated medications, was decreased from 23.2 ± 6.3 mmHg to 20.8 ± 8.7 mmHg after latanoprost therapy. Treatment with latanoprost also successfully prevented or postponed surgery in most patients (15).

Morphological evaluation of iris and trabeculectomy specimens treated with latanoprost (50 μg/day for 6 months) showed light and electron-microscopical findings similar to those of untreated eyes. No histological signs of inflammation, epithelial degeneration or vascular alteration were observed in treated or untreated eyes (16).

In a prospective, observer-masked, open-label trial in 37 patients with uncontrolled persistent open-angle glaucoma, 1 drop of latanoprost was effective in lowering intraocular pressure (from 20.5 ± 0.8 mmHg to 16.3 ± 0.6 mmHg) measured at 24 h postdose; the effect was maintained for 4 weeks (17).

Results from a clinical trial in 160 glaucoma patients administered latanoprost (0.005%) as adjunctive therapy with pilocarpine, carbachol or echothiophate iodide indicated that patients taking weaker miotic agents responded better to the addition of latanoprost (18).

Results of a study in 58 cataract patients indicate that a 15-minute latanoprost-soaked collagen shield is equivalent to oral acetazolamide for controlling acute postoperative intraocular pressure spikes after cataract surgery (19).

Latanoprost has been introduced in Germany as Xalatan® for the treatment of primary open-angle glaucoma and ocular hypertension (20).

Pharmacia & Upjohn has launched latanoprost (Xalatan®) in Spain, where it is indicated for the topical treatment of open-angle glaucoma and ocular hypertension in patients not responding to other treatments. The product is supplied as eyedrops, 2.5 ml (0.005%) (21).

1. Serle, J.B., Podos, S.M., Kitazawa, Y., Wang, R.F. *A comparative study of latanoprost (Xalatan) and isopropyl unoprostone (Rescula) in normal and glaucomatous monkey eyes*. Jpn J Ophthalmol 1998, 42(2): 95.

2. Willman, M.R., Fechtner, R.D., Khouri, A.S., Zimmerman, T.J. *Latanoprost is additive to multiple medical therapy including cholinergic agents*. Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 1307.

3. Economou, A., Li, A., Lee, P.-F., Simmons, S. *A comparative study of latanoprost and its effect in multiple drug regimens*. Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 1308.

4. Gemperli, A., Wilensky, J., Hillman, D. *The efficacy of latanoprost in patients with uncontrolled glaucoma on maximum medical therapy*. Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 1309.

5. Jeng, S., Tamesis, R.R., Camras, C.B., Yablonski, M.E., Neely, D.G. *Effect of latanoprost (LP) in glaucoma patients uncontrolled on maximum tolerated medical therapy (MTMT)*. Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 1310.

6. Vakian, A., Butler, P.J. *Efficacy of latanaprost in patients with medically resistant glaucoma*. Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 1311.

7. Lee, V.W., Yim, S.Y. *The clinical use of latanoprost 0.005% in patients after angle closure attacks*. Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 1302.

8. Karlik, J.S., Barber, J.C., Humphreys, A., Dutt, R.M. *The comparison of latanoprost versus apraclonidine as pretreatment in eyes undergoing argon laser trabeculoplasty*. Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 1303.

9. Diestelhorst, M., et al. *Comparison of fixed-ratio combinations of latanoprost and timolol. A randomised, double-masked, multicentre study in glaucoma patients with timolol and latanoprost as controls*. Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 1304.

10. Khouri, A.S., Fechtner, R.D., Willman, M.R., Zimmerman, T.J. *Additivity of latanoprost to beta blockers and topical carbonic anhydrase inhibitors*. Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 1305.

11. Brown, R.H., Lynch, M.G., Beck, A.D., Wilson, W.R. *The effect on IOP control of substituting latanoprost for pilocarpine in patients with chronic glaucoma*. Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 1306.

12. Martin, J.L., Bevacqua, A., Rahn, E.K., Habib, M. *Reduction of intraocular pressure with treatment of latanoprost once daily as a second or third topical medication in patients with advanced open angle glaucoma*. Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 1313.

13. Seong, G.J., Kim, S.K., Lee, Y.G., Hong, Y.J. *The effect of latanoprost on optic nerve head and peripapillary blood flow*. Invest Ophthalmol Visual Sci 1997, 38(4, Part 2): Abst 3601.

14. Watson, P.G. *Latanoprost: Two years' experience of its use in the United Kingdom*. Ophthalmology 1998, 105(1): 82.

15. McCracken, M.S., Shin, D.H., Bendel, R.E., Juzych, M.S., Hughes, B.A., Schulz, L., Baek, N.H. *Additive effect of latanoprost to maximum tolerated medications in chronic glaucoma patients with and without miotic therapy*. Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 1132.

16. Pfeiffer, N., Grierson, I., Sell, E., Davies, H., Wingken-Böhres, A., Hochgesand, D. *Morphological evaluation of the iris after treatment with latanoprost*. Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 1134.

17. Passo, M.S., Schalock, P.C. *One drop, one eye trial: Predicting response to latanoprost in uncontrolled POAG patients*. Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 1299.

18. Kruger, E., Greenfield, D.S., Liebmann, J.M., Wand, M., Kushnick, H., Patelska, B., Ritch, R. *Latanoprost with adjunctive miotic therapy in a compassionate case protocol*. Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 1300.

19. Searcy, G.D., Humphreys, A., Dutt, R.M. *Latanoprost in post-cataract intraocular pressure control*. Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 1301.

20. *German launch for Xalatan*. Daily Essentials Oct 23, 1997.

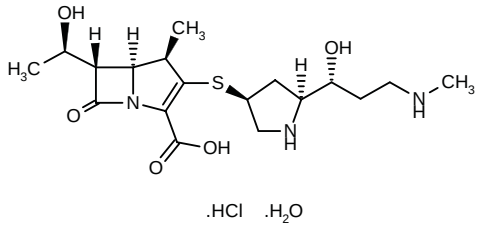
21. *Another market introduction for Xalatan*. Daily Essentials May 18, 1998.

Original monograph - Drugs Fut 1992, 17: 691.

Lenapenem Hydrochloride Hydrate
BO-2727

Carbapenem

EN: 197378



.HCl .H_2O

$C_{18}H_{29}N_3O_5S.HCl.H_2O$ **Banyu; Merck & Co.**

A new synthesis of BO-2727 has been described: The condensation of (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-(*tert*-butyldimethylsylyloxy)pyrrolidine-2-carbaldehyde (I) with ethyl acetate (II) by means of butyl lithium and hexamethyldisylazane (HMSA) in THF gives 3-[1-(*tert*-butoxycarbonyl)-4(*R*)-(*tert*-butyldimethylsylyloxy)pyrrolidin-2(*S*)-yl]-3-hydroxypropionic acid ethyl ester (III), which was submitted to column chromatography over silicagel yielding the pure 3(*R*)-hydroxypropionic acid (IV). The reduction of (IV) with $NaBH_4$ in THF afforded the expected diol (V), which was treated with tosyl chloride and triethylamine to give the monotosylate (VI). The reaction of (VI) first with methylamine in methanol, and then with *p*-nitrobenzyloxycarbonyl chloride (PNZ-Cl) in the same solvent yielded (2*S*,4*R*)-2-[1(*R*)-hydroxy-3-[*N*-methyl-*N*-(*p*-nitrobenzyloxycarbonyl)amino]propyl]pyrrolidin-4-ol (VII). The reaction of (VII) first with $SOCl_2$ and then with potassium thioacetate afforded the 4(*R*)-acetylsulfanyl derivative (VIII), which was hydrolyzed with NaOH in methanol/water to the corresponding thiol (IX). The condensation of (IX) with the carbapenem intermediate (X) by means of diisopropylethylamine (DIEA) in acetonitrile gave the precursor (protected) of BO-2727 (XI), which was finally deprotected by hydrogenation with H_2 over Pd/C in THF/ethanol/pH-7 buffer (1). Scheme 2.

In vitro studies showed that BO-2727 was 4- to 8-fold more active than meropenem, imipenem and biapenem against methicillin-resistant *Staphylococcus aeruginosa*, with an MIC_{90} of 12.5 mg/l. BO-2727 also had superior antibacterial activity against *Pseudomonas aeruginosa*, being 2- to 4-fold more active than imipenem against imipenem-resistant strains. In time-kill studies, the compound was dose-dependently bactericidal against *Staphylococcus aureus*, *Escherichia coli* and *P. aeruginosa* (2).

Assessment of the antibacterial activity of BO-2727 showed that MIC_{50}s and MIC_{90}s against *Streptococcus agalactiae*, *Escherichia coli*, *Peptostreptococcus magnus*, *Bacteroides fragilis* and *Prevotella bivia* were 0.05, 0.05, 0.1, 0.78, and 0.78 mg/l, respectively. Evaluation of the compound's efficacy in a rat polymicrobial pyometra model indicated that it may be useful for treating polymicrobial infections in humans (3).

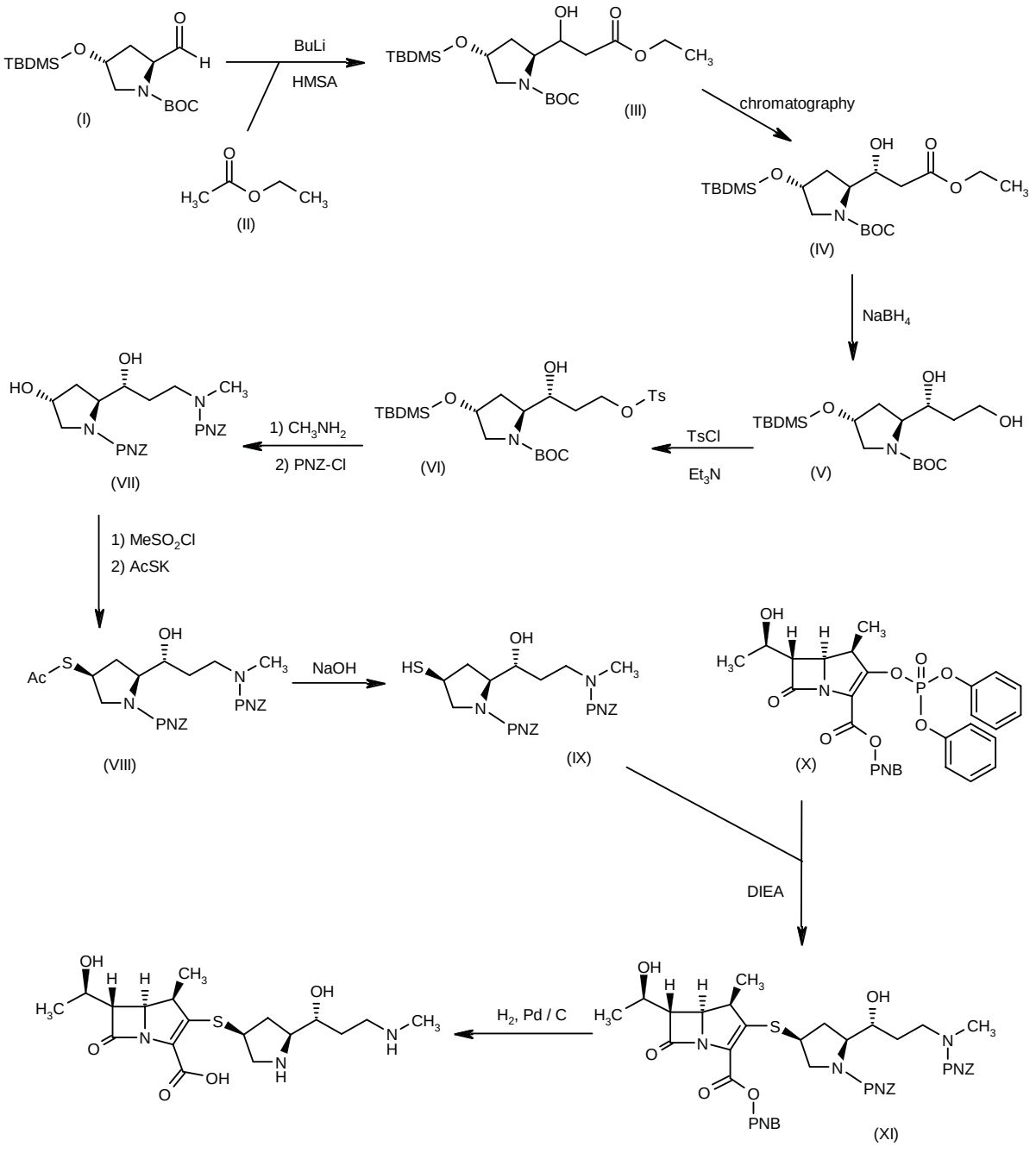
1. Ohtake, N., Okamoto, O., Mitomo, R., Kato, Y., Yamamoto, K., Haga, Y., Fukatsu, H., Nakagawa, S. *1β-Methyl-2-(5-substituted pyrrolidin-3-ylthio)carbapenems; 3. Synthesis and antibacterial activity of BO-2727 and its related compounds*. J Antibiot 1997, 50(7): 598.

2. Kato, Y., Otsuki, M., Nishino, T. *Antibacterial properties of BO-2727, a new carbapenem antibiotic*. J Antimicrob Chemother 1997, 40(2): 195.

3. Mikamo, H., Kawazoe, K., Izumi, K., Sato, Y., Tamaya, T. *In vitro and in vivo antibacterial activities of a new carbapenem BO-2727 for use in obstetrics and gynecology*. Chemotherapy 1998, 44(1): 12.

Original monograph - Drugs Fut 1994, 19: 731.

Scheme 2: Synthesis of Lenapenem



Additional References

Aralar, P.A. et al. *The antimycobacterial activity of the carbapenems, biapenem, imipenem, meropenem, panipenem and BO2727 against Mycobacterium avium complex (MAC).* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst E-165.

Hasizume, T. et al. *Affinities of BO-2727 for bacterial penicillin-binding proteins and morphological change of Gram-negative rods.* J Antibiot 1997, 50(2): 139.

Shibata, K. et al. *In vitro and in vivo evaluation of BO-2727 against imipenem- and/or meropenem-resistant Pseudomonas aeruginosa.* J Antibiot 1997, 50(2): 135.

Lepirudin
HBW-023
Refludan®

Anticoagulant

EN: 199872

$C_{287}H_{440}N_{80}O_{111}S_6$

Hoechst Marion Roussel; Behringwerke

Subcutaneous HBW-023 has been compared to i.v. sodium heparin in a multicenter, prospective, randomized, dose-ranging study in 121 evaluable patients with acute lower limb deep venous thrombosis. The anticoagulant activity of HBW-023 was superior to that of heparin and it was also associated with significantly fewer new ventilation/perfusion abnormalities compared to heparin (1).

Results of a study in 909 patients with unstable angina or suspected acute myocardial infarction indicated that HBW-023 (0.2 mg/kg/bolus + 0.10 mg/kg/h infusion or 0.4 mg/kg bolus + 0.15 mg/kg/h infusion) was superior to heparin (5000 IU bolus + 1000-1200 U/h) in preventing cardiovascular death, new myocardial infarction and the need for coronary artery bypass graft surgery (2).

The FDA has approved Hoechst Marion Roussel's lepirudin (Refludan™) for the treatment of heparin-induced thrombocytopenia type II, making this the first product available in the U.S. for the treatment of this condition (3).

Hoechst Marion Roussel has introduced lepirudin (Refludan™) in the U.K., where it is indicated for use as an anticoagulant in patients with heparin-associated thrombocytopenia type II and thromboembolic disease mandating parenteral antithrombotic therapy (4).

Refludan™ has been introduced in the U.S. by Hoechst Marion Roussel for the treatment of thromboembolic complications associated with heparin-induced thrombocytopenia, a rare, allergy-like side effect of heparin (5).

1. Schiele, F., Lindgaerde, F., Eriksson, H., et al. *Subcutaneous recombinant hirudin (HBW-023) versus intravenous sodium heparin in treatment of established acute deep vein thrombosis of the legs: A multicentre prospective dose-ranging randomized trial*. Thromb Haemost 1997, 77(5): 834.

2. Organization to Assess Strategies for Ischemic Syndromes (OASIS) Investigators. *Comparison of the effects of two doses of recombinant hirudin compared with heparin in patients with acute myocardial ischemia without ST elevation. A pilot study*. Circulation 1997, 769.

3. *First Rx for HIT type II approved in U.S.*. Daily Essentials March 10, 1998.

4. *New hirudin option now available in U.K.*. Daily Essentials April 27, 1998.

5. *HMR introduces Refludan in U.S.*. Daily Essentials July 2, 1998.

Original monograph - Drugs Fut 1994, 19: 734.

Additional References

Janssens, U. et al. *Recombinant hirudin in the treatment of heparin induced thrombocytopenia (HIT) type II*. J Am Coll Cardiol 1998, 31(2, Suppl. A): Abst 878-5.

Lamprecht, S. et al. *Estimation of the plasma concentration of recombinant (r)-hirudin (HBW023) that effectively inhibits platelet-dependent thrombogenesis*. Thromb Haemost 1997, Abst PS-2011.

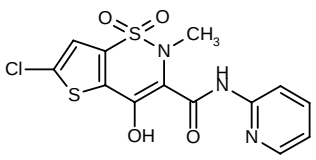
Meiring, S.M. et al. *Determination of the sites of excretion of recombinant (r)-hirudin (HBW 023) and the (r)-hirudin-thrombin complex in baboons*. Thromb Haemost 1997, Abst PS-365.

CPMP approves lepirudin. Daily Essentials March 24, 1997.

Lornoxicam
Safem®
Xefo®

Antiinflammatory

EN: 120668



$C_{13}H_{10}ClN_3O_4S_2$

Nycomed Pharma; Taisho; Merckle; Ivax; Zeneca

Lornoxicam was found to have antiinflammatory effects in the rat carrageenan model of inflammatory nociception. Ten rats were pretreated with lornoxicam (0.1, 0.3, 1, 3 and 9 mg/kg i.v.) and subsequently subjected to an intraplantar carrageenan (6 mg/150 mcl saline) procedure 3 h later. A dose-dependent decrease in carrageenan-induced edema of the paw and ankle was observed in addition to a significant reduction in the total number of spinal c-Fos-LI neurons with administration of 9 mg/kg (75 ± 2%) and 0.3 mg/kg (45 ± 3%). Results suggest that the action of lornoxicam may be peripheral (1).

In an open, crossover, randomized study comparing lornoxicam granules (8 mg) with lornoxicam tablets (8 mg) in 18 healthy male and female volunteers results showed that the two formulations were bioequivalent, although the granular formulation had a faster absorption (2).

Long-term administration of lornoxicam was examined in an open study in which 134 rheumatoid arthritis patients were administered the drug for 12, 24, 30 or 48 weeks. Significant improvements in the number of painful and swollen joints, pain score and upper limb motion were observed with all treatments. Symptom and global improvement scores ranged from 30-38% and 31-40% for all regimens, respectively. The final overall safety and efficacy ratings were 69% and 27%, respectively. Prolonged administration of the drug did not influence the incidence of side effects (3).

  CCC: 0377-8282/98

A double-blind study compared the efficacy of lornoxicam with indomethacin treatment in rheumatoid arthritis patients. When 189 patients were given either lornoxicam (12 mg t.i.d.) or indomethacin (75 mg t.i.d.) for 6 weeks, equivalent efficacy was noted for each drug (29.7% and 17.4% overall improvement ratings, respectively). Safety and efficacy ratings were 80.2% and 73.9% and 28.6% and 15.2% for lornoxicam- and indomethacin-treated patients, respectively. Side effects were experienced by 19.8% lornoxicam-treated patients and 26.1% indomethacin-treated patients (4).

1. Buritova, J., Besson, J.-M. *Dose-related anti-inflammatory/analgesic effects of lornoxicam: A spinal c-Fos protein study in the rat*. Inflamm Res 1998, 47(1): 18.

2. Bareggi, S.R., Gambaro, V., Valenti, M., Benvenuti, C. *Absorption of oral lornoxicam in healthy volunteers using a granular formulation in comparison with standard tablets*. Arzneim-Forsch Drug Res 1997, 47(6): 755.

3. Mizushima, Y., Ichikawa, Y., Kashiwazaki, S., Sugawara, S., Nagaya, I., Hirohata, K., Nobunaga, M. *Clinical evaluation of TS-110 against rheumatoid arthritis - A long-term administration study*. Jpn J Inflamm 1997, 17(4): 389.

4. Mizushima, Y., Ichikawa, Y., Kashiwazaki, S., Sugawara, S., Nagaya, I., Hirohata, K., Nobunaga, M., Iwasaki, Y. *Clinical evaluations of TS-110 against rheumatoid arthritis - Double blind comparative study using indomethacin as a control*. Jpn J Inflamm 1997, 17(4): 421.

Original monograph - Drugs Fut 1992, 17: 683.

Additional References

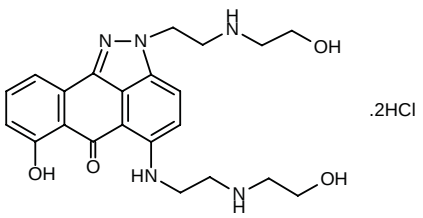
Kohl, C. et al. *Identification of CYP2C9 as the major player in the metabolism of lornoxicam (Xefo®)*. 6th Eur ISSX Meet (June 30-July 3, Gothenburg) 1997, Abst 162.

Radhofer Welte, S., Dittrich, P. *Determination of the novel non-steroidal anti-inflammatory drug lornoxicam and its main metabolite in plasma and synovial fluid*. J Chromatogr B 1998, 707(1-2): 151.

Yamada, T. et al. *Reproductive and developmental toxicity studies of lornoxicam*. Pharmacometrics 1997, 54(4): 235.

Losoxantrone Hydrochloride *Antineoplastic*

EN: 109025



$C_{22}H_{27}N_5O_4.2HCl$ **Warner-Lambert; DuPont Merck**

A phase III randomized trial comparing paclitaxel alone (175 mg/m^2, 3 h infusion) to a combination of paclitaxel and losoxantrone (50 mg/m^2) in 79 patients with stage IV breast cancer determined that the combination of drugs is better than paclitaxel alone. Overall, the combination was well tolerated, with neutropenia and thrombocytopenia being the most frequent side effects (1).

