Drugs of the Future 2001, 26(8): 793-827

CCC: 0377-8282/2001

# Information Update

**Volume 1-25, Number 8**

**Estimated developmental phase for this month's updated products:**

*Preclinical*

J-111225 (carbapenem antibiotic; Banyu)
J-114870 (carbapenem antibiotic; Banyu)
Lidamycin (antineoplastic antibiotic; Chin. Acad. Med. Sci., Taiho)

*Phase I*

Clevudine (anti-HBV; Bukwang, Triangle Pharm., Abbott)

*Phase II*

Adrogolide hydrochloride (antiparkinsonian, dopamine $D_1$ agonist; Abbott)
Alvameline tartrate (treatment of urinary incontinence; Forest, Lundbeck) - discontinued 2001
Asulacrine isethionate (oncolytic; Cancer Res. Campaign, Pfizer, Sparta)
BI-397 (glycopeptide antibiotic; Biosearch Italia, Versicor)
FK-960 (treatment of Alzheimer's dementia; Fujisawa)
Glufosfamide (oncolytic; Asta Medica)
HCT-1026 (treatment of urinary incontinence, treatment of osteoporosis, topical antiinflammatory; NicOx)
JTT-501 (antidiabetic; Japan Tobacco, Pharmacia)
L-651582 (oncolytic; Natl. Cancer Inst., Merck & Co.)
Liposomal NDDP (oncolytic, platinum complex; Aronex, M.D. Anderson Cancer Center)
Ono-4007 (oncolytic, immunomodulator; Ono)
TCV-309 (treatment of septic shock, PAF antagonist; Takeda)

*Phase III*

Adeovir dipivoxil (anti-HIV, anti-HBV; Gilead)
Emtricitabine (anti-HIV, anti-HBV; Emory Univ., Triangle Pharmaceuticals, Abbott)
Oral heparin (anticoagulant; Emisphere, DuPont Pharm.)
SNAC (absorption promoter; Emisphere, DuPont Pharm.)
Pimagedine (treatment of diabetic retinopathy; Alteon, Yamanouchi)
Pregabalin (antiepileptic, treatment of diabetic neuropathy; Pfizer)
YM-905 (treatment of urinary incontinence; Yamanouchi)

*Preregistered*

Bropirimine (oncolytic; Pharmacia, Yakult Honsha)
Itavastatin calcium (hypolipidemic; Nissan Chem., Kowa, Sankyo, Negma, SkyePharma)
Lepirudin (anticoagulant; Aventis Pharma)
Liposomal nystatin (antifungal; Aronex, M.D. Anderson Cancer Center, Ferrer, Abbott)
MK-0826 (carbapenem antibiotic; AstraZeneca, Merck & Co.)
Pazufloxacin (quinolone antibacterial; Toyama, Welfide)

*Recommended Approval/Year*

Teriparatide (treatment of osteoporosis, parathyroid hormone; Lilly, Inhale, Emisphere)/2001

*Launched/Year*

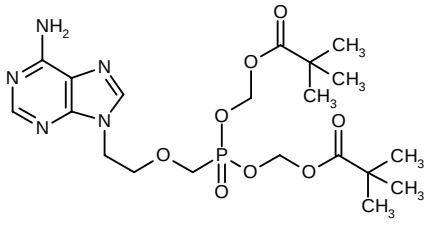
Alosetron hydrochloride (treatment of IBS, 5-$HT_3$ antagonist; GlaxoSmithKline)/2000 - withdrawn 2001
Bunazosin hydrochloride (antihypertensive, antiglaucoma; Eisai, Santen)/1985
Cyclosporine (immunosuppressant; SangStat, Novartis)/1983
Leflunomide (antiarthritic, oncolytic; Aventis Pharma, Sugen, Kyorin)/1998
Lornoxicam (antiarthritic, analgesic; Nycomed Amersham, CeNeS)/1997
Pantoprazole sodium (treatment of GERD; Byk Gulden, Solvay, American Home Products)/1994
Perindopril (antihypertensive, ACE inhibitor; Servier)/1988
Ropinirole hydrochloride (antiparkinsonian, treatment of RLS; GlaxoSmithKline, SkyePharma)/1996
Ropivacaine hydrochloride (anesthetic; AstraZeneca)/1996
Rosaprostol sodium (antiulcer; Ist. Biochim. Ital. Giovanni Lorenzini)/1985
Samarium ($^{153}$Sm) lexidronam (analgesic, antiarthritic; Aventis Pharma, Cytogen, Berlex)/1997
Sibutramine hydrochloride monohydrate (antiobesity; Knoll, AstraZeneca)/1998
Tacrolimus (treatment of atopic dermatitis, treatment of transplant rejection; Fujisawa)/1993
Zonisamide (antiepileptic, antimigraine; Dainippon Pharm., Elan, Draxis Health)/1989

## Adefovir Dipivoxil
## Preveon™

*Anti-HIV*
*Anti-HBV*

EN: 196738



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

A study examined the intestinal absorption properties of adefovir and its prodrug adefovir dipivoxil in 3 models: *in vitro* Caco-2 monolayers, *ex vivo* rat intestinal sheets and *in situ* perfusion of the rat ileum. Results showed that metabolism of the agent was more marked in the *ex vivo* and *in situ* models. However, total adefovir transport was similar in all models. In comparison to adefovir, application of adefovir dipivoxil resulted in significantly increased transport of total adefovir *in vitro* (about 100-fold) and *in situ* (about 10-fold); this was not observed in the *ex vivo* model. Similarly, verapamil also enhanced total adefovir transport *in vitro* and *in situ* but had no effect *ex vivo*. It was concluded that the *ex vivo* model was not as effective as the other models in assessing transport characteristics of the agent (1).

The safety and efficacy of adefovir dipivoxil (ADV) were examined in a 48-week trial involving 35 lamivudine-resistant patients coinfected with HIV and HBV and with detected M552V or M552I mutations in the HBV DNA polymerase gene. ADV (10 mg/day) was added to anti-HIV therapy and lamivudine (150 mg b.i.d.). ADV was generally well tolerated. Only 2 patients discontinued for reasons not related to ADV treatment. ADV significantly decreased HBV DNA from baseline (8.64 ± 0.08 $\log_{10}$ copies/ml) at week 12, 24 and 36 by –2.90 ± 0.12, –3.40 ± 0.12 and –4 ± 0.2 $\log_{10}$ copies/ml, respectively. With treatment, 4 patients became HBeAg negative, of whom 2 presented antibodies. No changes in ALT levels, serum electrolytes, renal function, HIV RNA levels or CD4 cell counts were observed (2).

Gilead's 2-year, randomized, double-blind, placebo-controlled phase III trial of adefovir dipivoxil once daily as monotherapy for the treatment of hepatitis B virus (HBV) infection has reached the primary endpoint in liver histology at week 48 compared to baseline. Improvement in liver histology was observed in 53% of patients treated with adefovir dipivoxil 10 mg compared to 25% of placebo-treated patients, as measured by liver biopsies. A complete analysis of the data is expected to be presented at scientific conferences later this year and in 2002. The efficacy and safety study evaluated two doses (10 mg and 30 mg) of adefovir dipivoxil compared to placebo. A total of 515 patients in the U.S., Canada, Europe, Australia and Southeast Asia are participating in the trial. During the first year of the study, 172 patients were randomized to the adefovir dipivoxil 10 mg arm, 173 to the adefovir dipivoxil 30 mg arm and 170 to placebo. In addition to improvement in liver histology, seroconversion was observed in 12% of patients treated with adefovir dipivoxil 10 mg for 48 weeks, compared to 6% of patients on placebo. Furthermore, patients in the adefovir dipivoxil 10 mg arm had a median reduction in HBV DNA from baseline of 3.56 $\log_{10}$ copies/ml, compared to a reduction of 0.55 $\log_{10}$ copies/ml in patients receiving placebo. In terms of the safety profile, the discontinuation rate was similar in the treatment and placebo arms. In addition, the incidence of grade 3 and 4 laboratory abnormalities and clinical adverse effects was similar in the adefovir dipivoxil 10 mg and placebo arms. Preliminary genotypic analyses from this study show no adefovir resistance mutations after 48 weeks of treatment. Another phase III trial is currently under way to evaluate adefovir dipivoxil (10 mg) monotherapy for the treatment of HBeAg negative patients (precore mutant HBV infection). A total of 185 patients have been enrolled in Australia, Canada, France, Greece, Israel, Italy and Southeast Asia. Gilead expects to report results from this study during the second half of this year. The company anticipates filing regulatory applications for adefovir dipivoxil in the U.S. and Europe during the first half of 2002 (3).

Preliminary data from an ongoing open-label pilot study evaluating the safety and efficacy of adefovir dipivoxil 10 mg once daily in the treatment of lamivudine-resistant chronic HBV infection in 35 patients coinfected with HIV and HBV were reported. Patients in this study have documented lamivudine-associated resistance mutations in the YMDD domain of HBV polymerase and a mean HBV DNA serum level of 8.64 $\log_{10}$ copies/ml at entry. They have received a median of 28 weeks of therapy with adefovir added to their existing anti-HIV therapy, including lamivudine. A mean decrease in HBV DNA from baseline of 3.40 $\log_{10}$ copies/ml was obtained at 24 weeks and the trial continues through 48 weeks of therapy. Adefovir was well tolerated (4).

A study analyzing serum samples from 28 out of 39 HBV-infected patients participating in a 48-60 week, open-label trial examining the safety and efficacy of adefovir dipivoxil (5-60 mg/day) did not detect emergence of HBV polymerase mutations associated with adefovir resistance (5).

Gilead has initiated phase I trials of adefovir dipivoxil for the treatment of chronic HBV infection in China. Outside China, Gilead is currently evaluating adefovir dipivoxil in phase III clinical studies in North America, Europe, Asia and Australia (6).

1. Annaert, P., Tukker, J.J., Van Gelder, J., Naesens, L., De Cliercq, E., Van Den Mooter, G., Kinget, R., Augustijns, P. *In vitro, ex vivo, and in situ intestinal absorption characteristics of the antiviral ester prodrug adefovir dipivoxil.* J Pharm Sci 2000, 89(8): 1054.

2. Benhamou, Y., Bochet, M., Tribault, V., Brosgart, C., Vig, P., Gibb, C., Fry, J., Opolon, P., Katlama, C., Poynard, T. *Safety and efficacy of adefovir dipivoxil for lamivudine resistant HBV in HIV infected patients.* J Hepatol 2001, 34(Suppl. 1): 24.

3. *Primary endpoint achieved in phase III trial of Gilead's adefovir dipivoxil for HBV.* DailyDrugNews.com (Daily Essentials) July 13, 2001.

4. Benhamou, Y., Bochet, M., Thibault, V. et al. *An open label pilot study of the safety and efficacy of adefovir dipivoxil in HIV/HBV co-infected patients with lamivudine resistant HBV.* Hepatology 2000, 32(4, Part 2): Abst 1199.

5. Xiong, X., Yang, H., Westland, C., Ho, V., Fry, J., Brosgart, C., Gibbs, C., Miller, M. *Genotypic analysis of HBV isolated from patients exposed to adefovir dipivoxil (ADV) for 48 to 60 weeks.* J Hepatol 2001, 34(Suppl. 1): 24.

6. *Gilead begins phase I study of adefovir dipivoxil in China for treatment of HBV.* DailyDrugNews.com (Daily Essentials) June 13, 2001.

*Original monograph* - Drugs Fut 1997, 22: 825.

**Additional References**

Bartholomeusz, A. et al. *Analysis of hepatitis B virus mutations in orthotopic liver transplant patients receiving sequential antiviral therapy.* Hepatology 2000, 32(4, Part 2): Abst 1189.

Benhamou, Y. et al. *An open label pilot study of the safety and efficacy of adefovir dipivoxil in HIV/HBV co-infected patients with lamivudine resistant HBV.* 8th Conf Retroviruses Opportunistic Infect (Feb 4-8, Chicago) 2001, Abst 36.