In a disposition study of radiolabelled losoxantrone (50 mg/m^2 i.v.) in 4 patients with solid tumors, total plasma radioactivity demonstrated a similar temporal pattern as the parent drug. Seventy percent of the total radioactivity was recovered in urine and feces, with the majority (87%) excreted in the feces in the form of unmetabolized drug. Urine contained 9% of the initial dose, with less than 10% of this activity representing two known metabolites of losoxantrone. These observations indicate that biliary excretion is the primary form of elimination in humans (2).

A phase III, randomized clinical trial evaluated losoxantrone 50 mg/m^2 in combination with paclitaxel 175 mg/m^2 (3 h infusion) *versus* paclitaxel alone as first-line chemotherapy in 148 patients with metastatic breast cancer. Response rates were 54% and 15%, respectively, for combination therapy and paclitaxel alone; median progression-free survival was 230 days for combination therapy and 111 days for paclitaxel alone. Grade 3-4 neutropenia occurred in 66% and 32% of losoxantrone and paclitaxel patients, respectively (3).

1. Kaufman, P., Harris, R., Skillings, J., Walde, D., Hong, A., Verma, S., Guevin, R., Finizio, M., Joseph, J. *A phase III randomized trial of losoxantrone + paclitaxel versus paclitaxel alone in patients (pts) with stage IV breast cancer*. Proc Amer Soc Clin Oncol 1997, Abst 549.5.

2. Joshi, A., Pieniaszek, H.J. Jr., Richards, L.E., Davidson,A.F., Ratain, M., Cooper, N., Finizio, M., Vokes, E. *Disposition of losoxantrone after intravenous administration of ^{14}C-losoxantrone to cancer patients*. J Clin Pharmacol 1997, 37(9): Abst 44.

3. Kaufman, P.A., Harris, R., Skillings, J., Walde, D., Hong, A., Verma, S., Guevin, R., Joseph, J., Finizio, M. *Losoxantrone + paclitaxel versus paclitaxel alone as first line chemotherapy for metastatic breast cancer (MBC): Final results of a phase III randomized trial*. Proc Amer Soc Clin Oncol 1998, Abst 475.

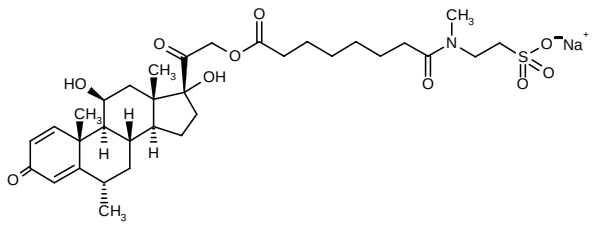
Original monograph - Drugs Fut 1989, 14: 742.

Additional Reference

Shea, J.A. et al. *Quantitation of residual N-methylpyrrolidone in losoxantrone hydrochloride by reversed-phase high-performance liquid chromatography*. J Chromatogr Sci 1998, 36(4): 187.

Methylprednisolone Suleptanate
U-67590A
Corticosteroid
Promedrol®
Medrosol®

EN: 129623



$C_{33}H_{48}NNaO_{10}S$ **Pharmacia & Upjohn**

HPLC analysis of photodegradation products of methylprednisolone suleptanate in aqueous solution revealed the presence of a 1,11-epoxy analog, supporting the existence of the bicyclo[3.1.0]hex-3-en-2-one intermediate during photorearrangement of steroidal cross-conjugated dienones (1).

1. Ogata, M., Noro, Y., Yamada, M., Tahara, T., Nishimura, T. *Photodegradation products of methylprednisolone suleptanate in aqueous solution - Evidence of a bicyclo[3.1.0]hex-3-en-2-one*. J Pharm Sci 1998, 87(1): 91.

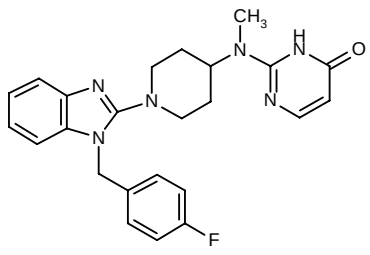
Original monograph - Drugs Fut 1997, 22: 833.

Additional Reference

Okamoto, H. et al. *Effect of ionic strength on solution stability of PNU-67590A, a micellar prodrug of methylprednisolone*. Pharm Res 1997, 14(9): 1181.

Mizolastine
Antihistaminic
Mizollen®
Zolim®
Mizolen®

EN: 134006



$C_{24}H_{25}FN_6O$ **Synthélabo; Mitsubishi Chem.; Ferrer; Schwarz**

Results of several different clinical studies in patients with seasonal and perennial allergic rhinitis have shown that mizolastine 10 mg daily rapidly suppresses wheal and flare reactions and exhibits antiinflammatory and leukotriene antagonistic properties. Drug-related side effects are similar to those with placebo and include sedation, cardiotoxic effects and impairment of psychomotor performance, driving skills and cognitive functions (1).

The pharmacokinetic evaluation of mizolastine administered as an i.v. infusion or orally in tablet or capsule form in 18 healthy volunteers showed that the drug's absorption profile fits a zero-order model after oral administration. Duration of absorption was greater for tablets than for capsules. Mean estimated clearance and apparent volume of distribution after i.v. administration were 4.9 l/h and 89.6 l, respectively, while the mean terminal half-life was 12.9 h (2).

Mizolastine (0.1 mg/kg p.o.) produced long-lasting suppression (4 h) of arachidonic acid-induced inflammation in the rat paw. This effect was not observed after the administration of terfenadine, loratadine and pyrilamine, indicating that mizolastine's inhibitory effect on the inflammatory response is not mediated by its histamine H_1 receptor antagonistic activity (3).

Mizolastine (0.03-3.0 mg/kg p.o.) administered to TNBS-treated mice was shown to reduce nociception, gross intestinal damage and histological damage by 49, 78 and 54%, respectively, while intestinal tissue weight and myeloperoxidase activity were reduced by 69 and 66%, respectively. In contrast, terfenadine (3-30 mg/kg p.o.) tested under the same conditions had no significant effect. These results indicate that the antiinflammatory actions of mizolastine observed in this model were not associated with its H_1-receptor blocking properties (4).

Results of a double-blind, placebo-controlled, crossover study in 24 healthy young volunteers administered mizolastine (10, 20 or 40 mg/day p.o.) demonstrated that the drug had no effect on ECG parameters, especially ventricular hyperpolarization, even up to the highest dose tested (5).

The pharmacokinetic and pharmacodynamic interactions of erythromycin (1 g b.i.d. for 16 days) and mizolastine (10 mg o.d. on days 11-16) were evaluated in 12 healthy volunteers in a double-blind, randomized, crossover study. Results showed significant increases in Cmax and AUC values when mizolastine was added to the regimen. Values for $t_{1/2}\,\beta$ were unaffected, as were relevant ECG parameters (6).

Mizolastine has been introduced in the U.K. as Mizollen® by Lorex Synthélabo for the symptomatic relief of seasonal and perennial allergic rhinoconjunctivitis and urticaria. The product is available as tablets containing 10 mg active drug (7).

Synthélabo has launched mizolastine (Mizolen®) in Spain, where it is indicated for the symptomatic treatment of seasonal or perennial allergic rhinitis and conjunctivitis, and for the treatment of urticaria (8).

1. Bachert, C. *Mizolastine in the treatment of allergic rhinitis and urticaria*. Allergologie 1998, 21(4): S9.

2. Mesnil, F., Dubruc, C., Mentre, F., Huet, S., Mallet, A., Thenot, J.P. *Pharmacokinetic analysis of mizolastine in healthy young volunteers after single oral and intravenous doses: Noncompartmental approach and compartmental modeling*. J Pharmacokinet Biopharm 1997, 25(2): 125.

3. Pichat, P., Angel, I., Arbilla, S. *Anti-inflammatory properties of mizolastine after oral administration on arachidonic acid-induced cutaneous reaction in the rat*. Arzneim-Forsch Drug Res 1998, 48(2): 173.

4. Goldhill, J., Pichat, P., Roome, N., Angel, I., Arbilla, S. *Effect of mizolastine on visceral sensory afferent sensitivity and inflammation during experimental colitis*. Arzneim-Forsch Drug Res 1998, 48(2): 179.

5. Chaufour, S., Caplain, H., Lilienthal, N., L'Héritier, C., Deschamps, C., Rosenzweig, P. *Mizolastine, a new H_1 antagonist, does not affect the cardiac repolarisation in healthy volunteers*. Clin Pharmacol Ther 1998, 63(2): Abst PIII-27.

6. Chaufour, S., Holt, B., Jensen, R., Dubruc, C., Deschamp, C., Rosenzweig, P. *Interaction study between mizolastine, a new H_1 antihistamine, and erythromycin*. Clin Pharmacol Ther 1998, 63(2): Abst PIII-28.

7. *U.K. market introduction for long-acting, nonsedating antihistamine*. Daily Essentials April 29, 1998.

8. *Another European market introduction for mizolastine*. Daily Essentials June 23, 1998.

Original monograph - Drugs Fut 1996, 21: 799.

Additional References

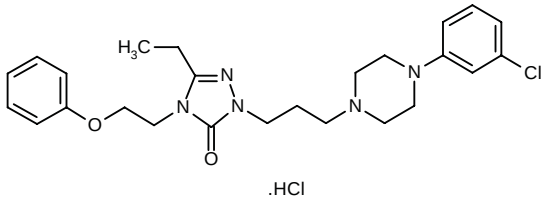
Chaufour, S. et al. *Lack of effect of mizolastine on the safety and pharmacokinetics of digoxin administered orally in repeated doses to healthy volunteers*. Int J Clin Pharmacol Ther 1998, 36(5): 286.

Kumagai, Y. et al. *Pharmacokinetics of mizolastine (MKC-431), a novel antiallergic drug, in the elderly*. Jpn J Clin Pharmacol Ther 1998, 29(4): 699.

First launch for Synthélabo antihistamine. Daily Essentials March 11, 1998.

Nefazodone Hydrochloride *Antidepressant*
Serzone®
Dutonin®
Nefadar®

EN: 090786



$C_{25}H_{32}ClN_5O_2.HCl$ **Bristol-Myers Squibb; Mead Johnson; Lipha; Cephalon**

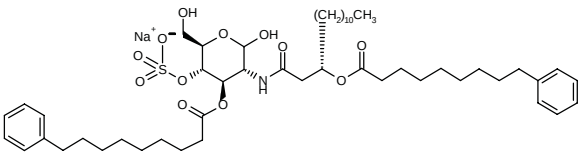
Investigators at McMaster University in Hamilton, Canada, have evaluated nefazodone (mean final dose of 462.5 mg/day) in an open trial in 16 patients with a primary diagnosis of social phobia and a mean disease duration of 19 years. As rated by the Clinical Global Improvement (CGI) scale, 13 patients were considered responders and 3 nonresponders; significant improvement was also reported for psychometric symptoms and disability ratings (1).

1. Van Ameringen, M., Mancini, C., Oakman, J., Collins, S. *An open trial of nefazodone in the treatment of social phobia*. Biol Psychiatry 1997, 42(1, Suppl.): Abst 14-32.

Original monograph - Drugs Fut 1987, 12: 758.

ONO-4007 *Antineoplastic*
Biological Response Modifier

EN: 193855



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

In freshly isolated human monocytes, ONO-4007 slightly enhanced the production of TNF-α, IL-1β, IL-6 and IL-12, whereas it strongly stimulated TNF-α production in GM-CSF- or M-CSF-primed monocytes. Lipopolysaccharide (LPS) significantly enhanced the production of all cytokines in freshly isolated monocytes. Whereas ONO-4007 had no effect on TNF-α production in whole blood, LPS and lipid A strongly stimulated the production of this cytokine. Furthermore, in contrast to ONO-4007, the effects of LPS in GM-CSF-treated human monocytes were attenuated in serum-free culture medium and by anti-CD14 antibody. Thus, it appears that ONO-4007 activates human monocytes/macrophages to release TNF-α only under primed conditions and via a different mechanism than LPS (1).

In vitro studies have shown that induction of TNF-α release was minimal when human monocytes were activated with ONO-4007. However, prior incubation of monocytes with granulocyte-macrophage colony-stimulating factor or macrophage colony-stimulating factor for 3 days resulted in potent ONO-4007-induced TNF-α production. Furthermore, ONO-4007 did not influence IL-1β, IL-6 or IL-12 in either primed or fresh monocytes, in contrast to lipopolysaccharide which increased production in fresh monocytes (2).

The antitumor efficacy of ONO-4007 has been assessed in rats bearing transplanted hepatocellular carcinoma KDH-8. In the groups of animals treated with doses of ONO-4007 (2.5 and 5 mg/kg i.v. on days 7, 14 and 21), only 3/10 and 5/10 rats died from tumors,

respectively, compared to all 10 untreated rats and 9/10 animals administered a dose of 1 mg/kg on this schedule. The expression of IL-1 and interferon alfa was enhanced in tumor tissues in animals treated with ONO-4007, and TNF-α activity was detected in tumor tissues, but not in spleen or peripheral blood, of these animals. The antitumor effects of ONO-4007 were attenuated by concomitant administration of rabbit anti-TNF-α antibody (3).

In vivo and *in vitro* studies have demonstrated that ONO-4001 is effective against TNF-α-sensitive tumors. ONO-4007 increased the mean survival time and cured 70% and 50% of rats implanted with hepatocellular carcinoma (KDH-8) at doses of 2.5 and 5.0 mg/kg, respectively, but had no effect in rats implanted with fibrosarcoma (KMT-17) or mammary adenocarcinoma (SST-2. *In vitro* studies using tumor tissue showed that ONO-4007 stimulated mRNA expression of IL-1α, IL-6 and TNF-α, while IL-2, IL-4, IL-10 and interferon expression were unaffected. Although ONO-4007 did not directly influence KDH-8 cell growth, it dose-dependently induced TNF-α production in tumor tissue (4).

In mice inoculated with MM46 mammary carcinoma, peak intratumoral TNF production was 100-fold less after treatment with ONO-4007 (10 mg/kg i.v.) than after treatment with LA-15-PP (0.1 mg/kg). Similarly, ONO-4007 was less potent than LA-15-PP in inducing systemic TNF production and acute pathological symptoms. Only tolerance in systemic TNF production occurred with ONO-4007, while LA-15-PP produced marked tolerance in systemic and intratumoral TNF production. Both compounds had significant antitumor effects (5).

In a phase I trial in 31 cancer patients administered escalating doses of ONO-4007 (0.5, 1.0, 2.0, 5.0, 10, 20, 50, 75 and 100 mg i.v.), dose-limiting toxicity was fever and chills and the maximum tolerated dose was found to be 100 mg. Patients receiving doses of 50-100 mg had detectable TNF-α production in serum, no tolerance to this effect developing on repeated administration. A phase II trial was commenced in colon cancer on the basis of these results. *In vitro* studies using peripheral blood mononuclear cells isolated from gastric cancer patients showed significantly enhanced TNF-α production by coculture with autologous tumor cells in the presence of ONO-4007 (6).

1. Matsumoto, N., Ikeda, H., Sasaki, Y. *ONO-4007, an antitumor lipid A analog, induces TNF-α production by human monocytes only under primed state*. 12th Annu Sci Meet Soc Biol Ther: Mol Approach Biother Cancer (Oct 22-25, Pasadena) 1997, Abst 84.

2. Matsumoto, N., Aze, Y., Akimoto, A., Fujita, T. *ONO-4007, an antitumor lipid A analog, induces tumor necrosis factor-α production by human monocytes only under primed state: Different effects of ONO-4007 and lipopolysaccharide on cytokine production*. J Pharmacol Exp Ther 1998, 284(1): 189.

3. Hosokawa, M., Kuramitsu, Y., Matsushita, K., Kobayashi, M. *Therapeutic effects of ONO-4007, a derivative of lipid A on a rat hepatocellular carcinoma and role of TNF-α production in treated tumor tissue*. 12th Annu Sci Meet Soc Biol Ther: Mol Approach Biother Cancer (Oct 22-25, Pasadena) 1997, Abst 82.

4. Kuramitsu, Y., Nishibe, M., Ohiro, Y., Matsushita, K., Yuan, L., Obara, M., Kobayashi, M., Hosokawa, M. *A new synthetic lipid A analog, ONO-4007, stimulates the production of tumor necrosis factor-α in tumor tissues, resulting in the rejection of transplanted rat hepatoma cells*. Anti-Cancer Drugs 1997, 8(5): 500.

5. Yamazaki, S.M. *Antitumor effects of synthetic lipid A analog, ONO-4007: Induction of intratumoral TNF with less tolerance in repeating administration*. 20th Int Cong Chemother (June 29-July 3, Sydney) 1997, Abst 2394.

6. Yamaue, H., Tanimura, H., Taguchi, T. *Induction of TNF-alpha in cancer patients by ONO-4007. Results of phase I trial and possible mechanism of TNF-α production*. 12th Annu Sci Meet Soc Biol Ther: Mol Approach Biother Cancer (Oct 22-25, Pasadena) 1997, Abst 83.

Original monograph - Drugs Fut 1997, 22: 841.

Additional References

Aze, Y. et al. *Induction of antitumor activity and intratumoral TNF production by ONO-4007, a synthetic lipid A analog*. J Immunother 1997, 19(6): 467.

Kobayashi, M. et al. *Differentiation-inducing therapy of leukemia by a lipid A-derivative*. 56th Annu Meet Jpn Soc Cancer Res (Sept 25-27, Kyoto) 1997, Abst NJO-05.

Kuramitsu, Y. et al. *Therapeutic effects of a new synthetic lipid A analog, ONO-4007, on rat hepatoma KDH-8 depend on tumor necrosis factor-sensitivity of the tumor cells*. Anti-Cancer Drugs 1997, 8(9): 898.

Kuramitsu, Y. et al. *The mechanism of locally enhanced production of tumor necrosis factor-α in tumor tissues by the administration of a new synthetic lipid A analog, ONO-4007, in hepatoma-bearing rats*. Anti-Cancer Drugs 1997, 8(9): 886.

Matsushita, K. et al. *ONO-4007 induces specific anti-tumor immunity mediated by tumor necrosis factor-alpha*. Anti-Cancer Drugs 1998, 9(3): 273.

Matsushita, K. et al. *Non-specific antitumor transplantation resistance after the treatment with ONO-4007 in KDH-8 bearing rats*. 56th Annu Meet Jpn Soc Cancer Res (Sept 25-27, Kyoto) 1997, Abst VAP-188.

Matsumoto, N. et al. *Role of intratumoral TNF production in antitumor activity of ONO-4007, a lipid A analog*. 56th Annu Meet Jpn Soc Cancer Res (Sept 25-27, Kyoto) 1997, Abst VAP-186.

Nakajima, A. et al. *The antitumoral effect and its mechanism of a synthetic lipid A analogue (ONO-4007) on murine methylcholanthrene induced fibrosarcoma (MCS)*. 56th Annu Meet Jpn Soc Cancer Res (Sept 25-27, Kyoto) 1997, Abst VAP-189.

Oue, T. et al. *TNF production of human alveolar macrophage induced by a synthetic lipid A analog, ONO-4007 in coculture with tumor cells*. 56th Annu Meet Jpn Soc Cancer Res (Sept 25-27, Kyoto) 1997, Abst VAP-197.

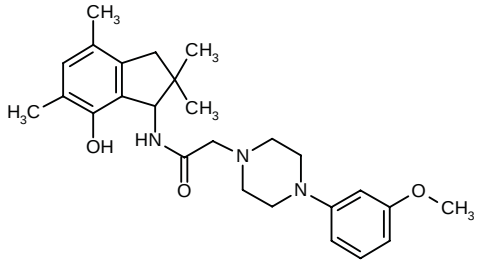
Satoh, M., Yamazaki, M. *Recovery from tolerance in the intratumoral TNF production by lipid A analog, ONO-4007*. 56th Annu Meet Jpn Soc Cancer Res (Sept 25-27, Kyoto) 1997, Abst VAP-192.

Yamazaki, M., Satoh, M. *Differences in TNF production between LPS and ONO-4007, a synthetic lipid A analog*. J Immunother 1997, 19(6): 467.

OPC-14117

Cerebroprotectant

EN: 174064



$C_{26}H_{35}N_3O_3$ **Otsuka**

In a clinical trial in 30 advanced HIV-infected patients with cognitive impairment, patients treated with OPC-14117 (240 mg/day) scored better on a clinical global impression scale compared to placebo-treated patients, while trends toward improvement in the cognitive test score were not statistically significant. Overall, the drug was as well tolerated as placebo. Adverse events led to 2 withdrawals for placebo and 3 for OPC-14117 (1).

Results from a double-blind, randomized, placebo-controlled phase II trial of OPC-14117 as a treatment for Huntington's disease were recently reported. Sixty-four ambulatory patients with Huntington's disease were administered 60, 120 or 240 mg/day of OPC-14117 or a placebo for 12 or 16 weeks followed by an 8- or 4-week period of withdrawal from the drug. Tolerability of OPC-14117 was assessed by the number of patients who completed the initial 12-week treatment program. A total of 56 patients completed the program, 4 patients (1 placebo- and 3 OPC-14117-treated patients) withdrawing due to persistent elevations in serum transaminases. Four other OPC-14117-treated patients withdrew from the program after experiencing either increased involuntary movements, persistent dry eyes or frequent vomiting. However, no significant differences were observed between treated and nontreated patients in terms of side effects, tolerability or the clinical features of Huntington's disease. OPC-14117 appeared to be a safe and tolerable treatment for Huntingon's disease, although monitoring of liver enzymes is recommended in long-term studies (2).

1. Kieburtz, K., Schifitto, G., McDermott, M., et al. *Safety and tolerability of the antioxidant OPC-14117 in HIV-associated cognitive impairment*. Neurology 1997, 49(1): 142.

2. Shoulson, I., Penney, J., Kieburtz, K., et al. *Safety and tolerability of the free-radical scavenger OPC-14117 in Huntington's disease*. Neurology 1998, 50(5): 1366.

Original monograph - Drugs Fut 1993, 18: 707.

Additional Reference

Greenamyre, J.T. et al. *Experimental therapeutics in a model of Huntington's disease*. Soc Neurosci Abst 1996, 22(Part 1): Abst 92.13.

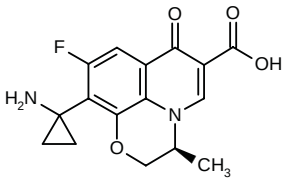
Pazufloxacin

Fluoroquinolone Antibacterial

T-3762 (as mesylate)

Pasil®

EN: 166473



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

Pazufloxacin treatment (200 mg t.i.d. for 3 days) produced negative culture results in only 28/42 men with gonococcal urethritis. Subsequent genetic and DNA sequence analysis revealed a high prevalence of fluoroquinolone-resistant isolates with Ser^{91}-to-Phe mutation in GyrA, indicating that this particular point mutation contributed to the low efficacy rate of pazufloxacin (1).

Orally administered pazufloxacin given as single or multiple doses showed good penetration into human gallbladder tissue and bile in patients. An efficacy rate of 93.3% was obtained in 10 patients with surgical infections administered doses of 100-200 mg t.i.d. for 3-10 days (2).

Pharmacokinetic evaluation of T-3762 (300 or 500 mg i.v.) in a phase II trial yielded maximum plasma concentrations of 15 μg/ml, with a half-life of 2 h. Maximum concentrations of the drug were found in urine and bile, with concentrations in bile being 2-3 times higher than those in blood. Drug concentrations in sputum were 5-14 μg/ml (3).

Intravenous T-3762 (300 or 500 mg b.i.d. or q.i.d for 3-14 days) was evaluated in 278 patients with mild or severe chronic respiratory tract infection. The clinical and total bacteriological efficacy rates were 75.1 and 69.2%, respectively. The drug was effective against Gram-positive, Gram-negative and multiple bacteria with eradication rates of 82.9, 67.3 and 42.9%, respectively. Major side effects involved the stomach and nervous system, and laboratory tests revealed increases in eosinophils and transaminases (4).

The antibacterial activity of intravenous T-3762 (300 or 500 mg b.i.d. or q.i.d. for 5 days) was evaluated in patients with complicated urinary tract infections. The drug was bactericidal against both Gram-positive (79.3%) and Gram-negative bacteria (91.9%), with an overall bactericidal rate of 85.9%. Side effects and abnormalities in laboratory values were reported in 1.1% and 8.0% of patients, respectively (5).

T-3762 (300 or 500 mg i.v. b.i.d. or q.i.d. for 3-14 days) was evaluated in 83 patients with postoperative infections, including peritonitis, pneumonia and septicemia. The drug was effective in 35/40 (87.5%) patients with mild

infection and 27/36 (75.0%) patients with severe infection. In cases of *Pseudomonas aeruginosa* infection, the compound was effective in 12/15 (80.0%) patients. The bactericidal rate was 68.8%. No adverse events were observed, although abnormal laboratory values were reported in 12.5% of patients (6).

1. Tanaka, M., Matsumoto, T., Sakumoto, M., et al. *Reduced clinical efficacy of pazufloxacin against gonorrhea due to high prevalence of quinolone-resistant isolates with the GyrA mutation*. Antimicrob Agents Chemother 1998, 42(3): 579.

2. Tanimura, H., Uchiyama, K., Ishimoto, K., Ochiai, M., Iwakura, S. *Concentrations of pazufloxacin in human bile and gallbladder tissue and its clinical effects on surgical infections*. 20th Int Cong Chemother (June 29-July 3, Sydney) 1997, Abst 4259.

3. Matsumoto, F. *The pharmacokinetics of intravenous T-3762, a new quinolone*. Jpn J Chemother 1997, 45(Suppl. B): Abst 8.

4. Shimada, K. *Clinical evaluation of intravenous T-3762, a new quinolone antibacterial, in infections in the field of internal medicine*. Jpn J Chemother 1997, 45(Suppl. B): Abst 9.

5. Matsumoto, T. *Clinical study of intravenous T-3762, a new quinolone antibacterial, in complicated urinary tract infections*. Jpn J Chemother 1997, 45(Suppl. B): Abst 10.

6. Tanimura, H. *Clinical study of intravenous T-3762, a new quinolone antibacterial, in infections during emergency surgery*. Jpn J Chemother 1997, 45(Suppl. B): Abst 11.

Original monograph - Drugs Fut 1993, 18: 717.

Additional References

Matsumoto, F. *The pharmacokinetics of intravenous T-3762, a new quinolone*. Jpn J Chemother 1997, 45(Suppl. B): Abst 8.

Matsumoto, T. *Clinical study of intravenous T-3762, a new quinolone antibacterial, in complicated urinary tract infections*. Jpn J Chemother 1997, 45(Suppl. B): Abst 10.

Mikamo, H. et al. *Therapeutic effects of an injectable new quinolone, pazufloxacin, against polymicrobial infections in the uterine endometritis model*. Chemotherapy 1998, 44(2): 99.

Niki, Y. et al. *Effect of pazufloxacin mesylate on theophylline concentration in serum*. 20th Int Cong Chemother (June 29-July 3, Sydney) 1997, Abst 4263.

Shimada, K. *Clinical evaluation of intravenous T-3762, a new quinolone antibacterial, in infections in the field of internal medicine*. Jpn J Chemother 1997, 45(Suppl. B): Abst 9.

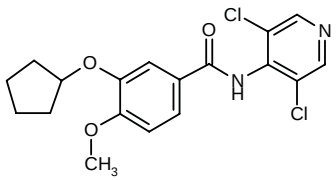
Taba, H. et al. *In vitro antimicrobial activities of new fluoroquinolones against clinical isolates of Streptococcus pneumoniae*. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst E-60.

Tanimura, H. *Clinical study of intravenous T-3762, a new quinolone antibacterial, in infections during emergency surgery*. Jpn J Chemother 1997, 45(Suppl. B): Abst 11.

Piclamilast

Antiinflammatory
Phosphodiesterase IV Inhibitor

EN: 197379



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

In vitro studies using bronchial rings from nonatopic patients showed that LTC_4 and allergen responses were unaffected by exposure to RP-73401 (300 nM) or motapizone (1 μM) alone, whereas a combination of RP-73401 (10 nM) and motapizone (100 nM) completely abolished the allergen responses (1).

The efficacy and toxicity of RP-73401 was evaluated in several *in vitro*, *in vivo* and *ex vivo* experiments. Inhibition studies of phosphodiesterase 4 in guinea pig macrophages yielded an IC_{50} of 0.48 nM, while lipopolysaccharide-induced TNF-α release in whole dog blood was inhibited (IC_{50} = 22.9 nM). Evaluation of inhibition of ovalbumin-induced bronchospasm in rats produced an ED_{50} value of 1 mg/kg. The nonemetic dose of RP-73401 was 0.1 mg/kg following oral administration in dogs, while the therapeutic ratio, defined as emesis/in vivo efficacy, in rats and dogs was 0.1 and 10 mg/kg, respectively (2).

Administration of inhaled and oral RP-73401 (400 mcg) in healthy male and female volunteers resulted in slightly higher AUC, C_{max}, t_{max} and $t_{1/2}$ values in females than in males. Maximum concentrations were reached after 0.5-1.0 h, with a half-life of 5-7.5 h in both groups. Compared to males in the fasted group, the fed group had reductions of 51% in C_{max} and a prolongation in t_{max} from 1.1 to 5.5 h, while AUC and $t_{1/2}$ values did not change (3).

1. Schmidt, D., Watson, N., Morton, B.E., Dent, G., Magnussen,H., Rabe, K.F. *Phosphodiesterase inhibitors and LTC_4-induced responses in passively sensitized human airways in vitro*. Am J Respir Crit Care Med 1998, 157(3): A660.

2. Escott, K.J., Birrell, M., Webber, S.E., Souness, J.E., Geiger, L.E., Aldous, D., Sargent, C.A. *Efficacy versus toxicity of PDE_4 inhibitors*. Am J Respir Crit Care Med 1998, 157(3): A413.

3. Vaccaro, S.K., Argenti, D., Shah, B., Gillen, M.S., Rohatagi, S., Jensen, B.K. *Effect of food and gender on the pharmacokinetics of RP 73401, a phosphodiesterase IV inhibitor (PDEI)*. J Clin Pharmacol 1997, 37(9): Abst 28.

Original monograph - Drugs Fut 1995, 20: 793.

Additional References

Aldous, D. et al. *The design and synthesis of PDE4 inhibitors*. 1st Ital Swiss Meet Med Chem (Sept 23-26, Torino) 1997, 46.

Boichot, E. et al. *In vitro anti-inflammatory activities of a new series of selective phosphodiesterase 4 inhibitors derived of 9-benzyladenines*. Am J Respir Crit Care Med 1998, 157(3): A141.

Escott, K.J. et al. *Pharmacological profiling of phosphodiesterase 4 (PDE4) inhibitors and analysis of the therapeutic ratio in rats and dogs*. Br J Pharmacol 1998, 123(Suppl.): Abst 40P.

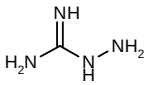
Marx, D. et al. *Inhibition of allergen induced bronchial hyperreactivity (BHR) in BP-2 mice by cyclosporine A, fluticasone and selective PDE4-inhibitors*. J Allergy Clin Immunol 1998, 101(1, Part 2): Abst 42.

Newbold, P. et al. *Effect of type IV phosphodiesterase inhibitors against antigen-induced eosinophilia in sensitised guinea-pigs*. Br J Pharmacol 1998, 123(Suppl.): Abst 44P.

Stevens, J.C. et al. *Human liver CYP2B6-catalyzed hydroxylation of RP 73401*. J Pharmacol Exp Ther 1997, 282(3): 1389.

Pimagedine *Symptomatic Antidiabetic*

EN: 182590



CH_6N_4 **Alteon; Yamanouchi; Gamida; Genentech**

Arterial stiffening and age-related cardiac hypertrophy were prevented in normotensive rats following aminoguanidine treatment (1 g/l in drinking water from age 24-30 months). Heart weight was reduced in 30-month old treated rats as compared to controls and mesangial surface in treated animals was also reduced 30%; the effects were independent of alterations in collagen and elastin content. No significant differences were observed in aortic wall media thickness and smooth muscle cell number between groups. Aminoguanidine treatment also prevented age-related increases in aortic impedance and decreases in carotid distensibility, suggesting that aminoguanidine affects the cross-linking of extracellular matrix proteins (1).

The effects of aminoguanidine and N^{ω}-nitro-L-arginine (NNA) on relaxation responses to acetylcholine (ACh) in rat intact aorta and small mesenteric arteries were investigated *in vitro*. Preconstricted vessel rings were treated with 10^{-8}-10^{-4} M ACh resulting in concentration-dependent relaxation. Following washout, rings were exposed to 10^{-5}-10^{-4} M of either aminoguanidine or NNA. NNA significantly and dose-dependently reduced ACh-induced relaxation in the aorta, whereas aminoguanidine was ineffective. In contrast, both agents inhibited ACh-induced relaxation (100%) in third-generation mesenteric arteries. Results suggest that relaxation in small arteries as opposed to intact aorta involves an inducible nitric oxide synthase-dependent mechanism (2).

Results of an *in vivo* study demonstrated that nitric oxide synthase is expressed during acute experimental autoimmune encephalomyelitis (EAE) in mice. SLJ/J mice injected with bovine myelin basic protein, killed *Mycobacterium tuberculosis* and *Bordetella pertussis* were treated on the first day of observed neurological deficit with aminoguanidine (100 mg/kg s.c. b.i.d.) or the vehicle for 11 days. Neurological scores were reduced in aminoguanidine-treated animals as compared to controls on the 4th day of EAE (1.6 ± 0.2 *vs.* 2.6 ± 0.3) and reductions in scores were maintained throughout the 14th day after EAE symptom onset (1.3 ± 0.3 *vs.* 2.4 ± 0.4) (3).

Aminoguanidine demonstrated beneficial and dose-dependent protective effects in rats subjected to occlusion of the middle cerebral artery. These benefits were equal regardless of whether treatment began 12 or 24 h after ischemia. The results suggest that iNOS inhibitors may be potentially useful in the treatment of ischemic stroke (4).

In rats with sciatic nerve crush injury, treatment with aminoguanidine (0.25, 0.5 or 1.0 g/kg by gavage) prior to and 1, 7, 14 and 21 days following injury did not protect animals against functional deficiency or produce changes in electrophysiological recovery as compared to untreated animals (5).

Arterial pressure and renal cortical blood flow were not altered in rats infused with aminoguanidine (60 mg/kg/h i.v.) for 40 min, whereas medullary blood flow was slightly increased and urine flow was significantly decreased during drug administration. In contrast, chronic infusion (10 mg/kg/h i.v.) in uninephrectomized rats on a high salt diet caused a significant increase in arterial blood flow 6 days after treatment onset; administration of L-arginine in drinking water blocked the aminoguanidine-induced increase. Although calcium-dependent nitric oxide synthase activity was reduced in 49% of treated animals, activity in the medulla was unaltered, indicating a possible specificity of aminoguanidine action (6).

Aminoguanidine treatment (250 mg/kg for 18 days) in diabetic rats resulted in an increased number of leukocyte-endothelial interactions including rolling, sticking and migration of leukocytes, usually found to be reduced in the diabetic state. When nondialyzed material from plasma of diabetic animals was injected i.v. to control nondiabetic rats, a decrease in the number of leukocyte-endothelial interactions was observed; this effect was inhibited by chronic aminoguanidine administration to the diabetic plasma donors. Nondialyzed material from normal rats had no effect. It was concluded that aminoguanidine may inhibit part of the glycosylation process associated with defective leukocyte behavior in diabetes mellitus (7).

After 2 months of treatment with aminoguanidine (50 mg/kg/day), rats were given N^{G}-nitro-L-arginine (25 mg/kg/day) for 1 week followed by L-arginine (2.5 mg/100g/min i.v.) to reverse inhibition of nitric oxide synthesis. Prior to L-arginine infusion, no differences between aminoguanidine-treated and control animals were noted in body or kidney weight, systolic blood pressure, urine flow rate or urinary protein or nitric oxide metabolite excretion. Following L-arginine treatment, mean arterial blood pressure was reduced 10-15% in all

animals. Aminoguanidine-treated animals had increases in urine flow, inulin clearance, and sodium and nitric oxide metabolite excretion as compared to controls (8).

In a rat model of focal cerebral ischemia, 4 and 24 h following transient occlusion of the middle cerebral artery for 2 h, rats were administered either aminoguanidine (30, 100 or 300 mg/kg i.p.) or 7-nitroindazole (10, 25 or 50 mg/kg i.p.). 7-Nitroindazole treatment resulted in dose-dependent protection of infarct size with rates of 12, 43 and 61% for the respective doses. Aminoguanidine was only effective at 100 mg/kg, resulting in a significant (32%) reduction in infarct volume; 30 mg/kg only tended to decrease infarct volume, while 71.4% of animals receiving 300 mg/kg died following occlusion (9).

In an *in vitro* study in streptozotocin-induced, surgically azotemic diabetic rats with hyperglycemia and renal insufficiency, a significantly higher rate of survival was observed in aminoguanidine-treated rats as compared to untreated rats, suggesting the therapeutic potential of the drug in human diabetes (10).

Results of *in vivo* studies in mice have shown that aminoguanidine (2.5% solution in drinking water) administered 7 days prior to and 5 days after immunization with *S. typhimurium* reduced splenic inflammatory responses, demonstrating that nitric oxide mediates *S. typhimurium*-induced immuosuppression (11).

Alteon has extended its phase II trial of pimagedine in diabetic patients with end-stage renal disease (ESRD) to phase III, with mortality as the primary endpoint of the study. This decision was based on an interim analysis of the ongoing phase II trial which indicated a positive trend in the mortality of treated patients *versus* placebo-treated patients (12).

The FDA has approved the continuation of Alteon's ACTION I trial of pimagedine and has denied approval for continuation of the ACTION II trial. This decision is concurrent with the recent recommendations of an independent external safety monitoring committee. ACTION I, a pivotal phase III clinical trial of pimagedine in patients with type I diabetes and progressive kidney disease, began in 1994 and involves 690 patients at 56 sites in North America. ACTION II, a pivotal phase III clinical trial for the treatment of type II diabetics with progressive kidney disease, will be discontinued due to an insufficient risk/benefit ratio based upon currently available data. The third pivotal phase III trial of pimagedine, involving diabetic patients with end-stage renal disease (ESRD), is currently ongoing. A separate independent committee overseeing the ESRD trial has recommended continuation of this trial after a review of the unblinded data (13).

1. Corman, B., Duriez, M., Poitevin, P., Heudes, D., Bruneval,P., Tedgui, A., Levy, B.I. *Aminoguanidine prevents age-related arterial stiffening and cardiac hypertrophy*. Proc Natl Acad Sci USA 1998, 95(3): 1301.

2. Forster, C., Iral, A., Razavi, H. *The effect of aminoguanidine on acetylcholine-induced relaxation responses in rat blood vessels*. Br J Pharmacol 1998, 123(Suppl.): Abst 13P.

3. Delay-Goyet, P., Champion, A., Cottez, D., Goniot, P., Chaillou, P., Stutzmann, J.-M. *Effect of aminoguanidine, an NO synthase inhibitor, in acute experimental auto-immune encephalomyelitis (EAE) in the mouse*. Multiple Scler 1997, 3(5): Abst P162.

4. Nagayama, M., Zhang, F., Iadecola, C. *Post-treatment with aminoguanidine reduces cerebral ischemic damage and neurological deficits in rats with middle cerebral artery occlusion*. Stroke 1998, 29(1): Abst P171.

5. Tariq, M., Arshaduddin, M., Biary, N., Al Deeb, S., Al Moutaery, K. *Effect of aminoguanidine, a nitric oxide synthase inhibitor, on sciatic nerve crush injury in rats*. Med Sci Res 1997, 25(12): 815.

6. Mattson, D.L., Maeda, C.Y., Bachman, T.D., Cowley, A.W. *Inducible nitric oxide synthase and blood pressure*. Hypertension 1998, 31(1): 15.

7. Sannomiya, P., Oliveira, M.A., Fortes, Z.B. *Aminoguanidine and the prevention of leukocyte dysfunction in diabetes mellitus: A direct vital microscopic study*. Br J Pharmacol 1997, 122(5): 894.

8. Waz, W.R., Van Liew, J.B., Feld, L.G. *Nitric oxide-inhibitory effect of aminoguanidine on renal function in rats*. Kidney Blood Press Res 1997, 20(4): 211.

9. Spinnewyn, B., Surget, M.O., Pallardy, C., Chabrier, P.E. *Comparison of the effects of aminoguanidine and 7-nitroindazole in a rat model of focal cerebral ischemia*. J Cereb Blood Flow Metab 1997, 17(Suppl. 1): S104.

10. Friedman, E.A., Distant, D.A., Fleishhacker, J.F., Boyd, T.A., Cartwright, K. *Aminoguanidine prolongs survival in azotemic-induced diabetic rats*. Am J Kidney Dis 1997, 30(2): 253.

11. Shearer, A.M., Eisenstein, T.K., Schwacha, M.G. *Aminoguanidine given in vivo prevents nitric oxide mediated immunosuppression following Salmonella typhimurium infection*. 97th Gen Meet Amer Soc Microbiol (May 4-7, Miami Beach) 1997, Abst E-25.

12. *Alteon's pimagedine progresses to phase III*. Daily Essentials Aug 4, 1997.

13. *FDA decides future of pimagedine trials*. Daily Essentials March 26, 1998.

Original monograph - Drugs Fut 1994, 19: 740.

Additional References

Behboo, R. et al. *Aminoguanidine inhibits the generation of nitric oxide in vitro and prolongs islet xenograft survival in rats*. Transplant Proc 1997, 29(4): 2152.

Brian, J.E. Jr., Faraci, F.M. *Tumor necrosis factor-α-induced dilatation of cerebral arterioles*. Stroke 1998, 29(2): 509.

Cotter, M.A., Cameron, N.E. *Metal chelator, free radical scavenger and aminoguanidine prevent defective endothelium-dependent relaxation in diabetic rat aorta*. 32nd Res Symp Amer Diabetes Assoc. The Role of Oxidants and Antioxidant Therapy in Diabetic Complications (Nov 15-17, Orlando) 1996, Abst 51.

Degenhardt, T.P. et al. *Aminoguanidine inhibits albuminuria in diabetic rats without inhibiting formation of AGEs in skin collagen*. 32nd Res Symp Amer Diabetes Assoc. The Role of Oxidants and Antioxidant Therapy in Diabetic Complications (Nov 15-17, Orlando) 1996, Abst 34.

Fujihara, C.K. et al. *Aminoguanidine ameliorates renal injury in the renal ablation model*. J Am Soc Nephrol 1997, Abst A2867.

Giardino, I. et al. *Aminoguanidine inhibits reactive oxygen species formation, lipid peroxidation, and oxidant-induced apoptosis*. Diabetes 1998, 47(7): 1114.

Gouri, E. et al. *Aminoguanidine treatment of diabetic rats does not prevent glycosylation of proteins or the toxic effects of the serum on PC-12 cells*. 32nd Res Symp Amer Diabetes Assoc. The Role of Oxidants and Antioxidant Therapy in Diabetic Complications (Nov 15-17, Orlando) 1996, Abst 43.

Goyan, J.E. *The A.G.E. pathway: Current approaches to therapeutic intervention*. IBC Post-Conf Workshop - Drug Discov Dev Diabet Complicat (Nov 1, Washington DC) 1996, 1996.

Holstad, M. et al. *Inhibition of nitric oxide formation by aminoguanidine: An attempt to prevent insulin-dependent diabetes mellitus*. Gen Pharmacol 1997, 29(5): 697.

Hou, F.F. et al. *Aminoguanidine inhibits advanced glycation end products formation on β_2-microglobulin*. J Am Soc Nephrol 1998, 9(2): 277.

Kavuklu, B. et al. *Aminoguanidine inhibits endotoxin-promoted bacterial translocation*. Clin Microbiol Infect 1997, 3(Suppl. 2): Abst P842.

Lee, F.Y. et al. *Aminoguanidine corrects hyperdynamic circulation without ameliorating portan hypertension and portal hypertensive gastropathy in anestethized portal hypertensive rats*. J Hepatol 1997, 26(3): 687.

Panagiotopoulos, S. et al. *Aminoguanidine has an anti-atherogenic effect in the cholesterol-fed rabbit*. Atherosclerosis 1998, 136(1): 125.

Rovira, I. et al. *Haemodynamic effects of aminoguanidine in experimental septic shock*. Br J Anaesth 1996, 76(Suppl. 2): Abst A.353.

Tatsuta, M. et al. *Enhancement by aminoguanidine of gastric carcinogenesis induced by N-methyl-N'-nitro-N-nitrosoguanidine in Wistar rats*. Oncol Rep 1997, 4(4): 733.