Bestman-Smith, J. et al. *Patterns of resistance to foscarnet, cidofovir, and adefovir conferred by specific mutations within the DNA pol gene of clinical HSV isolates.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst H-467.

Delaney, W.E. IV et al. *Resistance of hepatitis B virus to antiviral drugs: Current aspects and directions for future investigation.* Antivir Chem Chemother 2001, 12(1): 1.

Holy, A. et al. *Synthesis of N-(2-phosphonylmethoxyethyl) derivatives of heterocyclic bases.* Coll Czech Chem Commun 1989, 54: 2190.

Holy, A., Rosenberg, I. *Synthesis of 9-(2-phosphonylmethoxyethyl)adene and related compounds.* Coll Czech Chem Commun 1987, 52: 2801.

Morrey, J.D. et al. *Antiviral activity of adefovir dipivoxil in transgenic mice expressing hepatitis B virus.* Antivir Res 2001, 50(1): Abst 141.

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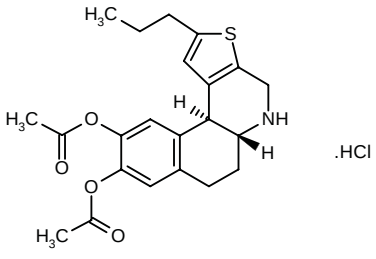
## Adrogolide Hydrochloride
## ABT-431

*Antiparkinsonian*
*Dopamine $D_1$ Agonist*

EN: 222577




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

A multicenter, randomized, double-blind trial and a multicenter, randomized, open trial in a total of 20 patients with advanced Parkinson's disease and fluctuating responses to levodopa complicated by dyskinesias examined the potential of ABT-431 to cause dyskinesia. Dyskinetic responses were elicited by an acute challenge with a suprathreshold dose of levodopa and ABT-431 (5, 10, 20 or 40 mg) 6 h later. Similar results were obtained in the two studies. Antiparkinsonian responses according to the Unified Parkinson's Disease Rating Scale and dyskinetic responses were dependent on ABT-431 dose. ABT-431 at doses of 20 and 40 mg had similar antiparkinsonian benefits and produced dyskinesias in a manner comparable to levodopa. Thus, ABT-431 is not more or less likely than levodopa to produce dyskinesias (1).

1. Rascol, O., Nutt, J.G., Blin, O. et al. *Induction by dopamine $D_1$ receptor agonist ABT-431 of dyskinesia similar to levodopa in patients with Parkinson disease.* Arch Neurol 2001, 58(2): 249.

*Original monograph* - Drugs Fut 1997, 22: 821.

**Additional Reference**

Giardina, W.J. et al. *ABT-431, a prodrug of the dopamine $D_1$ receptor agonist A-86929, is inactive in conditioned place preference and self-adminsitration tests of abuse liability.* Soc Neurosci Abst 2000, 26(Part 1): Abst 278.11.

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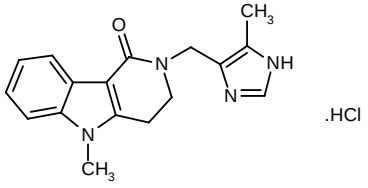
## Alosetron Hydrochloride
## Lotronex®

*Treatment of IBS*
*5-$HT_3$ Antagonist*

EN: 185981




$C_{18}H_{19}N_3O.HCl$ **GlaxoSmithKline**

Glaxo Wellcome has announced the voluntary withdrawal of Lotronex® (alosetron hydrochloride) from the U.S. market, effective immediately, at the request of the FDA. The step was taken after in-depth discussions with the agency about the interpretation of data relating to gastrointestinal adverse events occurring among patients treated with the product, including rare reports of fatalities, although no causal relationship with the drug has been established. During its discussions with the FDA, Glaxo Wellcome proposed a range of initiatives to educate physicians and patients about the management of the potential side effects and benefits of Lotronex®, including further label modifications and patient education programs. However, the FDA indicated that it does not consider these proposals adequate and requested the voluntary withdrawal of the product from the U.S. market.

Glaxo Wellcome is complying with the request, in spite of the fact that the company disagrees with the FDA's assessment of the safety and profile of the product (1).

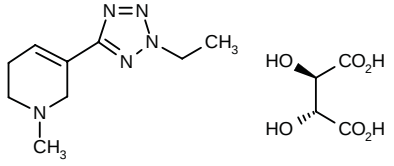
1. *Immediate withdrawal of Lotronex in U.S. announced by Glaxo Wellcome.* DailyDrugNews.com (Daily Essentials) Nov 29, 2000.

*Original monograph* - Drugs Fut 1992, 17: 660.

## Alvameline Tartrate
## LU-25-109T

*Treatment of Urinary Incontinence*

EN: 216348



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

Forest has indicated that a completed phase II study did not demonstrate efficacy for alvameline tartrate in the treatment of incontinence, and the development of this product is therefore being discontinued (1).

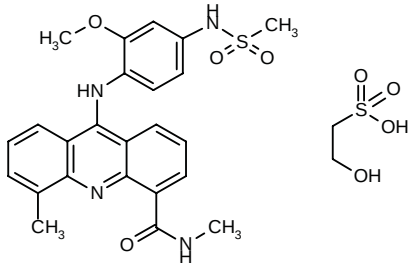
1. *Product developments announced by Forest.* DailyDrugNews.com (Daily Essentials) Feb 2, 2001.

*Original monograph* - Drugs Fut 1998, 23: 843.

## Asulacrine Isethionate
## Amsalog

*Oncolytic*

EN: 090375



$C_{24}H_{24}N_4O_4S.C_2H_6O_4S$ **Cancer Res. Campaign; Pfizer; Sparta**

A phase I trial conducted in 19 patients with refractory malignancies recommended an amsalog dose of 180 mg/m$^2$/day (2-h i.v. infusion/day for 5 days every weeks) for further studies. The DLT was myelosuppression seen with a dose of 200 mg/m$^2$/day. Toxicities seen were nausea, vomiting and fatigue and severe phlebitis when administered by a peripheral venous line. Thus, for doses greater than 100 mg/m$^2$, an indwelling central venous catheter was required. Linear pharmacokinetics were obtained between $C_{max}$ and AUC and dose; the $t_{1/2}$ was 2 h (1).