Turner, C.H. et al. *Effects of nitric oxide synthase inhibitors on bone formation in rats*. Bone 1997, 21(6): 487.

Wolffenbuttel, B.H.R. et al. *In vitro anti-oxidative effects of aminoguanidine are dependent on LDL-concentration*. 32nd Res Symp Amer Diabetes Assoc. The Role of Oxidants and Antioxidant Therapy in Diabetic Complications (Nov 15-17, Orlando) 1996, Abst 23.

Yildiz, G. et al. *Comparison of antioxidant activities of aminoguanidine, methylguanidine and guanidine by luminol-enhanced chemiluminescence*. Br J Pharmacol 1998, 124(5): 905.

Yu, P.H., Zuo, D.M. *Aminoguanidine inhibits semicarbazide-sensitive amine oxidase activity: Implications for advanced glycation and diabetic complications*. Diabetologia 1997, 40(11): 1243.

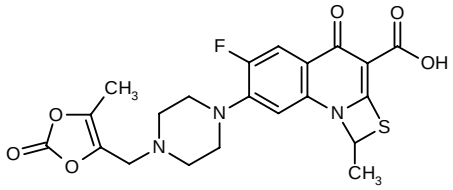
Alteon and Genentech collaborate on diabetic complications therapy. Daily Essentials Dec 15, 1997.

Alteon contracts with Ganes Chemicals as bulk supplier of pimagedine. Alteon Inc. Press Release 1997, Sept 18.

Prulifloxacin Quisnon®

Fluoroquinolone Antibacterial

EN: 151640



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

In a double-blind study comparing prulifloxacin (300 mg b.i.d.) and ofloxacin (200 mg t.i.d.) in 201 patients with bacterial pneumonia, clinical efficacy rates were 96.5% and 93.0% in the prulifloxacin- and ofloxacin-treated groups, respectively. Bacteriological elimination rates for prulifloxacin and ofloxacin were 90.3% and 95.2%, respectively. Side effects were observed in 2.1% and 3.3% of patients treated with prulifloxacin and ofloxacin, respectively, while laboratory abnormalities were found in 16.0% and 16.1% of the respective groups. Overall safety rates for both treatment groups were approximately 82%, with usefulness rates of 94.2% and 89.0% in the prulifloxacin- and ofloxacin-treated groups, respectively (1).

Results of a double-blind comparative study of prulifloxacin and ofloxacin in 211 patients with lower chronic respiratory infection demonstrated similar clinical efficacy rates for the two drugs (94.3% and 96.6% for prulifloxacin and ofloxacin, respectively). Bacteriological elimination rates were 77.5% and 82.5% for prulifloxacin and ofloxacin, respectively. The incidence of side effects was low in both treatment groups. Respective usefulness ratings were 94.3% and 94.4% for prulifloxacin and ofloxican (2).

A prulifloxacin-hydrolyzing enzyme was isolated from rat serum and identified as paraoxonase. Additional experiments with 67 healthy volunteers demonstrated a positive correlation between the enzyme and the hydrolysis of prulifloxacin in human serum, although there was a 9-fold variation in paraoxonase activity and a 2-fold variation in prulifloxacin hydrolysis (3).

1. Kobayashi, H., Kawai, S., Sakayori, S. et al. *A double-blind comparative study of prulifloxacin and ofloxacin in bacterial pneumonia*. Jpn J Chemother 1997, 45(5): 271.

2. Kobayashi, H., Kawai, S., Sakayori, S. et al. *A double-blind comparative study of prulifloxacin and ofloxacin in lower chronic respiratory tract infections*. Jpn J Chemother 1997, 45(5): 294.

3. Tougou, K., Nakamura, A., Watanabe, S., Okuyama, Y., Morino, A. *Paroxonase has a major role in the hydrolysis of prulifloxacin (NM441), a prodrug of a new antibacterial agent*. Drug Metab Dispos 1998, 26(4): 355.

Original monograph - Drugs Fut 1996, 21: 805.

Additional References

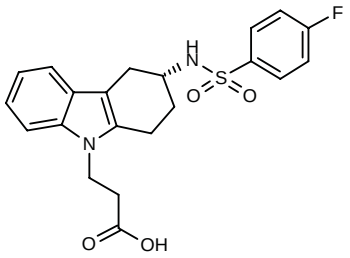
Ozaki, M. et al. *In vivo antibacterial activity of a prodrug of NM394, a thiazetoquinoline carboxylic acid derivative*. Chemotherapy 1998, 44(1): 21.

Taba, H. et al. *In vitro antimicrobial activities of new fluoroquinolones against clinical isolates of Streptococcus pneumoniae*. 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst E-60.

Ramatroban

Antiallergic/Antiasthmatic
Thromboxane A_2 Antagonist

EN: 137774



$C_{21}H_{21}FN_2O_4S$ **Bayer; Esteve**

Ramatroban (1-10 mg/kg) administered intraduodenally in bile duct-cannulated male rats and female dogs was absorbed rapidly and completely. Bioavailability following oral administration was complete in dogs but reached only 50% in rats due to presystemic elimination. Food affected the rate but not the extent of absorption in rats. Total plasma clearance was 1.2 l/h/kg and 0.7 l/h/kg in rats and dogs, respectively. AUC increased dose-dependently following oral administration in rats, while increases in C_{max} were unproportional. Excretion of the radiolabelled compound was mainly via biliary and fecal routes. In rats, a significant sex difference was observed after oral administration (1).

Radioactivity of [^{14}C]-ramatroban administered orally to rats was localized mainly in the liver and kidneys, with tissue-to-plasma ratios at tmax of 20 and 6.3, respectively. Penetration of the blood-brain barrier was minimal, and repeated oral administration did not produce significant accumulation. Drug distribution was similar in male and pregnant rats although a higher degree of radioactivity was observed in the females, with fetal concentrations reaching maximum values after 7 h. Drug distribution in the fetus and mother was similar, with high concentrations being reached in the kidney and gastrointestinal tract. AUC values in fetal plasma were 68% of those in maternal plasma (2).

The population pharmacokinetics of single (25-150 mg) and multiple (50-100 mg b.i.d. for 9 days) doses of oral ramatroban were evaluated in a cohort of 280 subjects, including healthy volunteers and patients with bronchial asthma and perennial allergic rhinitis. Analysis of the data produced model equations for the determination of total body clearance, apparent volume of distribution and the absorption rate constant, indicating that population pharmacokinetics in conjunction with post- marketing analysis may be useful for improving dosage guidelines for ramatroban in the future (3).

1. Boberg, M., Ahr, H.-J., Beckermann, B., Bühner, K., Siefert, H.-M., Steinke, W., Wünsche, C., Hirayama, M. *Pharmacokinetics and metabolism of the new thromboxane A_2 receptor antagonist ramatroban in animals. 1st communication: Absorption, concentrations in plasma, metabolism, and excretion after single administration to rats and dogs*. Arzneim-Forsch Drug Res 1997, 47(8): 928.

2. Steinke, W., Ahr, H.-J., Hirayama, M. *Pharmacokinetics and metabolism of the new thromboxane A_2 receptor antagonist ramatroban in animals. 2nd communication: Distribution to organs and tissues in male, female and pregnant rats, and characteristics of protein binding in plasma*. Arzneim-Forsch Drug Res 1997, 47(8): 939.

3. Tanigawa, T., Okumura, K., Kawano, K., Matsuki, T., Yukawa,E., Higuchi, S. *Population pharmacokinetics of ramatroban in healthy volunteers and patients with bronchial asthma/perennial allergic rhinitis*. Xenobiotic Metab Dispos 1997, 12(2): 121.

Original monograph - Drugs Fut 1991, 16: 701.

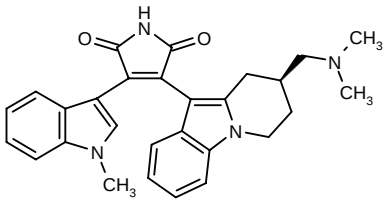
Additional Reference

Kasahara, K. et al. *Modulation of thromboxane A_2 blockade on the sensitivity to platinum agents in lung cancer cell lines*. Proc Amer Assoc Cancer Res 1997, Abst 26.

Ro-32-0432

Antiarthritic
Protein Kinase C Inhibitor

EN: 203111



$C_{28}H_{28}N_4O_2$ **Roche**

Exposure of WSU-CLL B-cell chronic lymphocytic leukemia cells to Ro-32-0432 alone (4 μM) inhibited the translocation of PKCα from the cytosol into the cell membrane, resulting in cell growth inhibition over 72 h. A combination of Ro-32-0432 and fludarabine (0.1-1 μM) produced an additive effect in loss of viability over time. Apoptosis was induced in 22% of cells cotreated with both drugs, compared to 2.05% (Ro-32-0432) and 4.4% (fludarabine) of cells treated with each drug alone (1).

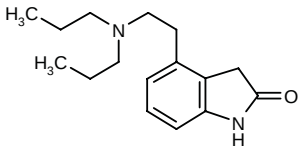
1. König, A., Schwartz, G.K., Al-Katib, A., Mohammad, R.M., Harmon, C., Gabrilove, J.L. *The protein kinase C inhibitor Ro 32-0432 enhances fludarabine-induced apoptosis in WSU-CLL chronic lymphocytic leukemia cells*. Blood 1997, 90(10, Suppl. 1, Part 2): Abst 3641.

Original monograph - Drugs Fut 1993, 18: 727.

Ropinirole
ReQuip®

Antiparkinsonian
Dopamine D_2 Agonist

EN: 100359



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

The pharmacokinetics of ropinirole in patients with Parkinson's disease were shown to be linear after single (2-12 mg) and repeated (1-6 mg b.i.d. or t.i.d.) oral dosing. Peak plasma levels were observed after 1-2 h following single doses, with C_{max} and AUC values increasing proportionally. Oral clearance indicated no significant change in elimination (elimination half-life of approx. 6 h) (1).

Results of a 6-month, randomized, placebo-controlled, double-blind study evaluating the efficacy and safety of ropinirole (0.25 mg t.i.d. titrated to 1.5-8 mg t.i.d.) in 241 patients with early Parkinson's disease showed that there was a significantly greater improvement in the Unified Parkinson's Disease Rating Scale motor score in ropinirole-treated patients compared to those on placebo. Ropinirole was well tolerated, with most adverse events related to peripheral dopaminergic activity (2).

The efficacy and safety of ropinirole and bromocriptine were compared in 335 patients with early Parkinson's disease in a 3-year, double-blind, randomized study. The mean Unified Parkinson's Disease Rating Scale total motor examination scores and the number of improvers on the Clinical Global Impression Scale indicate that ropinirole without the addition of selegiline is effective and superior to bromocriptine. Adverse events, mainly nausea, occurred in 80% of patients in both treatment groups. The incidence of serious adverse events was low in both groups (3% and 6.6% for ropinirole and bromocriptine, respectively) (3).

Results of a 6-month interim analysis of a 5-year study in patients with early Parkinson's disease showed that percentage improvement in the Unified Parkinson's Disease Rating Scale total motor examination score was 44% in levodopa-treated patients and 32% in ropinirole-treated patients; the proportion of responders did not differ significantly between the groups (levodopa, 58%; ropinirole, 48%). However, in patients with more advanced disease, levodopa produced improvement in a significantly higher proportion of patients than ropinirole on the Clinical Global Impression score. The major emergent adverse event in both groups was nausea, and the incidence of serious adverse events was low in both groups (9% and 8% for levodopa and ropinirole, respectively) (4).

1. Taylor, A.C., Beerahee, A., Citerone, D.R., Miller, A., Fuell, D. *Linear pharmacokinetics of ropinirole in patients with Parkinson's disease*. Br J Clin Pharmacol 1998, 45(2): 204P.

2. Adler, C.H., Sethi, K.D., Hauser, R.A., Davis, T.L., Hammerstad, J.P., Bertoni, J., Taylor, R.L., Sanchez Ramos, J., O'Brien, C.F. *Ropinirole for the treatment of early Parkinson's disease*. Neurology 1997, 49(2): 393.

3. Korczyn, A.D., Brooks, D.J., Brunt, E.R., Poewe, W.H., Rascol, O., Stocchi, F. *Ropinirole versus bromocriptine in the treatment of early Parkinson's disease: A 6-month interim report of a 3-year study*. Mov Disord 1998, 13(1): 46.

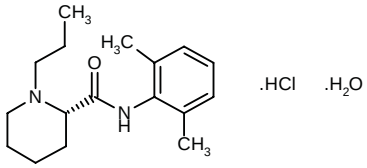
4. Poewe, W.H., Rascol, O., Brooks, D.J., Brunt, E.R., Korczyn, A.D., Stocchi, F. *Ropinirole in the treatment of early Parkinson's disease: A 6-month report of a 5-year levodopa-controlled study*. Mov Disord 1998, 13(1): 39.

Original monograph - Drugs Fut 1989, 14: 781.

Ropivacaine Hydrochloride
Naropin®

Local Anesthetic

EN: 150269



$C_{17}H_{26}N_2O.HCl.H_2O$ **Astra**

Patient-controlled interscalene analgesia with ropivacaine (0.75%, 30 ml) was compared to patient-controlled analgesia with nicomorphine (2 or 3 mg as 0.5 mg/h bolus) in 55 patients undergoings major shoulder surgery. Pain control and patient satisfaction at the end of the 2-day study period were rated better in the ropivacaine group than in the nicomorphine group. Side effects of nausea and pruritis were observed more frequently in nicomorphine-treated patients (1).

In a crossover, randomized, double-blind study comparing i.v. infusions of ropivacaine and bupivicaine in 12 volunteers, ropivacaine was found to have fewer central nervous and cardiovascular effects than bupivacaine. The maximun tolerated doses for CNS symptoms were higher in 9/12 subjects after ropivacaine compared to 3/12 with bupivacaine, and time to disappearance of all symptoms was shorter after ropivacaine (2).

Results of a multicenter, randomized, double-blind study in women in labor showed that ropivacaine (0.25%) was as effective as bupivacaine (0.25%) in relieving labor pain when administered epidurally (3).

1. Borgeat, A., Tewes, E., Biasca, N., Gerber, C. *Ropivacaine: A suitable drug for the management of pain after major shoulder surgery*. Anesth Analg 1998, 86(2, Suppl.): Abst S261.

2. Knudsen, K., Suurkula, M.B., Blomberg, S., Sjovall, J., Edvardsson, N. *Central nervous and cardiovascular effects of i.v.*

infusions of ropivacaine, bupivacaine and placebo in volunteers. Br J Anaesth 1997, 78(5): 507.

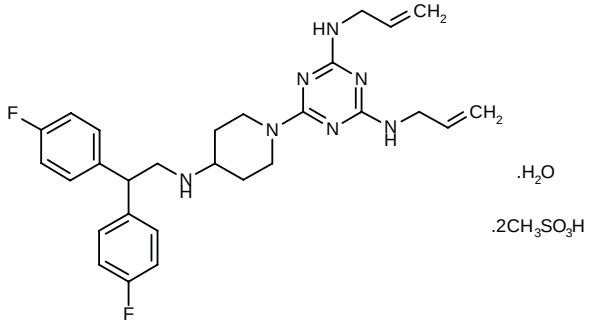
3. Muir, H.A., Writer, D., Douglas, J., Weeks, S., Gambling, D., Macarthur, A. *Double-blind comparison of epidural ropivacaine 0.25% and bupivacaine 0.25%, for the relief of childbirth pain*. Can J Anaesth 1997, 44(6): 599.

Original monograph - Drugs Fut 1989, 14: 767.

S-9788

Multidrug Resistance Modifier

EN: 190511



$C_{28}H_{33}F_2N_7.2CH_4O_3S$ **Servier**

The reversal of multidrug resistance by S-9788 was evaluated in a phase IB study in 38 patients with advanced colorectal or renal cell cancer. Patients treated with doxorubicin alone (50 mg/m^2 i.v. bolus) were additionally given S-9788 (56 mg/m^2 i.v. over 30 min, followed by escalating doses of 24-120 mg/m^2 i.v. over 2 h). Reversal of multidrug resistance by S-9788 was achieved at nontoxic doses. A significant increase in grade 3-4 granulocytopenia was observed in patients treated with the combination of the two drugs compared to those treated with doxorubicin alone. Cardiotoxicity induced by S-9788 was manifested by reversible increases in corrected QT intervals and clinically nonsignificant arrhythmias. Partial response was observed in 1 patient who progressed after treatment with doxorubicin monotherapy (1).

In a phase I trial, 26 patients with advanced solid tumors were treated with escalating doses of S-9788 alone (8-96 mg/m^2 as a 30-min infusion on day 1) and in combination with doxorubicin (50 mg/m^2 bolus on days 8 and 29). Maximum tolerated dose was 96 mg/m^2, with bradycardia being the main dose-limiting toxicity. A partial response was observed in 1 patient. Apparent elimination half-life of S-9788 was 46 + 23 h, with maximum plasma levels reaching 3.7 μM following this dosing regimen. Plasma pharmacokinetics were linear and did not appear to be affected by doxorubicin (2).

1. Punt, C.J.A., Voest, E.E., Tueni, E., Van Oosterom, A.T., Backx, A., De Mulder, P.H.M., Hecquet, B., Lucas, C., Gerard, B., Bleiberg, H. *Phase IB study of doxorubicin in combination with the multiple resistance reversing agent S9788 in advanced colorectal and renal cell cancer*. Br J Cancer 1997, 76(10): 1376.

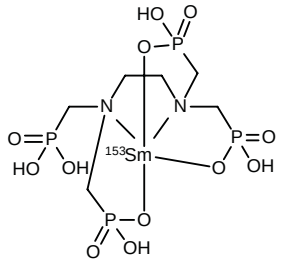
2. Tranchand, B., Catimel, G., Lucas, C. et al. *Phase I clinical and pharmacokinetic study of S9788, a new multidrug, resistance reversal agent given alone and in combination with doxorubicin to patients with advanced solid tumors*. Cancer Chemother Pharmacol 1998, 41(4): 281.

Original monograph - Drugs Fut 1993, 18: 711.

Samarium (^{153}Sm) Lexidronam Quadramet™

Analgesic

EN: 135050



$C_6H_{17}N_2O_{12}P_4{}^{153}Sm$ **Hoechst Marion Roussel; Cytogen; CIS Bio Int.; Syncor; DuPont Merck**

The safety and efficacy of Sm-153-EDTMP (0.5 or 1.0 mCi/kg) were evaluated in a randomized, dose-controlled study in 114 patients with painful bone metastases. At week 4, there were significant improvements in all patient-rated efficacy assessments such as degree of pain, level of daytime discomfort, quality of sleep and pain relief for both treatment groups (55% and 70% for the 0.5 mCi/kg and 1.0 mCi/kg doses, respectively). Female patients with breast cancer administered 1.0 mCi/kg experienced the most marked improvements as compared to baseline values. Marrow suppression was the only treatment-related side effect and was observed with equal severity in males and females (1).

A phase I-II trial assessed high-dose Sm-153-EDTMP (starting dose, 2.0 mCi/kg every 12 weeks x 4) in conjunction with total androgen blockade in newly diagnosed prostate cancer patients. Due to delayed hematopoietic toxicity in 2/5 patients eligible for the fourth dose and in 1 patient who had received 4 doses, the recommended dosing regimen was 2.0 mCi/kg every 16 weeks for 3 doses, with dose escalation in increments of 0.5 mCi/kg in the absence of grade 3 toxicity at 8 weeks follow-up (2).

The clinical safety of escalating doses of Sm-153-EDTMP was evaluated in patients with metastases and 'hot' bone scans. Unbound Sm-153-EDTMP was almost completely eliminated at 24 h postdosing. After a 3.0 mCi/kg dose in 1 patient, the estimated radiation doses to bone surface, red marrow and thoracic spine adenocarcinoma metastasis were 393, 274 and 2665 cGy, respectively, resulting in tumor to bone and tumor to marrow ratios of 6.8 and 9.7. The results indicate the high therapeutic potential of Sm-153-EDTMP therapy with stem cell

support for the treatment of osteosarcoma and osteoblastic bone metastases (3).

A newly published multicenter study confirms that samarium Sm 153 lexidronam injection (Quadramet®) provides significant pain relief from metastatic prostate and breast cancer that has spread to the bone. The study also concludes that the compound may lead to the decreased use of opioid analgesics, which often are associated with undesirable side effects. The study involved 118 patients at 10 institutions in North America and 7 in Europe. Each participant received either 0.5 or 1.0 mCi/kg of Quadramet® or placebo as a single intravenous injection. Results showed that patients receiving 1.0 mCi/kg of Quadramet® experienced a rapid onset of pain relief which persisted up to 16 weeks in the majority of patients who responded to treatment. In addition, patients receiving 1.0 mCi/kg of Quadramet® showed significant improvements over the placebo group in each of the first 4 weeks following administration. In contrast, the group receiving 0.5 mCi/kg showed no consistent improvements. Overall, there was a significant correlation between pain relief and decreased use of opioid analgesics in patients who received 1.0 mCi/kg of Quadramet®. Patients' white blood cell and platelet counts tended to return to pretreatment levels by week 8 (4).

DuPont Merck and Cytogen have announced the withdrawal of a lawsuit between them regarding the contract under which DuPont Merck distributes Cytogen's cancer pain relief product, samarium Sm153 lexidronam injection (Quadramet®). DuPont Merck will continue to manufacture, distribute and service the drug and has reaffirmed its previously stated intention to ensure its availability to all eligible cancer patients (5).

Cytogen has received approval from the Therapeutic Products Program of Health Canada to market samarium Sm153 lexidronam injection (Quadramet®) in Canada. The drug is indicated for the relief of bone pain in cancer patients with multiple osteoblastic skeletal metastases confirmed by positive radionuclide bone scan (6).

.

1. Resche, I., Chatal, J.F., Pecking, A., et al. *A dose-controlled study of Sm-153-ethylenediaminetetramethylenephosphonate (EDTMP) in the treatment of patients with painful bone metastases*. Eur J Cancer 1997, 33(10): 1583.

2. Higano, C.S., Bushnell, D., Quick, D., Eary, J. *Interim results of a phase I-II trial of high dose samarium-153 EDTMP (Sm-153) in conjunction with total androgen blockade for patients with newly diagnosed prostate cancer with bone metastases*. Proc Amer Soc Clin Oncol 1998, Abst 1286.

3. Anderson, P.M., Wiseman, G.A., Sloan, J.A., Hartmann, L.C., Arndt, C.A.S. *^{153}Samarium-EDTMP therapy for osteoblastic bone metastases and osteosarcoma: A dose escalation trial with stem cell support*. Proc Amer Soc Clin Oncol 1998, Abst 2076.

4. *Study shows Quadramet provides significant relief from bone pain*. Daily Essentials April 8, 1998.

5. *DuPont Merck and Cytogen continue Quadramet collaboration*. Daily Essentials May 29, 1998.

6. *Quadramet approved in Canada*. Daily Essentials June 26, 1998.

Original monograph - Drugs Fut 1989, 14: 799.

Additional References

Cytogen updates stockholders at annual meeting: Highlights include quadramet launch today by DuPont Merck Radiopharmaceuticals and corporate objectives. Cytogen Corp. Press Release 1997, May 21.

Cytogen updates stockholders. Daily Essentials Dec 31, 1997.

Cytogen's quadramet approved by FDA. Daily Essentials April 1, 1997.

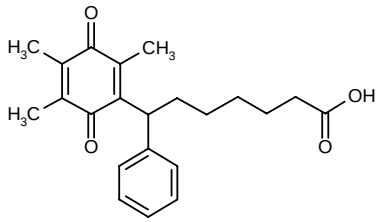
Dose-dependent pain relief with Quadramet in breast and prostate cancer patients. Daily Essentials Oct 16, 1997.

Samarium (153Sm) lexidronam launch. Cytogen Corp. Company Communication 1997, May 21.

Seratrodast
Bronica®

Antiallergic/Antiasthmatic
Thromboxane A_2 Antagonist

EN: 119024



$C_{22}H_{26}O_4$ **Takeda; Grelan; TAP; Astra**

Astra has selected seratrodast for development within the framework of its 1994 R&D collaboration with Takeda. The compound has potential in the treatment of asthma and chronic obstructive pulmonary disease (1).

1. *Astra obtains rights from Takeda to develop TxA_2 antagonist*. Daily Essentials April 30, 1998.

Original monograph - Drugs Fut 1990, 15: 783.

Additional References

Iwata, Y. et al. *Effect of short-term treatment with seratrodast in patients with bronchial asthma with PEF less than 80%*. Jpn J Allergol 1997, 46(2-3): 316.

Kubo, Y. et al. *Inhibitory effect of AA-2414 on substance P- and EPS-induced tracheal smooth muscle contraction*. Jpn J Allergol 1997, 46(8-9): Abst 283.

Samara, E. et al. *Population analysis of the pharmacokinetics and pharmacodynamics of seratrodast in patients with mild to moderate asthma*. Clin Pharmacol Ther 1997, 62(4): 426.

Samara, E.E. et al. *Single-dose, steady-state pharmacokinetics of seratrodast (AA-2414) in healthy male and female volunteers*. Clin Drug Invest 1997, 14(6): 494.

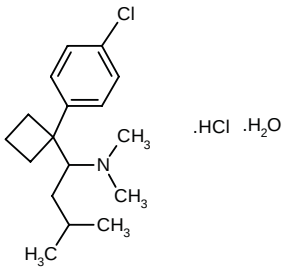
Tanaka, H. et al. *Urinary 11-dehydro-thromboxane (TX)B_2/ leukotriene E_4 ratio predicts the effects of TXA_2 receptor antagonist (seratrodast) in asthmatic patients*. Am J Respir Crit Care Med 1998, 157(3): A409.

Terao, S. et al. *The first development of a novel thromboxane A_2 receptor antagonist, seratrodast (Bronica®)*. 17th Symp Med Chem/6th Annu Meet Div Med Chem/2nd Conf Drug Discov (Nov 19-21, Tsukuba) 1997, Abst IL-8.

Sibutramine Hydrochloride Monohydrate

Reductil® *Antiobesity*
Meridia® *Norepinephrine Reuptake Inhibitor*
Arcalion® *5-HT Reuptake Inhibitor*

EN: 125655



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

Sibutramine 1-10 mg/kg p.o. reduced food intake in food-deprived rats (ED_{50} = 5.12 mg/kg) and in rats injected with neuropeptide Y in the paraventricular nucleus of the hypothalmus (ED_{50} = 5.99 mg/kg). However, eating induced by muscimol injections was not affected by the drug (1).

Zucker rats administered sibutramine (10 mg/kg p.o. for 1 week) had significant increases in the glucose utilization index in certain skeletal muscle groups, as well as in the average rate of glucose infusion during euglycemic-hyperinsulinemic clamp (2).

The effect of sibutramine on food intake in rats was examined *in vivo*. Results showed that sibutramine increases both serotonergic and noradrenergic mechanisms. Twenty-four-hour fasted rats were injected either in the dorsal raphe with muscimol (100 ng/0.5 µl) or the paraventricular nucleus with neuropeptide Y (235 pmol/0.5 µl). Sibutramine (1-10 mg/kg) reduced food intake (ED_{50} = 5.12 ± 0.85 mg/kg) and NPY-stimulated eating (ED_{50} = 5.99 ± 0.50 mg/kg) but had no effect on muscimol-stimulated eating and metergoline did not alter the hypophagic effect of sibutramine (3).

The effects of sibutramine 10 mg/kg/day p.o. on plasma glucose and insulin levels were evaluated in hyperglycemic, hyperinsulinemic, obese mice. After 14 days of treatment, no significant differences were observed in plasma glucose and insulin levels in drug-treated mice, as compared to mice treated with vehicle. However, in mice treated with sibutramine, plasma glucose levels decreased significantly after 28 days of treatment and returned to control levels after drug withdrawal (4).

Changes in body weight and food intake were evaluated during a 4-week administration period of sibutramine 3 or 10 mg/kg/day p.o. in obese Zucker rats. The 10 mg/kg dose produced a 39% reduction in body weight which was maintained for 5 weeks following drug withdrawal. Food intake was reduced during the first 2 weeks of treatment, but increased significantly during withdrawal. The tolerance to treatment-induced hypophagia indicates that the thermogenic properties of sibutramine may be responsible for the reduction in body weight (5).

8-OH-DPAT reversed hypophagia induced by sibutramine administration (10 mg/kg p.o.) in Sprague-Dawley rats, while WAY-100635 potentiated this effect. Neither compound produced any effect when administered without sibutramine. The results indicate that food intake reduction induced by sibutramine is probably mediated by the serotonergic system (6).

Sibutramine was evaluated for its ability to reduce food intake in 12 nondieting obese women. Subjects received sibutramine 10 or 30 mg/day for three 14-day cycles with a 14-day washout period in between. Compared with placebo, treatment produced significant reductions in food intake in terms of both grams and energy, and a significant increase in energy consumed from carbohydrates (7).

In a multicenter, double-blind, randomized study in 61 obese hypertensive patients whose hypertension was controlled with a β-blocker, treatment with sibutramine (20 mg/day) resulted in a reduction in body weight and a slight increase in mean pulse rate as compared to treatment with placebo. Mean blood pressure was not increased. It appears that several mechanisms other than increased sympathetic tone may be responsible for the changes in pulse rate seen with sibutramine (8).

Hyperlipidemic obese patients were treated for 4 months with sibutramine (10 mg) or a placebo in a randomized, double-blind, placebo-controlled study. Improvements were observed in triglyceride, total cholesterol, LDL and HDL levels, although these were not significantly different from placebo-treated patients. Improvements in lipid profiles were greatest in those sibutramine-treated individuals exhibiting the greatest weight loss (9).

In 6 placebo-controlled studies, obese patients with baseline fasting plasma glucose (FPG) levels of > 5.5 mM received a placebo or sibutramine (10, 15 or 30 mg). Weight-induced reductions in FPG were observed that were proportional to the degree of weight loss. No significant differences were observed between the placebo and treated groups; however, more patients receiving sibutramine experienced significant weight loss (10).

The results of a multicenter, placebo-controlled, double-blind trial in 120 obese patients at risk of developing diabetes demonstrated that sibutramine (15 mg/day x 24 weeks) was significantly more effective than placebo in reducing weight and waist circumference. Nonsignificant decreases in median fasting glucose and fasting serum

insulin were observed in both groups, while glucose tolerance improved significantly following sibutramine treatment (11).

In a 24-week, multicenter trial in 75 obese subjects, treatment with sibutramine 10 mg/day, dietary counseling and recommended increased daily excercise resulted in a mean weight loss of 11.8 ± 5.6 kg. There was a significant reduction in triglycerides and VLDL, as well as an unexpected increase in LDL and a decrease in HDL/LDL ratio (12).

In a 6-month, open-label study in 50 obese subjects, treatment with sibutramine (10 mg), in addition to a hypocaloric diet, resulted in a mean weight loss of 11.2 + 6.3 kg and a reduction in visceral fat mass, as well as significant improvements in cardiovascular risk factors (13).

In a double-blind, placebo-controlled study, 12 obese female patients were administered a placebo or sibutramine (10 and 30 mg/day x 14). The compound produced a dose-dependent decrease in food intake and significant reductions in hunger, the amount patients wanted to eat and energy intake (kcal) on days 7 and 14. An increase in fullness was also experienced by sibutramine-treated patients (14).

A randomized, double-blind, placebo-controlled trial demonstrated that a significant proportion of initial responders to sibutramine therapy (10 and 15 mg/day) lose 5-10% of their baseline weight by 3 and 12 months. An assessment of initial response to treatment may be a valuable aid in determining dose increments or the value of continuing treatment (15).

Meta-analysis of obese patients treated with sibutramine for 3-12 months in 6 placebo-controlled studies showed that sibutramine-treated patients displayed significantly improved lipid profiles proportional to the amount of weight loss experienced (16).

In 16 placebo-controlled studies, meta-analysis of obese patients treated with sibutramine (10 mg or 15 mg for 3-12 months) indicated that long-term treatment is associated with statistically and clinically significant reductions in waist circumference and waist-hip ratio, suggesting improvements in visceral adiposity and decreased cardiovascular risk (17).

The effects of sibutramine on energy expenditure were evaluated in 19 obese females administered either sibutramine (15 mg/day) or placebo for 12 weeks, in addition to dietary advice. Apart from the weight loss observed in both groups, resting energy expenditure fell in the placebo group and increased slightly in the sibutramine group, indicating that sibutramine causes weight loss via a reduction in energy intake (18).

In a 12-week, double-blind, placebo-controlled study in 156 obese patients, treatment with sibutramine (10 mg) resulted in significant reductions in body weight, body mass index and waist circumference, as well as changes in blood glucose, serum triglycerides and HLD cholesterol. These effects were associated with an overall improvement in metabolic syndrome (19).

The FDA has approved sibutramine hydrochloride monohydrate capsules (Meridia®) for the management of obesity, *i.e.*, for weight loss and maintenance of weight loss when used in conjunction with a reduced calorie diet (20).

Eisai and Knoll (BASF) have concluded a licensing agreement for the joint development and marketing in Japan of Knoll's antiobesity drug sibutramine hydrochloride monohydrate. Under terms of the agreement, the two companies will share costs of clinical development in Japan. The product will be marketed under two different tradenames by Eisai and Hokuriku Seiyaku, Knoll's majority-owned subsidiary in Japan (21).

Knoll's sibutramine hydrochloride monohydrate (Meridia®) is being distributed in the U.S. and is supplied as 5-, 10- and 15-mg capsules. Sibutramine is also approved in Mexico, where it will be marketed as Raductil® (22).

1. Grignaschi, G., Fanelli, E., Scagnol, I., Samanin, R. *Effect of sibutramine in various feeding paradigms in rats*. Int J Obes 1997, 21(Suppl. 2): Abst 167.

2. Vettor, R., Pagano, C., Granzotto, M., Sagrillo, E., Ferretti, E., Marzolo, M., Scagnol, I., Federspil, G. *Effect of sibutramine on basal and insulin-mediated glucose utilization in skeletal muscle of genetically obese (fa/fa) Zucker rats*. Int J Obes 1997, 21(Suppl. 2): Abst 168.

3. Grignaschi, G., Fanelli, E., Scagnol, I., Samanin, R. *Studies on the mechanisms by which sibutramine reduces food intake in rats*. Pharmacol Res 1997, 35(Suppl.): 24.

4. Jones, R.B., Jackson, H.C., Cheetham, S.C., Anthony, D.M., Sills, S.D., Heal, D.J. *Effect of chronic administration of sibutramine and its withdrawal on plasma glucose and insulin levels in obese (ob/ob) mice*. Int J Obes 1997, 21(Suppl. 2): Abst 162.

5. Jackson, H.C., Cheetham, S.C., Jones, R.B., Forni, J.J., Pleasance, I.M., Slater, N.A., Heal, D.J. *Effect of chronic administration of sibutramine and its withdrawal on body weight gain and food intake in obese Zucker rats*. Int J Obes 1997, 21(Suppl. 2): Abst 163.

6. Jackson, H.C., Pleasance, I.M., Heal, D.J. *Sibutramine-induced hypophagia is inhibited by the 5-HT_{1A} agonist 8-OH-DPAT and potentiated by the 5-HT_{1A} receptor antagonist WAY100635*. Int J Obes 1997, 21(Suppl. 2): Abst 164.

7. Rolls, B.J., Shide, D.J., Thorwart, M.L., Ulbrecht, J.S. *Sibutramine reduces food intake in non-dieting women with obesity*. Obes Res 1998, 6(1): 1.

8. Liebowitz, M.T., Weinstein, S.P., McMahon, F.G. *Sibutramine induces weight loss but not BP increase in obese hypertensive patients taking β-blockers*. Am J Hypertens 1998, 11(4, Part 2): 107A.

9. Oya, M., Dominguez, R., Heath, M. *The effect of sibutramine induced weight loss in obese subjects with hyperlipidaemia*. Int J Obes 1997, 21(Suppl. 2): Abst 153.

10. Shepherd, G., Fitchet, M., Kelly, F. *Sibutramine: A meta-analysis of the change in fasting plasma glucose in patients with a high baseline fasting value (≤ 5.5 mmol/l)*. Int J Obes 1997, 21(Suppl. 2): Abst 154.

11. Leutenegger, M., Hanotin, C., Thomas, F., Leutenegger, E. *Sibutramine in the treatment of obese patients presenting a risk of developing diabetes*. Int J Obes 1997, 21(Suppl. 2): Abst 157.

12. Hansen, D.L., Toubro, S., Astrup, A. *Effects of sibutramine on blood lipids*. Int J Obes 1997, 21(Suppl. 2): Abst 158.

13. Wauters, M., Peiffer, F., Gubbels, N., Van De Sompel, A.M., Corthouts, R., De Schepper, A., De Leeuw, I., Van Gaal, L. *Visceral fat decreases after six months treatment with sibutramine in obese subjects*. Int J Obes 1997, 21(Suppl. 2): Abst 159.

14. Rolls, B.J., Shide, D.J., Ulbrecht, J.S. *Sibutramine and food intake in obese women*. Int J Obes 1997, 21(Suppl. 2): Abst 70.

15. Smith, I., Fitchet, M., Kelly, F. *Sibutramine: Predictability of long term weight loss*. Int J Obes 1997, 21(Suppl. 2): Abst 150.

16. Fitchet, M., Shepherd, G., Kelly, F. *Sibutramine: A meta-analysis of changes in fasting serum lipids in placebo controlled studies*. Int J Obes 1997, 21(Suppl. 2): Abst 151.

17. Fitchet, M., Shepherd, G., Kelly, F. *Sibutramine: Meta-analysis of change in waist circumference and waist hip ratio in long term studies*. Int J Obes 1997, 21(Suppl. 2): Abst 152.

18. Walsh, K.M., Lean, M.E.J. *Effects of sibutramine on energy expenditure in obese females*. Int J Obes 1997, 21(Suppl. 2): Abst 160.

19. Schwandt, P., Krause, J., Krümke, W., Heath, M. *Sibutramine in the treatment of obese patients with metabolic syndrome*. Int J Obes 1997, 21(Suppl. 2): Abst 161.

20. *FDA approves sibutramine for the treatment of obesity*. Daily Essentials Nov 25, 1997.

21. *Eisai in-licenses antiobesity drug for Japanese market*. Daily Essentials Jan 14, 1998.

22. *New antiobesity agent now being distributed in U.S.* Daily Essentials Feb 13, 1998.

Original monograph - Drugs Fut 1988, 13: 736.

Additional References

Cheetham, S. et al. *Sibutramine does not decrease rat brain 5-HT reuptake sites and, like fluoxetine, protects against the deficits produced by D-fenfluramine*. Int J Obes 1997, 21(Suppl. 2): Abst 165.

Cole, J.O. et al. *Sibutramine: A new weight loss agent without evidence of the abuse potential associated with amphetamines*. J Clin Psychopharmacol 1998, 18(3): 231.

Gundlah, C. et al. *In vivo criteria to differentiate monoamine uptake inhibitors (MARIs) from serotonin releasing drugs: Sibutramine is a MARI*. Soc Neurosci Abst 1996, 22(Part 1): Abst 244.13.

Hansen, D.L. et al. *Sibutramine reduce weight loss induced decline in BMR*. Int J Obes 1997, 21(Suppl. 2): Abst 156.

Jackson, H.C. et al. *Comparison of the effects of sibutramine and other monoamine reuptake inhibitors on food intake in the rat*. Br J Pharmacol 1997, 1758.

Johnson, F. et al. *Effects of renal dysfunction on the pharmacokinetics of sibutramine and its metabolites*. J Clin Pharmacol 1997, 37(9): Abst 31.

Prow, M.R. et al. *Effects of sibutramine, BTS 54 354, BTS 54 505 and comparators on head-twitch behaviour in mice*. J Psychopharmacol 1997, 11(3, Suppl.): Abst 182.

Srini, V.S., Lim, P.H.C. *Oral drugs efficacy study in impotence*. Int J Impot Res 1997, 9(Suppl. 1): Abst A92.

Turner, S.L. et al. *Sibutramine improves insulin sensitivity of cultured L6 muscle cells*. Int J Obes 1997, 21(Suppl. 2): Abst 155.

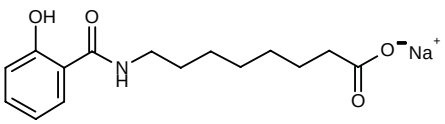
Knoll Pharmaceutical Company begins nationwide distribution of new anti-obesity agent, Meridia. Knoll Pharmaceutical Co. Press Release 1998, Feb 12.

Sibutramine: New hope for obese patients. Daily Essentials Aug 5, 1997.

SNAC
P414

Absorption Promoter

EN: 245771



$C_{15}H_{20}NNaO_4$ **Emisphere Technol.**

An *in vitro* assay involving Immobilized Artificial Membrane chromatography has been developed in order to screen SNAC and other compounds which facilitate gastrointestinal absorption of heparin. The high throughput assay predicted the activity of test compounds with approximately 70% accuracy when validated in vivo using the intracolonic rat model to test the efficacy of oral heparin delivery agents (1).

In vivo studies have demonstrated the efficacy of SNAC as an oral heparin delivery agent in rats and primates. Rat colons were instilled with either a single oral dose of heparin solution (25 mg/kg) and SNAC (50 mg/kg), heparin (100 mg/kg) or SNAC (50 mg/ml). Coadministration of heparin resulted in a 6-fold increase in the activated partial thromboplastin time assay (APTT) indicating intestinal absorption of heparin; SNAC or heparin alone were ineffective. Intestinal absorption and plasma levels of heparin in primates were also measured using the APTT assay and anti-factor Xa assay, respectively. Animals were administered a single oral dose of heparin solution (15 mg/kg) with SNAC (150 mg/kg), resulting in a bioavailability of 8.3% and APTT levels 4.4 times greater than basal levels. APTT levels increased 8.9-fold from baseline when SNAC was increased to 300 mg/kg. Heparin or SNAC administered alone did not alter APTT or plasma heparin levels (2).

1. Harris, E., Kalbag, S., Leone-Bay, A., Paton, D.R. *The prediction of gastrointestinal heparin delivery by acylated non-α-amino acids using immobilized artificial membrane chromatography as an in vitro screen*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 086.

2. Leone-Bay, A., Paton, D.R., Freeman, J. et al. *Synthesis and evaluation of compounds that facilitate the gastrointestinal absorption of heparin*. J Med Chem 1998, 41(7): 1163.

Original monograph - Drugs Fut (Rev Art) 1997, 22: 885.

Additional References

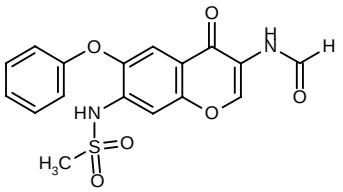
Leone-Bay, A. et al. *Acylated non-α-amino acids as novel agents for the oral delivery of therapeutic levels of USP heparin*. 213th ACS Natl Meet (April 13-17, San Francisco) 1997, Abst MEDI 012.

Salvador, C.A. et al. *In vitro assays for the prediction of gastrointestional absorption of recombinant human growth hormone by N-acylated non-α-amino acids*. 215th ACS Natl Meet (March 29-April 2, Dallas) 1998, Abst MEDI 058.

T-614

Antiinflammatory
Treatment of Osteoporosis

EN: 153332



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

The effects T-614 on lysosomal function have been evaluated *in vitro*. T-614 protected the human monocytic cell line THP-1 from L-leucine methyl ester-mediated killing, being more active than other methanesulfonanilide NSAIDs such as nimesulide; of the classical NSAIDs tested, only diclofenac had a protective effect at high concentrations. The mechanism of protection appeared to be different from that of conventional lysosomal inhibitors such as chloroquine and NH_4Cl (1).

Results of ongoing investigations have demonstrated that the cytokine-inhibitory effects of T-614, specifically its suppression of IL-6 production, may be due to inhibition of NFκB activation. This action may ultimately be responsible for the pharmacological actions of the drug (2).

Two doses of T-614 (50 and 75 mg/day) were evaluated and compared to placebo in a group of 209 patients with rheumatoid arthritis treated for 16 weeks in a double-blind trial to determine the optimal dose. Significant improvement was obtained in 73.5% of those on the high dose of T-614, 59.6% of those on the lower dose and 11.9% of those on placebo. Side effects included vomiting, stomachache and exanthema, as well as transient increase in liver enzymes. The optimal dose was considered to be 50 mg/day (3).

In a multicenter, dose-escalating trial in 80 rheumatoid arthritis patients, T-614 was administered at a dose of 25 mg/day for 4 weeks, followed by an increase to 50 mg/day for 12 weeks. Gradual dose escalation appeared to result in a reduction in the incidence of side effects (4).