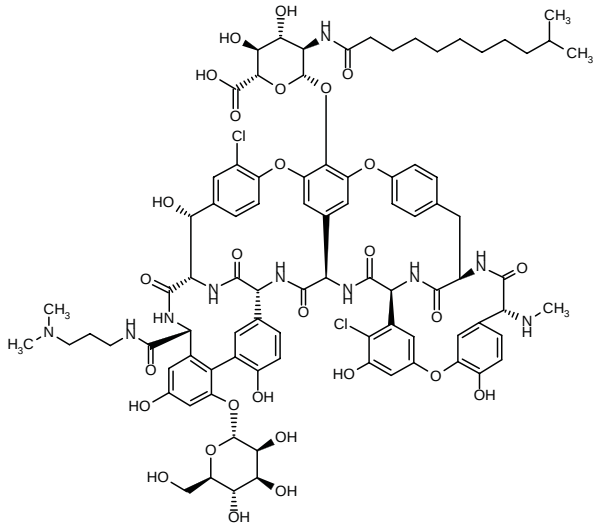
1. Fyfe, D., Price, C., langley, R.E., Pagonis, C., Houghton, J., Osborne, L., Woll, P.J., Gardner, C., Baguley, B.C., Camichael, J. *A phase I trial of amsalog (CI-921) administered by intravenous infusion using a 5-day schedule.* Cancer Chemother Pharmacol 2001, 47(4): 333.

*Original monograph* - Drugs Fut 1984, 9: 575.

## BI-397
## Dalbavancin
## V-Glycopeptide

*Glycopeptide Antibiotic*

EN: 264176



$C_{88}H_{100}Cl_2N_{10}O_{28}$ **Biosearch Italia; Versicor**

V-glycopeptide (VGE), a second-generation glycopeptide belonging to the same class as vancomycin, is under development for the intravenous treatment of serious systemic infections caused by Gram-positive pathogens. Interim results from an ongoing phase I pharmacokinetic and safety trial in healthy subjects were reported. The subjects were administered single 0.5-h i.v. infusions of 70-360 mg of VGE, or 70 mg/day VGE for 7 days in the multiple-dose part of the study. All doses were well tolerated. Pharmacokinetics were proportional to dose and the drug displayed a long half-life of about 174 h, as well as low intersubject variability. Serum bactericidal activity was detected at 24 h following a dose of 360 mg, further supporting a once-daily dosing regimen (1).

A phase I clinical trial currently being conducted in the U.S. is evaluating the *in vivo* bactericidal activity of VGE against both methicillin-sensitive *Staphylococcus aureus* and methicillin-resistant *S. aureus*. VGE showed a rapid

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and long-lasting killing effect *in vivo* against *S. aureus* and single doses of the compound were sufficient to induce dramatic and sustained reductions in bacterial loads (2).

Versicor has initiated a phase II trial of dalbavancin (formerly VGE and BI-397) for the treatment of complicated skin and soft tissue infections caused by Gram-positive bacteria, principally methicillin-resistant *S. aureus* and methicillin-resistant *Staphylococcus epidermidis*. Versicor is Biosearch Italia's licensee for dalbavancin for the U.S. and Canada. The open-label, randomized, controlled study is expected to enroll approximately 60 patients with skin and soft tissue infections, such as abscesses, infected ulcers, burns and cellulitis. Patients will be treated with one of two dalbavancin dosing regimens or a standard-care agent such as vancomycin. Patients will be examined for clinical and microbiological responses at the conclusion of therapy and for 2 weeks following therapy (3).

1. White, R.J., Brown, G.L., Cavelero, M. *V-glycopeptide: Phase I single and multiple-dose placebo controlled intravenous safety, pharmacokinetic, and pharmacodynamic study in healthy subjects.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-2196.

2. *Positive results for new glycopeptide show dramatic and sustained reductions in bacterial load.* DailyDrugNews.com (Daily Essentials) Dec 11, 2000.

3. *Versicor begins phase II trial of novel glycopeptide antibiotic.* DailyDrugNews.com (Daily Essentials) May 23, 2001.

*Original monograph* - Drugs Fut 1999, 24: 839.

**Additional Reference**

Jones, R.N. et al. *In vitro evaluation of BI 397, a novel glycopeptide antimicrobial agent.* J Chemother 2001, 13(3): 244.

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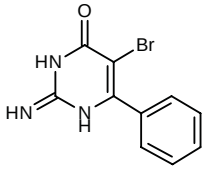
## Bropirimine
## Remisar®

*Oncolytic*

EN: 090374



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

A study conducted in clinical patients reported no interaction between bropirimine and 5-FU on human dihydropyrimidine dehydrogenase (DPD) when administered concomitantly (1).

1. Yamazaki, S., Hayashi, M., Toth, L.N., Ozawa, N. *Lack of interaction between bropirimine and 5-fluorouracil on human dihydropyrimidine dehydrogenase.* Xenobiotica 2001, 31(1): 25.

*Original monograph* - Drugs Fut 1984, 9: 567.

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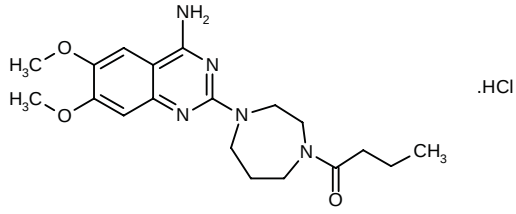
## Bunazosin Hydrochloride
## Detantol®

*Antihypertensive*
*Antiglaucoma*

EN: 115088



$C_{19}H_{27}N_5O_3.HCl$ **Eisai; Santen**

Santen has obtained approval to market Detantol (bunazosin hydrochloride) 0.01% eye drops for the treatment of glaucoma and ocular hypertension in Japan (1).

1. *New intraocular pressure-lowering agent introduced to Japanese market.* DailyDrugNews.com (Daily Essentials) July 31, 2001.

*Original monograph* - Drugs Fut 1978, 3: 582.