1. Sawada, T., Shinohara, S., Tohma, S., Inoue, T., Yamamoto, K. *Protection of L-leucine methyl ester mediated killing of THP-1 by a new anti-inflammatory drug, T614*. Arthritis Rheum 1997, 40(9, Suppl.): Abst 988.

2. Konishi, Y., Yamamoto, T., Mitamura, M., Morimoto, K., Aikawa, Y., Tanaka, K. *Suppression of NFκB activation by T-614, a new anti-rheumatic drug*. Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-124.

3. Hara, M. et al. *Multicenter, dose-finding study of T-614 in rheumatoid arthritis patients*. Ryumachi 1998, 38(2): Abst F 18-11.

4. Hara, M. et al. *A multicenter, dose-ranging study of T-614 in rheumatoid arthritis patients*. Ryumachi 1998, 38(2): Abst F 18-12.

Original monograph - Drugs Fut 1993, 18: 714.

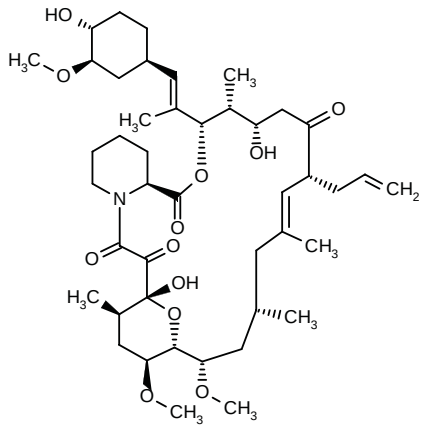
Additional Reference

U.S. testing of Toyama antiarthritic to begin soon. Daily Essentials Oct 20, 1997.

Tacrolimus
Prograf®
Protopic®

Immunosuppressant

EN: 124071



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

The synthesis of the C16-C34 fragment of tacrolimus (FK-506), the key intermediate on the total synthesis of tacrolimus has been described: Scheme 3.

1) The reaction of (*Z*)-2-butene (I) with (–)-β-methoxydiisopinocamphenylborane (IPCB-OCH_3; II) by means of potassium *tert*-butoxide and butyl lithium in THF gives the butenyl borane (III), which is condensed with 2-benzylacetaldehyde (IV) by means of BF_3 ethearate in ether to yield the monobenzylated diol (V). The silylation of (V) with *tert*-butyldimethylsilyl chloride (TBDMS-Cl) and imidazole affords the fully protected olefine (VI), which is oxidized with OsO_4 and *N*-methylmorpholine *N*-oxide (NMO) in acetone/water/benzene to give a diastereomeric mix-

ture of the diols (VII) and (VIII) separated by column chromatography. The epoxidation of (VII) with NaH and tosyl imidazole in THF afforded epoxide (IX), which was condensed with the protected furfuryl alcohol (X) by means of butyl lithium and BF_3 ethearate in THF giving the diol (XI). The oxidation of (XI) with *m*-chloroperbenzoic acid (MCPBA) with simultaneous trapping of the intermediate with 2-methoxypropene (XII) afforded the spiroenone (XIII), which was condensed with alkyne (XIV) by means of trimethylaluminum and a zircornium complex yielding the expected spiroketone (XV). Subsequent reduction of the ketonic group of (XV) with L-selectride in THF afforded the enantiomerically pure alcohol (XVI), which was treated with *p*-methoxybenzyl trichloroacetimide (XVII) and a catalytic amount of triphenylmethyl tetrafluoroborate to give the expected *p*-methoxybenzyl ether (XVIII). The desilylation of (XVIII) with tetrabutylammonium fluoride (TBAF) in THF gives the diol (XIX), which was selectively resilylated at the primary OH group yielding the secondary alcohol (XX). The selective debenzylation of (XX) with H_2 over W-2 Ra-Ni in ethanol afforded the vicinal diol (XXI), which was submitted to cleavage with sodium periodate in THF to obtain the aldehyde (XXII). Finally, this compound is condensed with the vinyl bromide (XXIII) by means of butyl lithium and magnesium bromide in THF to afford the desired C16-C34 fragment of FK-506, the key intermediate in the total synthesis described in Tetrahedron 1997, 53(39): 13257.

2) The alkyne intermediate (XIV) has been obtained by condensation of the chiral tosylate (XXVII) with lithium acetylide giving the chiral pentynol ether (XVIII). (XVIII) then was deprotected with *p*-toluenesulfonic acid and silylated with TBDMS-Cl.

3) The undesired diol (VIII) can also be converted into the epoxide (IX) by reaction with benzoyl chloride and dimethylaminopyridine (DMAP) to give the expected benzoate, which was subsequently treated with methanesulfonyl chloride and DMAP, and finally epoxidated with sodium methoxide in methanol.

4) The diol (VII) can be selectively obtained by reaction of methyl 5-*O*-benzyl-β-D-ribofuranoside (XXIV) with methylmagnesium chloride and copper bromide giving methyl 5-*O*-benzyl-3-deoxy-3-*C*-methyl-β-D-xylofuranoside (XXV). (XXV) was treated with ethanethiol and TBDMS-Cl in the presence of imidazole and a catalytic amount of DMAP affording the dithioacetal (XXVI). Finally, this compound is treated with $HgCl_2$ and $CaCO_3$, and reduced with $NaBH_4$ in THF/methanol to afford the desired diol (VII).

5) The intermediate vinyl bromide (XXIII) has been obtained according to a previously reported method (Ragan, J.A. *et al.* J Org Chem 1989, 54(18): 4267) (1).

The completion of the total synthesis of FK-506, starting with the key intermediate C16-C34 fragment obtained as described in Tetrahedron 1997, 53(39): 13221, has been presented: Scheme 4.

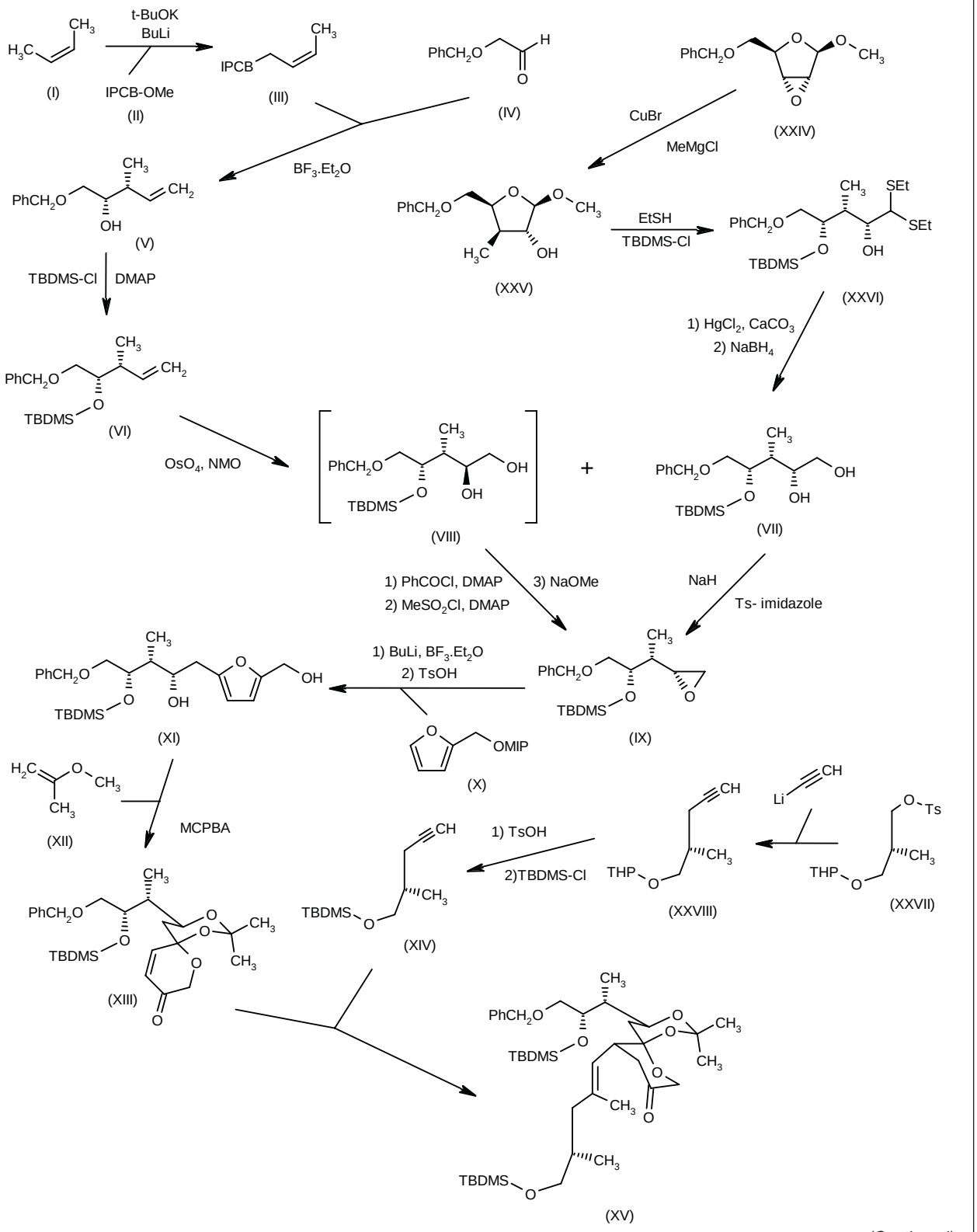
1) The silyl ether (I) was partially deprotected with tetrabutylammonium fluoride (TBAF) in THF giving the diol (II), which is selectively tosylated with tosyl chloride at the primary OH group yielding the monotosylate (III). The protection of the secondary alcohol of (III) with triethylsilyl chloride (TES-Cl) affords the protected tosylate (IV), which by treatment with lithium iodide and sodium benzenesulfinate is converted into the sulfone (V). The condensation of (V) with aldehyde (VI) by means of butyl lithium followed by Dess-Martin oxidation gives a nonisolated ketosulfone intermediate, which was treated with tributyltin hydride and azobis(isobutyronitrile) (AIBN) yielding ketone (VII). The diastereoselective reduction of (VII) with $NaBH_4/CeCl_3$ in methanol/ethyl ether affords alcohol (VIII), which was methylated with trimethyloxonium tetrafluoroborate in dichloromethane giving the methyl ether (IX). The treatment of (IX) with lithium bis(trimethylsilyl)-amide (Li-HMDS) and $Mg(HMDS)_2$ causes enolization and ring opening affording alcohol (X), which was protected with *tert*-butyldimethylsilyl triflate yielding the fully silylated compound (XI). The hydrolysis of the ester group of (XI) with NaOH, followed by a selective elimination of the triethylsilyl group with trifluoroacetic acid and esterification of the resulting alcohol with piperidine-2(*S*)-carboxylic acid (XII) by means of dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP) afforded ester (XIII), which was submitted to cyclization by means of triethylsilyl triflate and 2-chloro-1-methylpyridinium iodide (MCPI) in dichloromethane/methanol gaving the macrocyclic compound (XIV). Elimination of the *p*-methoxybenzyl group of (XIV) with dichlorodicyanobenzoquinone (DDQ) in dichloromethane yielded the alcohol (XV) which was converted into the iodo derivative (XVI) with I_2, triphenylphosphine and imidazole in hot toluene. The reductive fragmentation of the spiroketal rings of (XVI) with zinc/silver-graphite in THF afforded compound (XVII) with the adequate configuration in the C21-C24 fragment. The 1,3-dioxole ring of (XVII) was cleaved by selective oxidation with dimethyldioxirane (DMD) in acetone giving the tricarbonyl compound (XVIII) (silylated FK-506), which was finally desilylated by means of HF in acetonitrile/ water.

2) Aldehyde (VI) was prepared according to a previously reported method (Ireland, R.E. et al. J Org Chem 1992, 57: 5071) (2).

An ointment formulation of tacrolimus has been evaluated in a new rat model of chronic contact dermatitis induced by repeated topical application of DNCB to the ear. Both tacrolimus (0.1%, 0.3%) and topical corticosteroids significantly suppressed swelling and suppressed or tended to suppress increased serum total IgE titers and eosinophil and mast cell infiltration into the lesions when administered starting 1 week after the initial sensitization (3).

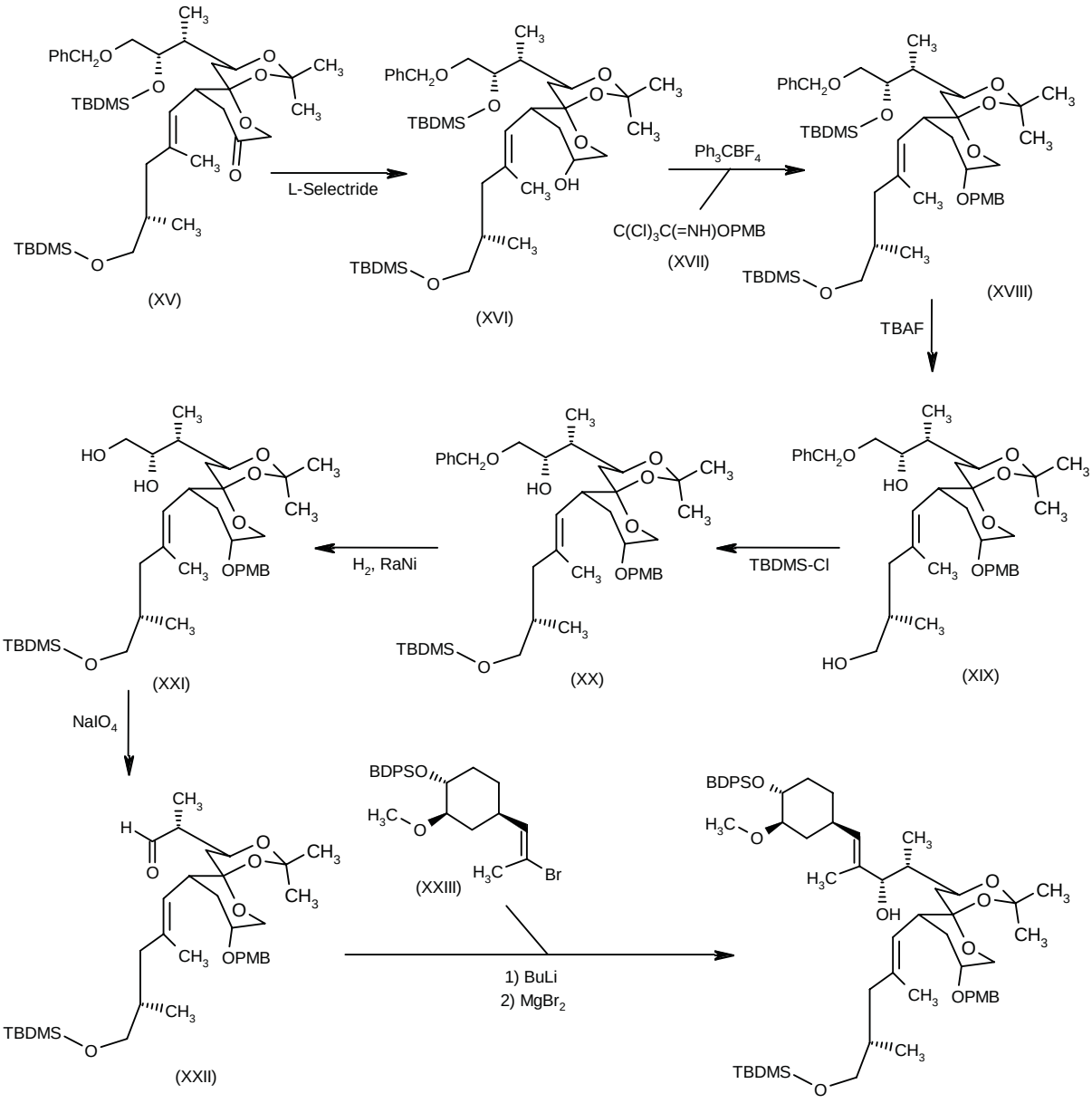
The potential efficacy of FK-506 for the treatment of rheumatoid arthitrits has been evaluated in rats with experimental adjuvant arthritis. At a dose of 0.32 mg/kg/day i.m. for 28 days starting on the day of adjuvant injection, FK-506 prevented the development of arthritis and suppressed synovial tissue proliferation, inflammatory cell infiltration and bone and cartilage destruction com-

Scheme 3: Synthesis of the C16-C34 Fragment of FK-506



(Continued)

Scheme 3: Continued

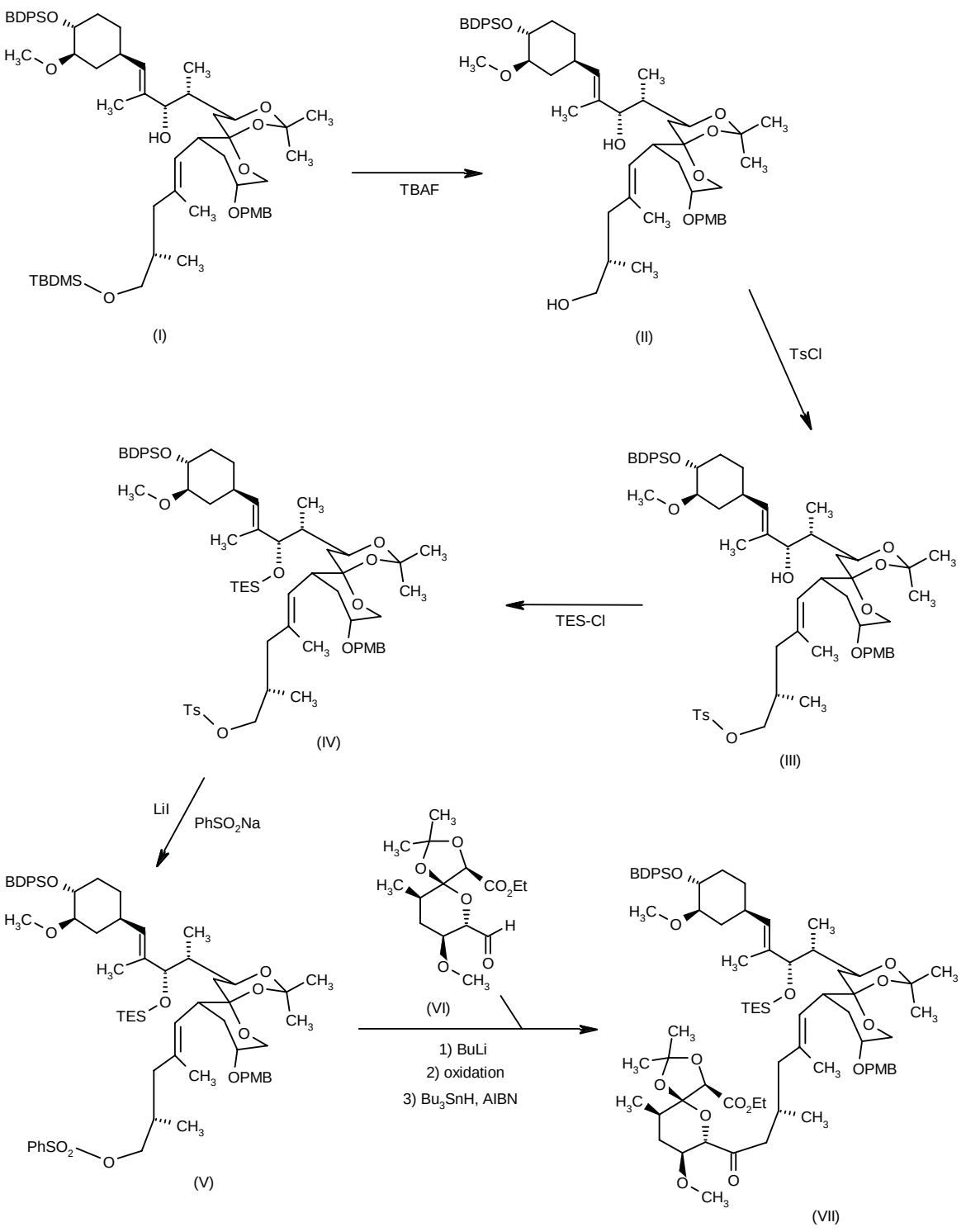


pared to the untreated control group. In addition, FK-506 treatment was associated with a reduction in the expression of fibroblast growth factor and tyrosine-phosphorylated proteins in synovial sections (4).

A randomized, placebo-controlled, double-blind, multicenter study in 213 patients investigated the efficacy of short-term treatment of atopic dermatitis with tacrolimus. Patients received twice-daily applications of either tacrolimus ointment (0.03, 0.1 or 0.3%) or vehicle applied to the skin for 3 weeks. Decreases in trunk and extremity scores for dermatitis were 66.7, 83.3 and 75% with doses of 0.03, 0.1 and 0.3%, respectively, as compared to only 22.5% in placebo-treated patients. Similar results were obtained for neck and face and no significant differences were noted between the different doses of tacrolimus. A burning sensation was the only reported side effect (5).