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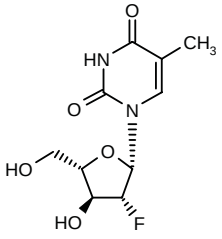
## Clevudine
## Levovir

*Anti-HBV*

EN: 217965



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

A randomized, placebo-controlled, escalating dose, phase I study examined the pharmacokinetics and safety of clevudine (150, 300, 900 and 1200 mg p.o. under fasting conditions or a high-fat meal) in 12 healthy male volunteers. Treatment was well tolerated and the $C_{max}$ and AUC values were relatively dose-proportional. Food had no effect on the bioavailability of the agent. The $t_{1/2}$ values obtained (8.3-13.5 h) under fasting conditions were thought to be underestimated since evaluation lasted only 24 h (1).

Based on clevudine's preclinical activity and safety, a placebo-controlled phase I trial was conducted in 12 healthy volunteers administered single oral doses of 150,

300, 600, 900 and 1200 mg under fasting conditions, and 600 mg with a high-fat meal. Plasma concentrations increased in a dose-proportional manner over the entire dose range, and AUC increased proportionally with dose at 600-1200 mg. The long half-life of the drug (7.9-13.5 h) suggested the feasibility of once-daily dosing. The bioavailability of clevudine was not influenced by food and urinary recovery data suggested either incomplete absorption and/or metabolism of drug. Treatment was well tolerated; all 4 adverse events reported on clevudine were mild and resolved spontaneously (2).

1. Blum, M.R., Chittick, G.E., Wang, L.H., Fang, L., Szczech, G.M. *Phase I pharmacokinetic and safety evaluation of clevudine (L-FMAU), a new agent under development for the treatment of hepatitis B virus (HBV) infection.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst A-510.

2. Blum, M.R., Chittick, G.E., Wang, L.H., Kellholz, L.J., Fang, L., Szczech, M., Roussesu, F.S. *Clevudine (L-FMAU) a new agent under development for the treatment of hepatitis B virus (HBV): Evaluation of the safety, pharmacokinetics and effect of food following single-dose administration in healthy male volunteers.* Hepatology 2000, 32(4, Part 2): Abst 1705.

*Original monograph* - Drugs Fut 1998, 23: 821.

**Additional References**

Delaney, W.E. IV et al. *Resistance of hepatitis B virus to antiviral drugs: Current aspects and directions for future investigation.* Antivir Chem Chemother 2001, 12(1): 1.

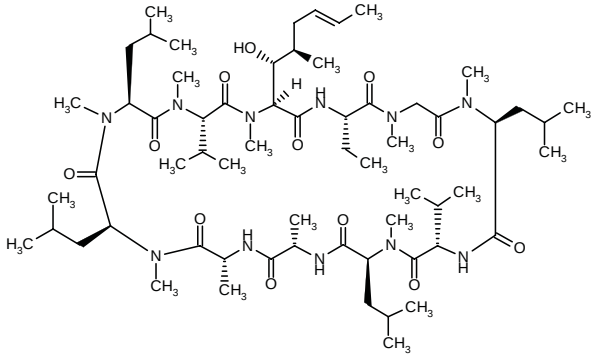
Korba, B.E. et al. *Treatment of chronic type B hepatitis with clevudine followed by vaccine enhances, broadens immune response and delays disease progression in the WHV/woodchuck model.* Antivir Res 2001, 50(1): Abst 13.

Sacks, S.L. et al. *Post-clevudine (L-FMAU) suppression of woodchuck hepatitis virus (WHV) covalently closed circular (CCC) and WHV total (T) DNA.* Antivir Res 2001, 50(1): Abst 12.

## Cyclosporine
## Ciclosporin
## Neoral®

*Immunosuppressant*

EN: 091277



$C_{62}H_{111}N_{11}O_{12}$

**SangStat; Novartis**

Novartis presented data from two new studies which demonstrate that a change in the procedures used for monitoring blood levels of Neoral® (ciclosporin) significantly reduces the incidence of acute rejection. Results show that measuring Neoral® blood levels 2 h after dosing (C2), in contrast to the conventional trough monitoring (C0), improved clinical outcomes without increasing the incidence of adverse events. In one study involving 307 liver transplant recipients, acute organ rejections were reduced by 25% in the C2 monitored group, and in a second study involving 204 kidney transplant recipients, the reduction in moderate and severe acute rejections was 34% (1).

SangStat has obtained an exclusive license to technology for a novel ciclosporin capsule formulation. The company expects to use this technology to develop and market in Europe a ciclosporin capsule that is significantly smaller than any other ciclosporin capsule currently on the market. SangStat has already conducted pilot studies in healthy volunteers demonstrating the new capsule's bioequivalence to Neoral® ciclosporin capsules when taken with water. The other filing requirements, including stability testing, are under way. SangStat expects to file a marketing authorization application (MMA) with the Medicines Control Agency by mid-2001 and plans to withdraw its MAA in the U.K. for its current ciclosporin capsule product, Sang-2000, in favor of the newer formulation. The company intends to follow the mutual recognition procedure for pan-European approval (2).

1. *Novartis updates transplantation pipeline at ongoing congress.* DailyDrugNews.com (Daily Essentials) Aug 30, 2000.

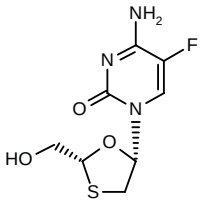
2. *SangStat obtains technology to develop smaller ciclosporin capsule.* DailyDrugNews.com (Daily Essentials) Oct 16, 2000.

*Original monograph* - Drugs Fut 1979, 4: 567.

## Emtricitabine
## Coviracil®

*Anti-HIV*
*Anti-HBV*

EN: 190016



$C_8H_{10}FN_3O_3S$

**Emory Univ.; Triangle Pharmaceuticals; Abbott**

A quick and reliable quantification method for the determination of emtricitabine in human plasma using an internal standard has been developed. Emtricitabine and the internal standard (lamivudine) were extracted on a Packard Multiprobe II and the separation was performed by HPLC on a Aquasil $C_{18}$ HPLC column under isocratic

conditions with 0.1% formic acid/acetonitrile (93/7) as mobile phase. The detection was performed by MS/MS in SRM mode using atmospheric pressure chemical ionization. Quantification was based on peak area ratios (emtricitabine/lamivudine) using least square regressions. Using this method 96 samples could be prepared in less than 1 h and the analysis times was less than 5.0 min per sample (1).

The antiviral efficacy of racemic emtricitabine was compared to that of emtricitabine using the HuPBMC-SCID mouse model of HIV infection. One week after infection, mice were orally administered 0.01, 0.1 and 1 mg/ml of either agent. Racemic emtricitabine was found to have a higher $C_{max}$ and an earlier $t_{max}$ than emtricitabine in uninfected mice. Both agents demonstrated similar potency and dose-dependent antiviral activity in infected mice, reducing plasma viral load to ≥ 500 copies/ml. $ED_{50}$ values determined by pharmacodynamic modeling of viral load data were 5.6 and 15 mg/kg/day for racemic emtricitabine and emtricitabine, respectively (2).

Data were reported from a phase I/II dose-selection trial following a double-blind, randomized design and evaluating the efficacy and safety of emtricitabine in patients chronically infected with hepatitis B virus (HBV). In this 24-week trial, the anti-HBV activity of 3 different doses of emtricitabine (25, 100 and 200 mg once daily) was compared in 98 patients with chronic HBV infection. All doses demonstrated significant activity, with median reductions in viral load from baseline of 2.3, 2.9 and 3.0 $log_{10}$, respectively, on 25, 100 and 200 mg once daily. Suppression of HBV DNA levels to below the limit of detection was observed in 61, 24 and 22% of patients receiving 200, 100 and 25 mg once daily, respectively. The treatment was generally well tolerated. The dose of 200 mg once daily was thus selected as the optimal dose for phase III trials (3).

A once-a-day HAART regimen with emtricitabine, didanosine (ddI) and efavirenz demonstrated long-term potency as first-line therapy in treatment-naive HIV-infected patients. Emtricitabine 200 mg, ddI 400 mg or 250 mg (depending on weight) and efavirenz 600 mg were administered once daily to 40 HIV-infected patients with median baseline HIV RNA levels of 4.77 $log_{10}$ copies/ml and median baseline CD4 counts of 373 cells/μl. Through 48 weeks, 95% of the treated patients maintained plasma HIV RNA levels below 400 copies/ml. At weeks 24 and 48, CD4 count increased by a median of 159 and 205 cells/μl, respectively. Mild to moderate central nervous system symptoms, diarrhea and rash were reported during the first half of the study (4).

The combination of emtricitabine (200 mg), ddI (400 mg if ≥ 60 kg, 250 mg if < 60 kg) and efavirenz was evaluated as a once-daily treatment for HIV infection. Patients (n = 40) with a CD4 cell count of at least 100/$mm^3$ and a plasma HIV RNA of at least 5000 copies/ml received the combination for 15 months. Plasma HIV RNA levels dropped to below 400 copies/ml in 98% of patients at week 24, and at the end of the 64-week study period, 90% of the patients had maintained this level. The median baseline CD4 count of 373 cells/μl was increased by a median of 159 and 219 cells/μl at weeks 24 and 64, respectively. Mild to moderate central nervous system symptoms, diarrhea, rashes and biochemical abnormalities were the most common treatment-related adverse events. Adverse events caused 2 patients to discontinue treatment (5).

A double-blind, randomized trial was performed in 98 patients to determine the therapeutic dose of emtricitabine for the treatment of chronic hepatitis B infection. Patients were administered emtricitabine 25, 100 and 200 mg once daily. The change in viral load ($log_{10}$ C/ml) from baseline at week 36 was –1.7, –3.1 and –3.2 for the 25, 100 and 200 mg doses, respectively. The percentage of patients with undetectable HBV DNA at week 36 was 31, 24 and 64% for the 25, 100 and 200 mg doses, respectively. Based on these findings, the 200 mg dose was chosen for therapeutic trials (6).

Two randomized trials have compared the efficacy and safety of lamivudine 150 mg b.i.d. with emtricitabine 200 mg once daily in triple HIV therapy combination regimens. In the first study, patients receiving triple therapy with lamivudine were randomized to switch to emtricitabine or continue with lamivudine. The second study was a double-blind trial in which emtricitabine and lamivudine were compared in a background of stavudine and either nevirapine or efavirenz. Overall, more than 900 patients were enrolled in these studies, most of whom tolerated the drugs well. Adverse events were mostly mild to moderate in both trials. In the second study, 58 patients experienced grade 3-4 hepatotoxicity. Virological failure (2 consecutive visits with > 400 copies/ml) was experienced in less than 12% of patients in either trial. Overall, the two agents appeared to have equivalent safety and antiviral efficacy (7).

The incidence of hepatotoxicity in a randomized, double-blind trial comparing emtricitabine to lamivudine in a background of stavudine and either nevirapine or efavirenz in HIV-infected patients has been reported. At 48 weeks, treatment-emergent grade 4 elevations in liver enzymes were observed in 36 of 468 enrolled patients. All of these cases were in the group receiving nevirapine. These elevations occurred within the first 4 weeks of therapy in 33 of the 36 cases. One of the 36 cases was HBsAg positive at screening without evidence of active hepatitis and 2 had serological evidence of hepatitis C infection. Similar numbers of cases occurred in each blinded treatment arm, though the incidence in females was double that of males. Two patients, one of whom was HBsAg positive at screening, died after developing liver failure. Severe liver toxicity was clinically attributed to nevirapine in combination with stavudine and blinded treatment medication (8).

A dose-escalation study was conducted to evaluate the safety and pharmacokinetics of emtricitabine in 49 hepatitis B-infected patients. Patients received 25, 50, 100, 200 and 300 mg emtricitabine sequentially for 56 days. Dose-dependent antiviral activity was seen with all drug doses. The median $log_{10}$ average AUC minus

baseline values were –1.72, –2.11, –2.23, –2.45 and –2.52 for the 25, 50, 100, 200 and 300 mg doses, respectively. At the 100 mg dose, antiviral activity was at least 90% of the maximal activity and the activity was increased by about 5% with the 200 mg dose. The drug was well tolerated with no dose-related toxicities observed (9).