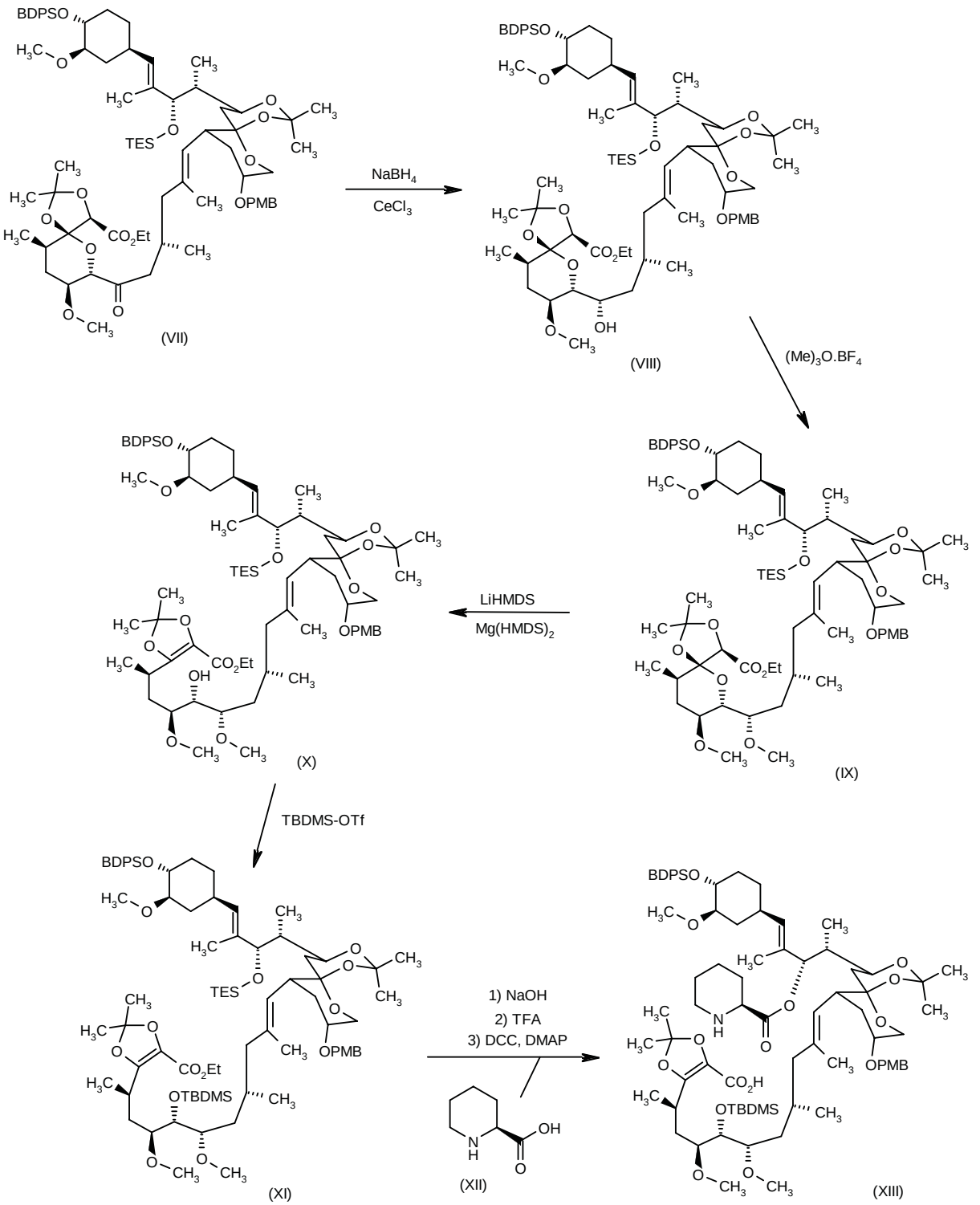
The efficacy of tacrolimus as a treatment for chronic inflammatory demyelinating polyradiculitis was examined in 1 female patient diagnosed with a slowly progressing Guillain-Barre-like disease. The patient had not respond-

Scheme 4: Synthesis of FK-506



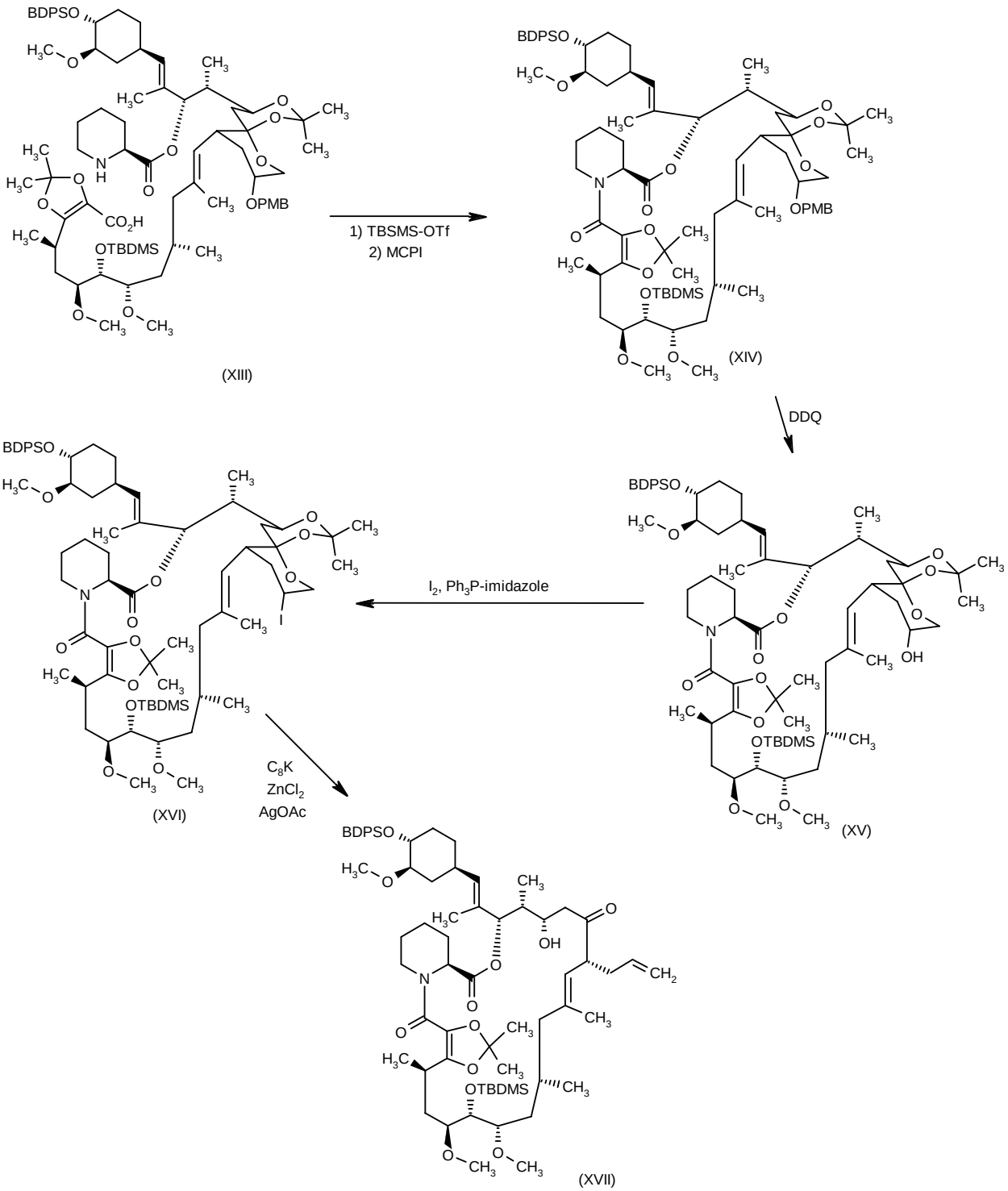
(Continued)

Scheme 4: Continued



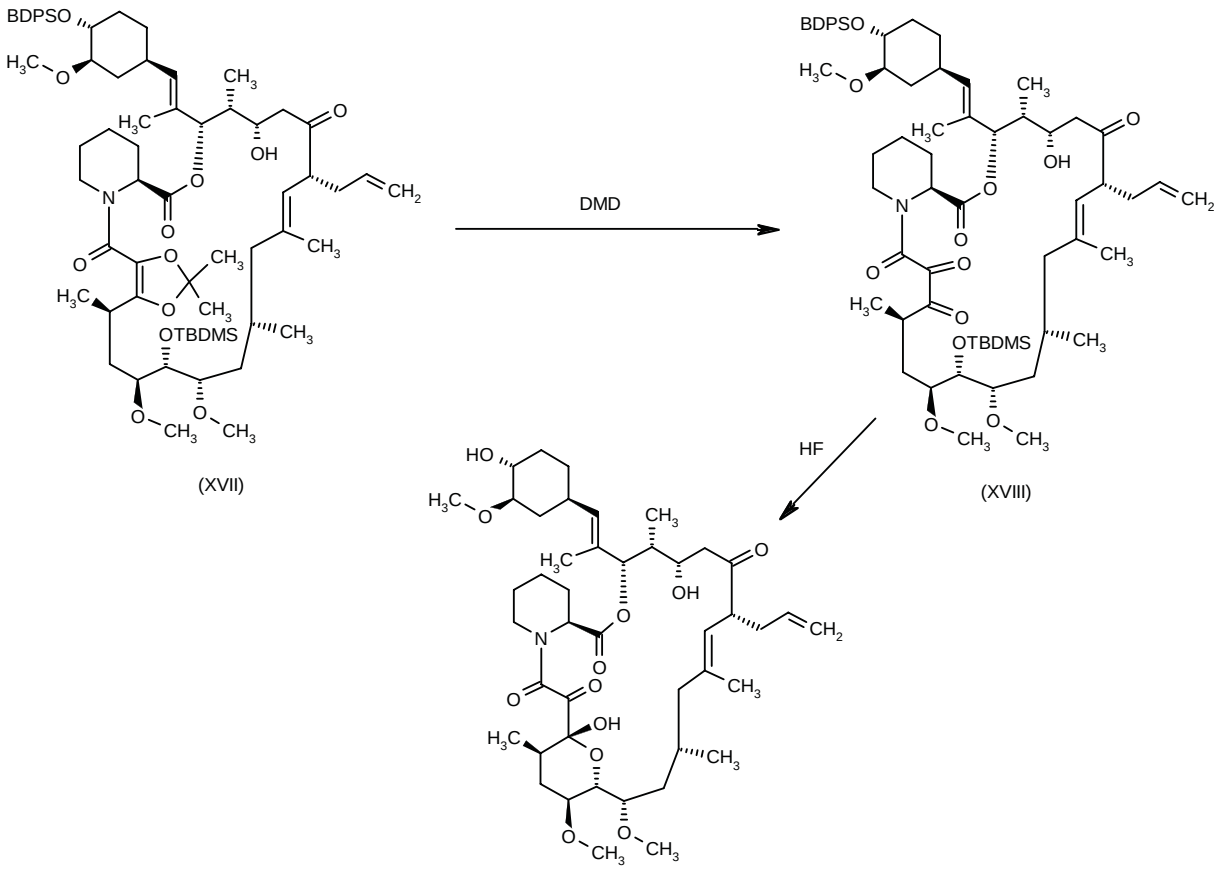
(Continued)

Scheme 4: Continued



(Continued)

Scheme 4: Continued



ed to azathioprine, prednisolone or cyclophosphamide treatment, although apheresis therapy improved outdoor walking. Upon disease progression, the patient was given tacrolimus (0.26 mg/kg) for 2 days, followed by a gradual decrease in dose to 0.03 mg/kg. Prednisolone treatment was discontinued and rehabilitation has been successful without any neurological symptoms for more than 1 year (6).

The clinical and radiological aspects of FK-506-induced leukoencephalopathy were examined in a single-lung transplantation patient. Biopsy confirmed a leukoencephalopathic condition with microglial and astrocytic activation. The patient exhibited seizure activity and neuroimaging showed diffuse changes in the brain.The patient improved clinically upon discontinuation of treatment (7).

Fujisawa has filed an NDA in Japan for tacrolimus hydrate (Protopic®) ointment for the treatment of atopic dermatitis (8).

1. Ireland, R.E., Liu, L.B., Roper, T.D. *Total synthesis of FK-506. 1. Construction of the C16-C34 fragment*. Tetrahedron 1997, 53(39): 13221.

2. Ireland, R.E., Liu, L.B., Roper, T.D., Gleason, J.L. *Total synthesis of FK-506. 2. Completion of the synthesis*. Tetrahedron 1997, 53(39): 13257.

3. Fujii, Y., Gogi, H., Takakura, K., Sakuma, S., Goto, T. *Effect of tacrolimus ointment on a pharmacological model of skin inflammation by repeated topical application of antigen in rats*. Clin Rep 1997, 31(8): 7.

4. Fukui, W., Sano, H., Hashiramoto, A., Yamada, R., Miyazaki,S., Kato, H., Kondo, M. *Effect of FK506 on adjuvant arthritis in rats: Studies on the expression of fibroblast growth factor-1 and tyrosine phosphorylated proteins*. Jpn J Inflamm 1998, 18(1): 25.

5. Ruzicka, T., Bieber, T., Schöpf, E., et al. *A short-term trial of tacrolimus ointment for atopic dermatitis*. New Engl J Med 1997, 337(12): 816.

6. Ahlmén, J., Andersen, O., Hallgren, G., Peilot, B. *Positive effect of tacrolimus in a case of CIDP*. 3rd Int Conf New Trends Clin Exp Immunosuppr (Feb 12-15, Geneva) 1998, 110.

7. Thyagarajan, G.K., Cobanoglu, A., Johnston, W. *FK506-induced fulminant leukoencephalopathy after single-lung transplantation*. Ann Thorac Surg 1997, 64(5): 1461.

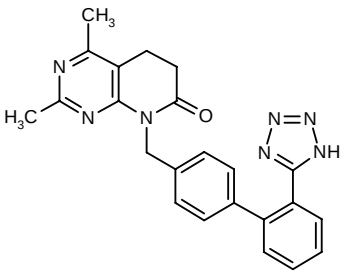
8. *Fujisawa: FY 1998 highlights*. Daily Essentials June 1, 1998

Original monograph - Drugs Fut 1989, 14: 746.

Tasosartan
ANA-756
WAY-ANA-756
WAY-126756
Verdia®

Antihypertensive
Angiotensin AT_1 Antagonist

EN: 189224



$C_{23}H_{21}N_7O$ **American Home Products; Wyeth-Ayerst**

The safety and tolerability of tasosartan (10-600 mg) were evaluated in 8 trials involving 1051 patients with essential hypertension administered the drug for up to 12 weeks. The overall incidence of adverse events was similar in tasosartan- and placebo-treated patients, with headache, asthenia and dizziness being the most common. The incidence of cough, peripheral edema and discontinuation due to adverse events was also similar in both groups (1).

Tolerability of tasosartan was evaluated in 2084 patients receiving doses of 10-600 mg once or twice daily for 3-16 weeks. The drug demonstrated a smooth onset of action, with no evidence of first-dose hypotension. Blood pressure slowly returned to baseline values following drug withdrawal. The frequency of discontinuation due to adverse events was similar in the tasosartan- and placebo-treated groups, while discontinuation rates due to nontherapy-related adverse events were higher in the placebo group. The drug was deemed to have an excellent tolerability profile (2).

Evaluation of pharmacodynamic and pharmacokinetic interactions between tasosartan and atenolol in 16 Caucasian patients aged 18-65 year with stage 1 or 2 essential hypertension showed that the combination of the two drugs was safe and well tolerated. A regimen of tasosartan 50 mg/day for 5 days, followed by tasosartan and atenolol for the next 14 days, and tasosartan alone for the last 5 days produced small but statistically significant reductions in C_{max} and AUC values for both drugs, while oral clearance for atenolol increased by 30%. Pharmacokinetic parameters for enoltasosartan, the active metabolite of tasosartan, were unaffected by combination therapy, although 77% and 40% increases in the area under the change from baseline in diastolic blood pressure curve were observed during coadministration as compared to monotherapy with either drug. Plasma renin levels increased 2-fold with the combination regimen as compared to atenolol alone, and decreased by 1.5-fold in comparison to tasosartan monotherapy (3).

Dose proportionality of tasosartan and its active metabolite enoltasosartan was evaluated following single and multiple doses. Patients receiving oral doses (10, 30, 100 or 300 mg/day x 14 days) demonstrated rapid elimination of the drug with a $t_{1/2}$ of 1.0-5.4 h after both single and multiple doses, while enoltasosartan concentrations rose slowly with a t_{max} of 4-8 h and a mean $t_{1/2}$ of 52-65 h. Linear relationships between dose and C_{max} and AUC values were observed for both tasosartan and enoltasosartan. Blood pressure showed a tendency to decrease following administration of multiple tasosartan doses (4).

Interactions between tasosartan (50 mg/day) and enalapril (20 mg/day) were evaluated in 16 adult hypertensive patients. Coadministration of the two drugs produced a 9% decrease in enalapril AUC values and an 11% increase in enalapril oral clearance; 11% increases were also observed for tasosartan AUC and oral clearance. Minor but significant decreases were observed for tmax, C_{max} and AUC values for enoltasosartan. The combination therapy produced significantly greater reductions in systolic and diastolic blood pressures than monotherapy with either drug, as was the case with increased plasma renin activity. The synergistic effects may be due to incomplete inhibition of ACE activity by enalapril alone, indicating that combination therapy may be advantageous for patients with hypertension (5).

A population pharmacodynamic analysis of data pooled from 4 phase II trials of tasosartan (10-300 mg once daily or 50-100 mg b.i.d.) involving 535 patients with essential hypertension showed that the maximum effect (E_{max}) in patients administered the lowest dose of the once-daily regimen was more negative at later time points. The E_{max} with the twice-daily dosing was also achieved with the lowest dose but was not time-dependent (6).

Based on the results of 4 phase II and 4 phase III double-blind studies, the pharmacokinetics of enoltasosartan were shown to fit a two-compartment model, with smaller clearance and bioavailability in older individuals and individuals with reduced body weight. Race- and gender-related effects were not observed, while creatinine clearance was confounded with age and weight (7).

The effects of missed doses of tasosartan and losartan 100 mg daily were evaluated in patients with essential hypertension during 4 or 6 weeks. Steady-state reductions in sitting systolic and diastolic blood pressures were greater following treatment with tasosartan than with

losartan. Reductions in blood pressure were better maintained with tasosartan, while in the losartan-treated group, blood pressures tended to return to control values after each missed dose. Frequencies of adverse events were similar in both treatment groups (8).

The efficacy of tasosartan was examined in a randomized, double-blind, placebo-controlled, parallel-group, multicenter trial involving 278 patients with baseline sitting blood pressure of 95-114 mmHg. Patients were administered either 10, 30, 100 or 300 mg/day tasosartan or a placebo for 4 weeks. Tasosartan was well tolerated and found to significantly decrease clinical and ambulatory blood pressure in a dose-dependent manner; effects were maintained over 24 h (9).

The FDA's Cardiovascular and Renal Drugs Advisory Committee has recommended approval of tasosartan (Verdia™) for the treatment of hypertension (10).

Wyeth-Ayerst has withdrawn its NDA for tasosartan (Verdia®) as a result of an unresolved question arising from ongoing discussions with the FDA regarding the drug's safety profile (11).

Subsequent to the company's announcement that its NDA for tasosartan (Verdia®) had been withdrawn in the U.S., Wyeth-Ayerst has confirmed that the compound is still under regulatory review in Europe, and that phase III trials are ongoing in France and Canada (12).

1. Oparil, S. *Safety and tolerability of tasosartan in the treatment of hypertension*. J Cardiovasc Pharmacol 1997, 37(9): Abst 49.

2. Oparil, S., Gradman, A., Papademetriou, V., Weber, M. *Tolerability profile of tasosartan, a long-acting angiotensin II AT_1 receptor blocker, in the treatment of patients with essential hypertension*. Curr Ther Res 1997, 58(12): 930.

3. Battle, M.M., Klamerus, K.J., Mayer, P.R., Neefe, D.L., Andrawis, N.S., Abernethy, D.R., Burghart, P.H., Whitehead, B.F., Weinryb, I. *Tasosartan and atenolol: Interaction in hypertensives*. J Hypertens 1997, 15(Suppl. 4): Abst 27.

4. Battle, M.M., Klamerus, K.J., Neefe, D.L., Burghart, P.H., Weinryb, I., Mayer, P.R. *Dose proportionality study of tasosartan in patients with stage 1-2 hypertension*. J Cardiovasc Pharmacol 1997, 37(9): Abst 11.

5. Battle, M.M., Weinryb, I., Neefe, D.L., Klamerus, K.J., Burghart, P.H., Mayer, P.R. *Pharmacokinetic (PK) and pharmacodynamic (PD) interactions between tasosartan and enalapril in hypertensives*. J Cardiovasc Pharmacol 1997, 37(9): Abst 12.

6. Séchaud, R., Battle, M.M., Sambol, N.C. *Population pharmacodynamics of tasosartan*. Clin Pharmacol Ther 1998, 63(2): Abst PI-81.

7. Sambol, N.C., Battle, M.M. *Population pharmacokinetics (PK) of enoltasosartan*. Clin Pharmacol Ther 1998, 63(2): Abst PI-84.

8. Lacourciere, Y., et al. *Extended therapeutic control in essential hypertension: Comparison of the impact of missed doses of tasosartan and losartan*. Am J Hypertens 1998, 11(4, Part 2): 105A.

9. Lacourciere, Y., Pool, J.L., Svetkey, L., Gradman, A.H., Larochelle, P., de Champlain, J., Smith, W.B. *A randomized, double-blind, placebo-controlled, parallel-group, multicenter trial of four doses of tasosartan in patients with esential hypertension*. Am J Hypertens 1998, 11(4, Part 1): 454.

10. *FDA panel recommends approval of Verdia*. Daily Essentials Jan 28, 1998.

11. *Wyeth-Ayerst withdraws Verdia NDA*. Daily Essentials March 5, 1998.

12. *Tasosartan international status updated*. Daily Essentials April 22, 1998.

Original monograph - Drugs Fut 1997, 22: 850.

Additional References

Battle, M.M. et al. *Influence of a high-fat meal on the bioavailability of tasosartan*. J Hypertens 1998, 16(Suppl. 2): Abst P31.007.

Battle, M.M. et al. *Effects of tasosartan and glybucide coadministration in patients with noninsulin-dependent diabetes mellitus*. J Hypertens 1997, 15(Suppl. 4): Abst 26.

Battle, M.M. et al. *Tasosartan and atenolol: Interaction in hypertensives*. Am J Hypertens 1997, 10(4, Part 2): 125A.

Battle, M.M. et al. *Pharmacokinetic and pharmacodynamic study of the potential drug interaction between tasosartan and warfarin in healthy subjects*. J Hypertens 1998, 16(Suppl. 2): Abst P15.67.

Battle, M.M. et al. *Study of the potential drug interaction between tasosartan and digoxin in healthy volunteers*. J Hypertens 1998, 16(Suppl. 2): S304.

Battle, M.M. et al. *The effects of age and gender on the pharmacokinetics and pharmacodynamics of tasosartan in patients with stage 1 to 2 essential hypertension*. J Hypertens 1998, 16(Suppl. 2): S304.

Hultin, T.A. et al. *Comparative metabolism of tasosartan in mice, rats, dogs and monkeys*. 6th Eur ISSX Meet (June 30-July 3, Gothenburg) 1997, Abst 226.

Lacourciere, Y. *Treatment of ambulatory hypertensives with tasosartan alone or combined with hydrochlorothiazide*. J Hypertens 1998, 16(Suppl. 2): Abst 8Z.4.