A phase I, multicenter, open-label pharmacokinetic study was conducted to determine the safety and optimal dosing regimen of emtricitabine in children. Two single escalating oral doses of emtricitabine (60 and 120 mg/m$^2$) were administered to HIV-infected or exposed children between 2-17 years of age. There was a minimum 1-week interval between doses which were given in solution formulation. A third dose (~120 mg/m$^2$) was given in capsule form to the older children. The drug appeared to be well tolerated in the 23 study subjects. Plasma concentrations correlated well with the increase in dose and the capsule and solution formulations provided comparable exposure. The 120 mg/m$^2$ dose appeared to be appropriate for further evaluation as it resulted in a plasma AUC which was the median value of the AUC found in adults given a 200 mg dose (10).

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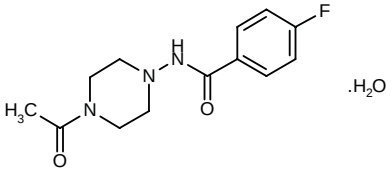
## FK-960
## FR-59960

*Treatment of Alzheimer's Dementia*

EN: 243654



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

An *in vitro* study recording intracellular excitatory postsynaptic potentials (EPSPs) and currents (EPSCs) from CA1 neurons in the rat hippocampus showed that FK-960 (100 nM) significantly enhanced the amplitude of EPSPs. No effects of the agent were observed on membrane potential, resistance or early GABAergic inhibitory postsynaptic current. Since FK-960 had no effect on the decay phase of EPSCs, indicating no effect on desensitization or deactivation, it was suggested that the agent acts on postsynaptic AMPA receptors. The effects of FK-960 on EPSPs were blocked by methyllycaconitine and α-bungarotoxin, suggesting that the agent, via modulation of $\alpha_7$-nicotinic acetylcholine receptors, upregulates the action of acetylcholine at synapses in the hippocampus (1).

An *in vitro* study recording depolarization-induced $Ba^{2+}$ current from *Xenopus* oocytes expressing a combination of rabbit $\alpha_1$, human $\alpha_2\delta_1$ and human $\beta_{1B}$ subunits of the N-type calcium channel, showed that FK-960 significantly potentiated the $\alpha_{1B}$ current in a reversible, concentration-dependent manner. Maximum effects were observed with a concentration of 100 nM. The agent had a fast onset of action but did not alter activation or

steady-state inactivation of the channel. The $\alpha_A$ current was also potentiated by FK-960 treatment although to a lesser extent. The agent had no effects on $\alpha_{1C}$ or $\alpha_{1E}$ current (2).

Results from an *in vitro* study using rat hippocampal slices showed that FK-960 significantly increased the release of somatostatin in response to high potassium concentrations. The agent had no effect on basal somatostatin release or release of acetylcholine, serotonin, D-aspartate or GABA (3).

An *in vitro* study using isolated rat hippocampal neurons showed that FK-960 reversed somatostatin-induced, G-protein-dependent inhibition of calcium channel current. A modest dose-dependent potentiation of current was observed when neurons were treated with FK-960 alone (maximum effects with 0.1 μM); no effects on activation were observed (4).

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*Original monograph* - Drugs Fut 1997, 22: 830.

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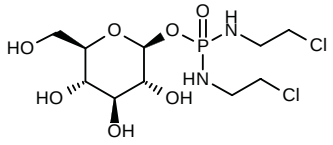
## Glufosfamide
## D-19575

*Oncolytic*

EN: 190991




$C_{10}H_{21}Cl_2N_2O_7P$ **Asta Medica**

The apoptotic mechanisms of glufosfamide ((0.1 M) and mitomycin C (550 ng/ml) were examined in a study using a crosslink-sensitive repair deficient cell line (V79 mut) and a resistance cell line (V79 wt). Results showed that the cytotoxic effects of both agents in the V79 mut cell line were due to induction of caspase 3-, 8- and 9-mediated apoptosis; treatment had no effect on caspase activity in the resistant V79 wt cell line. Although mitomycin C induced increases in Bcl-2 protein expression in V79 wt cells, glufosfamide had no effect on this protein in either cell type (1).

A phase I trial conducted in 21 patients with refractory solid tumors examined the pharmacokinetics and determined the MTD of glufosfamide (800-6000 mg/m$^2$ 6-h i.v. infusion every 3 weeks). The MTD was 6000 mg/m$^2$ and a dose of 4000 mg/m$^2$ was recommended for phase II studies. In 2 of the 6 patients receiving the MTD, dose-limiting but reversible renal tubular acidosis and a slight increase in creatinine were seen after administration of the second and third courses. Three of these 6 patients developed short-lived grade 4 neutropenia/leukopenia. All other toxicities were generally mild. Linear pharmacokinetics were obtained between AUC and dose and a short $t_{1/2}$ value was observed for the agent. A complete response was seen in 1 patient with advanced pancreatic adenocarcinoma and 2 patients with refractory colon carcinomas and 1 heavily pretreated breast cancer patient exhibited minor shrinkage of tumors. It was suggested that patients receiving the agent be closely monitored for serum potassium and creatinine to detect possible renal toxicity (2).

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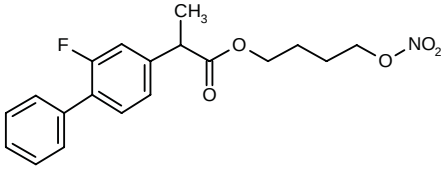
## HCT-1026

*Treatment of Urinary Incontinence*
*Treatment of Osteoporosis*
*Topical Antiinflammatory*

EN: 224707




$C_{19}H_{20}FNO_5$ **NicOx**

A I/II clinical study evaluating 2 concentrations of HCT-1026 ointment (0.3% and 1%) *versus* placebo and a reference NSAID (niflumic acid 3% ointment) has been successfully completed in 16 healthy subjects. The ointments were applied in duplicate and left for 3.5 h, after which the irritant was applied at each test site, as well as 48 h later. HCT-1026 1% ointment showed antiinflammatory activity significantly more potent than the reference NSAID 4 h after application, thus confirming the results of an initial phase I/II study in acute contact urticaria. A dose-effect response with HCT-1026 0.3% and 1% ointments was also seen 4 h after application. At 48 h after application, HCT-1026 was the only compound that showed persistent antiinflammatory activity. In addition, the compound exhibited an excellent local and general safety profile (1).