Lacourciere, Y., Poirier, L. *Tasosartan: A once-a-day angiotensin II (AII) receptor antagonist with a documented dose-response*. J Hypertens 1997, 15(Suppl. 4): Abst P3.101.

Neefe, D.L. et al. *Tasosartan and nicardipine interaction in patients with essential hypertension*. J Hypertens 1997, 15(Suppl. 4): Abst 234.

Neefe, D.L. et al. *Multiple dose safety, pharmacokinetic (PK) and pharmacodynamic study of tasosartan in patients with mild to moderate hypertension*. J Hypertens 1997, 15(Suppl. 4): Abst P3.109.

Neutel, J.M. et al. *Efficacy and tolerability of tasosartan, a novel angiotensin II antagonist: Results from a 10-week double-blind, placebo-controlled, dose-titration study*. J Hypertens 1997, 15(Suppl. 4): Abst P3.110.

Ochalski, L.A. et al. *Role of angiotensin II AT_1 receptors in regional hemodynamics in conscious Goldblatt (2K-1C) hypertensive rats*. J Am Soc Nephrol 1996, 7(9): Abst A1453.

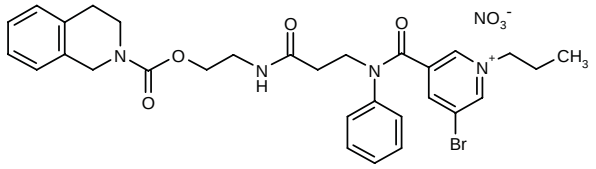
Viigimaa, M. et al. *Combination therapy with tasosartan and hydrochlorothiazide in severe essential hypertension: Comparison with enalapril*. J Hypertens 1998, 16(Suppl. 2): S360.

Two NDAs up for review this week by Cardiovascular and Renal Drugs Advisory Committee. Daily Essentials Jan 26, 1998.

TCV-309

PAF Antagonist
Antipsoriatic
Treatment of Septic Shock

EN: 164606



$C_{30}H_{34}BrN_5O_7$ **Takeda**

TCV-309, in contrast to dexamethasone and indomethacin, did not suppress eosinophil infiltration in Wistar rats induced by Sephadex beads, indicating that PAF is not involved in this type of eosinophil infiltration (1).

The protective effects of TCV-309 administered alone or in combination with PGE_1 were evaluated in a swine model of lung transplantation. TCV-309 blocked the effect of platelet activating factor when administered 1 h prior to cross-clamping for donor and recipient, thus protecting the lungs from extended ischemic injury. Coadministration of PGE_1 appeared to potentiate the drug's effect (2).

TCV-309 had no effect on bacterial growth in cultured medium, whereas in human whole blood, it significantly inhibited Gram-negative and Gram-positive bacteria-induced TNF, IL-6 and IL-8 production (3)

1. Miyake, M., Sakamoto, T., et al. *Effects of dexamethasone, indomethacin and TCV-309 (PAF receptor antagonist) on eosinophil infiltration in airways after i.v. injection of cefadex beads*. Jpn J Allergol 1997, 46(8-9): Abst 306.

2. Qayumi, A.K., English, J.E., Duncan, S., Ansley, D.M., Pearson, B., Nikbakht Sangari, M., Sammartino, C., Fradet, G. *Extended lung preservation with platelet-activating factor-antagonist TCV-309 in combination with prostaglandin E-1*. J Heart Lung Transplant 1997, 16(9): 946.

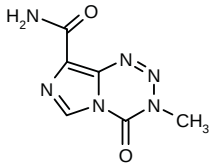
3. Ogata, M., Suenaga, T., Noguchi, T., Kawasaki, T., Shigematsu, A. *A PAF antagonist (TCV-309) inhibited Gram negative and positive bacteria induced cytokine production*. Am J Respir Crit Care Med 1998, 157(3): A104.

Original monograph - Drugs Fut 1993, 18: 721.

Temozolomide
Temodal®

Antineoplastic

EN: 108485



$C_6H_6N_6O_2$ **CRC Technol.; Schering-Plough; Natl. Cancer Inst. (US)**

A phase II study in 10 patients with advanced hepatocellular carcinoma in various stages of cirrhosis and portal hypertension demonstrated that the pharmacokinetics of temozolomide (150 mg/m^2 p.o. on days 1-5 q28d) and its active agent MTIC were similar in patients with mild to moderate hepatic dysfunction, and did not differ significantly from those of patients with normal liver function (1).

In a phase II trial in 12 patients with metastatic renal cell carcinoma, treatment with temozolodine (200 mg^2/day p.o. x 5 days of 28-day cycles) resulted in stable disease in 1 patient after 9 cycles; no objective responses were observed. Toxicity included grade 3 and 4 thrombopenia in 3 patients and 1 patient, respectively, and grade 2 nausea and vomiting, which were successfully controlled with granisetron (2).

In a phase II study of oral temozolodine (200 mg/m^2/day x 5 days) in children with progressive brain stem gliomas, 7 of 15 evaluable patients had static disease responses; no partial or complete responses were observed. Duration of static disease was short and median survival was only 5.5 months, indicating the lack of efficacy of the drug at this dosing regimen (3).

In a phase I study, patients with metastatic malignant melanoma were treated with temozolomide (750 mg/m^2 or 1.0 g/m^2 p.o. x 5 days every 28 days) and continuous interferon α-2b (5 MU/m^2 s.c. t.i.w., escalated by 2.5 MU/m^2 between cohorts). Results showed that temozolomide was rapidly absorbed and eliminated. Dose-limiting toxicities included thrombocytopenia, hematologic toxicity and nonhematologic toxicity, including nausea/vomiting. The combination of drugs produced antitumor activity and stability of tumor growth in 3/12 and 4/12 patients, respectively (4).

A multicenter phase II trial has assessed the efficacy and safety of temozolomide in patients with progressive or recurrent supratentorial high-grade gliomas. Of 103 eligible patients treated on a schedule of 150-200 mg/m^2/day p.o. for 5 days every 28 days, 11 achieved an objective response and 48 had stable disease, with a median duration of response of 4.6 months. The major toxicity was predictable myelosuppression (5).

No sequence-dependent toxicologic or pharmacokinetic effects were observed in patients with solid neoplasms during a phase I study of BCNU (50 or 75 mg/m^2

i.v. on day 1 or day 5) administered with temozolomide (35 or 55 mg/m2 p.o. daily x 5 days) every 42 days (6).

A phase I study in 25 evaluable children and adolescentes with recurrent solid tumors treated with temozolomide (100-260 mg/m^2/day p.o. for 5 days every 21-28 days) determined from dose limiting toxicity data that the initial dose of the drug in phase II studies should start at 180 mg/m^2/day x 5 days or 215 mg/m^2/day x 5 days (both in 28 day cycles) for those with or without prior craniospinal irradiation, respectively (7).

Temozolomide uptake was investigated in 5 patients with recurrent high grade astrocytomas. Tumor uptake was found to be significantly greater than that of contralateral brain, although perfusion was significantly poorer. No difference in tissue retention was observed between tumor and normal contralateral brain (8).

Results of a phase I study in patients (n=10) with advanced cancer treated with a combination of temozolomide (100-200 mg/m^2/day x 5 days) and cisplatin (75-100 mg/m^2 on day 1), every 4 weeks showed that cisplatin does not alter the pharmacokinetics of temozolomide and that the combination of drugs is well tolerated, with nausea/vomiting and neutropenia the most common drug-related toxicities (9).

A phase II study of oral temozolomide (150-200 mg/m^2 daily x 5 every 28 days) in 161 patients with anaplastic astrocytoma and oligoastrocytoma determined that the drug is safe and effective, causing mild nausea/vomiting, neutropenia and thrombocytopenia. Complete and partial response was 42%, with 24% stable disease (10).

Schering-Plough has submitted a centralized MAA to the European Medicines Evaluation Agency seeking approval to market temozolomide (Temodal®) for the treatment of recurrent malignant gliomas such as glioblastoma multiforme and anaplastic astrocytoma (11).

Sparta has signed a license agreement with Schering-Plough for the use of their Spartaject™ drug delivery system for temozolomide, which is in development for the treatment of recurrent malignant gliomas such as glioblastoma multiforme and anaplastic astrocytoma. Application of the system to temozolomide may allow for intravenous administration in patients who require high-concentration levels in the blood and/or for the administration of the drug in localized areas in direct contact with certain tumors (12).

1. Findlay, M., Clarke, S.J., Boyer, M., Sullivan, A., Dugan, M., Statkevich, P., Reyderman, L., Teriana, N., Cox, K. *Temodal® (temozolomide; TMZ) in patients with hepatocellular carcinoma (HCC), cirrhosis and portal hypertension: A phase II/pharmacokinetic (PK) study*. Proc Amer Soc Clin Oncol 1998, Abst 923.

2. Di Palma, M., Vannetzel, J.M., Bensadoun, H., Benoit, G., Cvitkovic, E., Boyer, P., Misset, J.L. *Phase II study of temozolomide (TEM) in metastatic renal cell carcinoma (MRCC)*. Proc Amer Soc Clin Oncol 1998, Abst 1271.

3. Lashford, L.S., Pearson, A.D.J., Thiesse, P., Jasparn, T., Vassal, G., Dugan, M., Frappaz, D. *Efficacy of Temodal® in diffuse, intrinsic brain stem gliomas (BSG)*. Proc Amer Soc Clin Oncol 1998, Abst 2086.

4. Kirkwood, J.M., Agarwala, S.S., Diaz, B., Donnelly, S., Statkevich, P., Dugan, M. *Phase I study of temozolomide in combination with interferon alfa-2b in metastatic malignant melanoma*. Proc Amer Soc Clin Oncol 1997, Abst 1767.

5. Bower, M., Newlands, E.S., Bleehen, N.M., Brada, M., Begent, R.J.H., Calvert, H., Colquhoun, I., Lewis, P., Brampton, M.H. *Multicentre CRC phase II trial of temozolomide in recurrent or progressive high-grade glioma*. Cancer Chemother Pharmacol 1997, 40(6): 484.

6. Hammond, L., Eckardt, J., Kuhn, J., et al. *Phase I and pharmacokinetic (PK) trial of sequences of BCNU and temozolomide (TMZ) in patients with solid neoplasms*. Proc Amer Soc Clin Oncol 1997, Abst 750.

7. Nicholson, H.S., Krailo, M., Seibel, N.L., Ames, M.M., Renick-Ettinger, A., Reaman, G.H. *Phase I study of temozolomide (TEM) in children and adolescents. A report from the Children's Cancer Group (CCG)*. Proc Amer Soc Clin Oncol 1997, Abst 751.

8. Brock, C.S., Matthews, J.C., Brown, G., Osman, S., Luthra, S.K., Brady, F., Newlands, E.S., Price, P. *Temozolomide uptake in human astrocytomas demonstrated in vivo*. Proc Amer Soc Clin Oncol 1997, Abst 812.

9. Eckhardt, S.G., Atkins, Y., Agarwala, S.S., et al. *A phase I study of temozolomide combined with cisplatin (CDDP) in patients with advanced cancer*. Proc Amer Soc Clin Oncol 1997, Abst 830.

10. Levin, V., Yung, A., Prados, M., et al. *Phase II study of Temodal® (temozolomide) at first relapse in anaplastic astrocytoma (AA) patients*. Proc Amer Soc Clin Oncol 1997, Abst 1370.

11. *Temodal submitted for approval in E.U.* Daily Essentials Jan 13, 1998.

12. *Sparta licenses drug delivery technology for temozolomide to Schering-Plough*. Daily Essentials April 27, 1998.

Original monograph - Drugs Fut 1994, 19: 746.

Additional References

Baker, S.D. et al. *Absorption, metabolism and excretion of ^{14}C-temozolomide in patients with advanced cancer*. Proc Amer Soc Clin Oncol 1997, Abst 749.

Dhodapkar, M. et al. *Phase I trial of temozolomide (NSC 362856) in patients with advanced cancer*. Clin Cancer Res 1997, 3(7): 1093.

Fruehauf, J.P. et al. *In vitro synergistic activity of L-buthionine-S, R-sulfoximine (BSO) with BCNU and temozolomide on human glioblastoma multiforme*. Proc Amer Soc Clin Oncol 1998, Abst 763.

Graziani, G. et al. *Inhibition of DNA repair enzyme potentiates apoptosis induced by temozolomide*. Cancer Detect Prev 1996, 20(5): Abst 372.

Kim, H.K. et al. *High-performance liquid chromatographic determination and stability of 5-(3-methyltriazen-1-yl)-imidazo-4-carboxamide, the biologically active product of the antitumor agent temozolomide, in human plasma*. J Chromatogr B 1997, 703(1-2): 225.

Newlands, E.S. et al. *Temozolomide: A review of its discovery, chemical properties, pre-clinical development and clinical trials*. Cancer Treat Rev 1997, 23(1): 35.

Newlands, E.S. et al. *Temozolomide: Drug scheduling in vivo and in combination with radiation*. Proc Amer Soc Clin Oncol 1997, Abst 1403.

Raymonds, E. et al. *Activity of temozolomide against human tumor colony-forming units*. 7th Annu Symp Cancer Res (July 25, San Antonio) 1997, Abst 21.

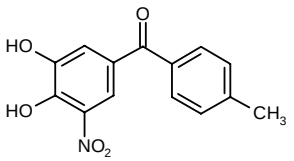
Wang, Y.F. et al. *Antitumor imidazotetrazines. Part 36. Conversion of 5-aminoimidazole-4-carboxamide to imidazo[5,1-d][1,2,3,5]tetrazin-4(3H)-ones and imidazo[1,5-a][1,3,5]triazin-4(3H)-ones related in structure to the antitumor agents temozolomide and mitozolomide*. J Chem Soc Perkins Trans I 1998, 1669.

Wedge, S.R. et al. *Effect of single and multiple administration of an O-6-benzylguanine/temozolomide combination: An evaluation in a human melanoma xenograft model*. Cancer Chemother Pharmacol 1997, 40(3): 266.

Tolcapone
Tasmar®

Antiparkinsonian
COMT Inhibitor

EN: 163695



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

A multicenter clinical study was performed in a group of 250 parkinsonian patients in order to discern whether tolcapone reduces sleep disabilities. The compound was administered at doses of 100 and 200 mg t.i.d. in combination with levodopa/decarboxylase inhibitor following a double-blind, placebo-controlled design. Patients were treated for periods of 6-12 weeks, and sleep disabilities were rated using a patient questionnaire. Subjects in the 200-mg tolcapone group reported significantly greater reductions in sleep disabilities as compared to baseline than patients in the placebo group. Furthermore, a responder analysis indicated that a significantly higher percentage of patients in the high-dose tolcapone group than patients in the placebo group qualified as responders (46% *vs.* 21%). As judged by the Sleep and Rest subscale of the Sickness Impact Profile (SIP), parkinsonian patients in both the low- and high-dose tolcapone groups showed greater improvement in sleep parameters than subjects on placebo. Thus, the 200-mg t.i.d. dose of tolcapone appears to be appropriate for the treatment of patients with Parkinson's disease in whom sleep disability is a significant component of the disease symptomatology (1).

The effects of tolcapone (200 or 400 mg t.i.d.) were evaluated in 97 patients with Parkinson's disease and whose "wearing-off" phenomenon was controlled by more frequent levodopa administration. Patients receiving 200 mg tolcapone demonstrated better improvement in estimated mean scores for all efficacy parameters, and reported fewer dopaminergic and nondopaminergic adverse events than patients treated with the 400-mg dose. Adverse events included nausea, cramps, dyskinesia and dystonia (2).

Tolcapone-induced inhibition of catechol-*O*-transferase was evaluated in 298 patients with Parkinson's disease treated with levodopa but without motor fluctuations. After 6 months, patients receiving tolcapone (100 or 200 mg t.i.d.) demonstrated significant reductions in the Unified Parkinson's Disease Rating Scale score for activities of daily function and motor function (3).

In a single-blind, randomized study in healthy volunteers, tolcapone (5, 10, 25, 50, 100, 200, 400 and 800 mg) administered in combination with carbidopa/levodopa (25 mg/100 mg) produced 2-fold increases in AUC and half-life, without affecting C_{max}. The effects were most pronounced following the 200-mg dose (4).

Tolcapone was evaluated in an open trial in 21 patients with major depressive disorder. At a dose of 400 mg b.i.d. for eight weeks, symptomatic improvement, as measured by several scales, was observed, suggesting that tolcapone may have promise in the treatment of major depressive disorder (5).

The effects of catechol-*O*-methyltransferase inhibition by oral tolcapone (200 mg) on the pharmacokinetics of various levodopa/benserazide formulations were evaluated in 16 healthy volunteers. Plasma half-life, AUC and bioavailability of levodopa increased approximately 2-fold by the combination regimen, while C_{max} and t_{max} were virtually unaffected. Thus, tolcapone may potentiate the beneficial effects of levodopa in the treatment of Parkinson's disease (6).

Administration of tolcapone (100, 200, 400 or 800 mg t.i.d.) in combination with levodopa/carbidopa (100 mg/25 mg) in 36 elderly volunteers produced a 2-fold increase in the AUC and elimination half-life of levodopa, without affecting its C_{max}. These effects were observed after 1 day of treatment and reached their maximum after the 100-mg and 200-mg doses. Tolcapone pharmacokinetics were linear and stable with accumulation observed following the 800-mg dose. Treatment was well tolerated, although nausea and vomiting were reported with the 400-mg and 800-mg doses (7).

The ability of tolcapone, added to levodopa plus a decarboxylase inhibitor, to reduce the "wearing-off" phenomenon in parkinsonian patients has been assessed in a double-blind, randomized, placebo-controlled, parallel-group study. One hundred and fifty-four patients with Parkinson's disease received tolcapone at doses of 50, 200 or 400 mg t.i.d. or placebo for 6 weeks. Tolcapone was more effective than placebo in reducing the "wearing-off" phenomenon at all three doses and was generally well tolerated (8).

Tolcapone (Tasmar®) was introduced in the U.K. and Germany on August 29, 1997 as 100- and 200-mg tablets for the treatment of Parkinson's disease (9).

Roche has received FDA approval for tolcapone (Tasmar®) for the treatment of Parkinson's disease (10).

1. Stiasny, K., Deptula, D., Dorflinger, E. *The beneficial effects of tolcapone (Tasmar) on sleep disability in Parkinson's disease patients with motor fluctuations*. 50th Annu Meet Amer Assoc Neurol (April 25-May 2, Minneapolis) 1998, Abst S30.005.

2. Dupont, E., Burgunder, J.M., Findley, L.J., et al. *Tolcapone added to levodopa in stable parkinsonian patients: A double-blind placebo-controlled study*. Mov Disord 1997, 12(6): 928.

3. Waters, C.H., Kurth, M., Bailey, P., Shulman, L.M., Le Witt, P., Dorflinger, E., Deptula, D., Pedder, S. *Tolcapone in stable Parkinson's disease: Efficacy and safety of long-term treatment*. Neurology 1997, 49(3): 665.

4. Sedek, G., Jorga, K., Schmitt, M., Burns, R.S., Leese, P. *Effect of tolcapone on plasma levodopa concentrations after coadministration with levodopa/carbidopa to healthy volunteers*. Clin Neuropharmacol 1997, 20(6): 531.

5. Moreau, J.-L., Fava, M., Jenck, F., Martin, J.R., Magni, G., Moroz, G. *Preclinical and clinical evidence for antidepressant properties of the COMT inhibitor tolcapone*. Biol Psychiatry 1997, 42(1, Suppl.): Abst 14-105.

6. Jorga, K., Fotteler, B., Schmitt, M., Nielsen, T., Zurcher,G., Aitken, J. *The effect of COMT inhibition by tolcapone on tolerability and pharmacokinetics of different levodopa/benserazide formulations*. Eur Neurol 1997, 38(1): 59.

7. Jorga, K.M., Sedek, G., Fotteler, B., Zürcher, G., Nielsen,T., Aitken, J.W. *Optimizing levodopa pharmacokinetics with multiple tolcapone doses in the elderly*. Clin Pharmacol Ther 1997, 62(3): 300.

8. Myllyla, V.V., Jackson, M., Larsen, J.P., Baas, H. *Efficacy and safety of tolcapone in levodopa-treated Parkinson's disease patients with "wearing-off" phenomenon: A multicentre, double-blind, randomized, placebo-controlled trial*. Eur J Neurol 1997, 4(4): 333.

9. *Tasmar launched in U.K., Germany*. Daily Essentials Sept 3, 1997.

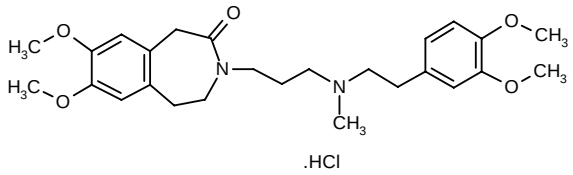
10. *Tasmar cleared by FDA*. Daily Essentials Feb 3, 1998.

Original monograph - Drugs Fut 1991, 16: 719.

Zatebradine Hydrochloride

Antianginal

EN: 090566



.HCl

$C_{26}H_{36}N_2O_5$.HCl

Boehringer Ingelheim

In a rat model of myocardial infarction, zatebradine (100 mg/kg/day) administered 30 min after coronary artery ligation significantly reduced the rate of mortality as compared to placebo (46% *vs.* 66%, respectively). Reductions in heart rate were also observed, while left ventricular systolic pressure was not affected. Stroke volume index increased in all animals. Left ventricular volume increased in zatebradine-treated animals with small-size infarction, whereas in animals with large-size infarction it was unaffected (1).

The results from a study in patients with chronic stable angina pectoris showing no significant effect on myocardial ischemia for the bradycardic agent zatebradine hydrochloride in spite of a significant decrease in resting and exercise heart rate suggest that the use of such agents as antiischemics should be reassessed (2).

1. Hu, K., Gaudron, P., Kaden, J., Hagebeuker, A., Fraccarollo, D., Schönaich, E., Ertl, G. *Long-term effects of heart rate reduction by zatebradine on mortality, hemodynamics and remodeling in rats with experimental myocardial infarction*. J Am Coll Cardiol 1998, 31(2, Suppl. A): Abst 1159-107.

2. Glasser, S.P., Michie, D.D., Thadani, U., Baiker, W.M. *Effects of zatebradine (ULFS 49 CL), a sinus node inhibitor, on heart rate and exercise duration in chronic stable angina pectoris*. Am J Cardiol 1997, 79(10): 1401.

Original monograph - Drugs Fut 1985, 10: 639.