Encouraging clinical trial results with HCT-1026 have been reported. In one study, HCT-1026 ointment (1%) showed potent antiinflammatory activity similar to that of a class II steroid. The trial involved 24 healthy subjects with UV-induced erythema (sunburn-like reaction). The randomized, double-blind trial, using intraindividual comparison, evaluated 2 concentrations of HCT-1026 ointment (0.3% and 1%) *versus* the reference class II steroid cream betamethasone and placebo. Drugs and placebo were administered for 4 days as 6 applications on 4 test zones exposed to 3 different UV doses (1, 1.5 and 2 minimal erythema dose [MED]). The clinical evaluation of erythema (spatial extension of the lesion and presence of edema and desquamation) on the higher dose of HCT-1026 ointment (1%) showed reduced inflammation for the two highest doses of UV exposure, similar to the class II steroid. The local and systemic safety of HCT-1026 was excellent and no sign of skin intolerance was observed. The results suggest that, overall, a better evaluation of the products was observed with the clinical evaluation (visual score) as compared to colorimetric assessment which only measures redness. This is probably due to the vasoconstrictive effect of the reference steroid. Results from a phase II trial demonstrated that oral HCT-1026 for 1 week produced improvement in clinical symptoms and bladder capacity in patients with overactive bladder due to spinal cord injury (neurogenic bladder). Additional phase II studies are ongoing in more than 50 patients for the indications of urinary incontinence and osteoporosis (2).

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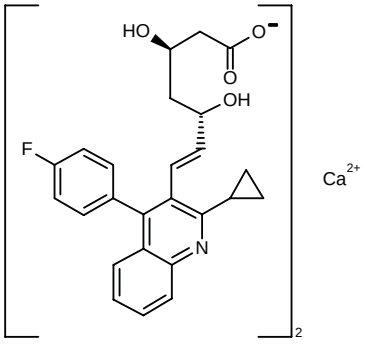
*Original monograph* - Drugs Fut 1999, 24: 858.

## Itavastatin Calcium
## Pitavastatin Calcium
## NK-104

*Hypolipidemic*

EN: 192009




$C_{50}H_{46}CaFNO_8$

**Nissan Chem.; Kowa; Sankyo; Negma; SkyePharma**

An *in vitro* study using human and animal hepatic microsomes and hepatocytes examined the metabolism of NK-104. Results showed that hepatic metabolism and inhibition in the human liver were minimal and the potential for P450-mediated drug-drug interactions with the agent were low. β-Oxidation of the agent was observed in rats while lactonization and glucuronidation were seen in humans and monkeys. Large amounts of 8-hydroxy NK-104 (M13) were detected in monkey microsomes but not in the other species. CYP2C9 was found to be predominantly responsible for the hydroxylation of NK-104 with some contribution of CYP2C8 in experiments using recombinant human P450 microsomes. NK-104 showed no inhibitory effects on tolbutamide 4-hydroxylation (CYP2C9) or taxol 6α-hydroxylation (CYP2C8) (1).

Results from an *in vitro* study using cultured rat aortic smooth muscle cells showed that NK-104 decreased the expression of osteopontin protein and mRNA. The effects of the agent were reversed by treatment with mevalonate. *In vivo* studies using STZ-induced diabetic rats showed that treatment with the agent (3 mg/kg/day for 7 days) reduced the upregulated expression of osteopontin mRNA seen in the aorta and kidney in this experimental model. Results suggest that NK-104 may be an effective treatment of hypercholesterolemia in individuals with diabetes (2).

An *in vitro* study using HepG2 cells showed that NK-104 increased LDL-receptor activity ($IC_{50}$ = 1 nM to 1 μM) by increasing receptor number. The agent inhibited cholesterol synthesis with an $IC_{50}$ value of 5.5 nM. LDL binding, incorporation and degradation increased 2.7-, 2.4- and 3-fold, respectively, as compared to controls with 1 μM NK-104. An increase in receptor number was observed with NK-104 treatment that correlated with the inhibition of cholesterol synthesis (3).

  CCC: 0377-8282/2001 

In a rat model of postprandial lipemia, a single oral dose of NK-104 (1 mg/kg) prior to a fat load was shown to suppress chylomicron triglyceride secretion by 40% and reduce triglyceride levels at 6 h by 54%. Further experiments in jejunal microsomes from fat-loaded rats administered NK-104 (2 mg/kg) demonstrated a significant reduction in intestinal microsomal triglyceride transfer protein (MTP) levels (21%). It was concluded that the triglyceride-lowering effects of NK-104 after a meal are due to suppression of chylomicron triglyceride secretion via a reduction in intestinal MTP activity (4).

A study using guinea pigs compared the hypolipidemic effects of NK-104 (0.3, 1, 3 mg/kg) with simvastatin (3, 10, 30 mg), pravastatin (10, 30, 100 mg/kg), fluvastatin (3, 10 mg/kg), cerivastatin (0.3 mg/kg) and atorvastatin (3, 10, 30 mg/kg) following 2 weeks of oral treatment. Although all statins dose-dependently reduced total cholesterol, NK-104 produced the most marked effect. Significant decreases in triglycerides and liver cholesterol content were only observed with NK-104 and atorvastatin. Simvastatin and pravastatin significantly increased liver triglyceride content. Simvastatin increased triglyceride content in liver endoplasmic reticulum while NK-104 had only slight effects. Although simvastatin increased activity of microsomal triglyceride transfer protein, NK-104 had no effect (5).

The hypocholesterolemic effects of NK-104 (0.1, 0.3 and 1 mg/kg p.o. for 2 weeks starting at week 4) were shown in a study using guinea pigs fed a high fat (15% w/w in laurate) diet for 6 weeks. Treatment resulted in decreases in LDL-cholesterol of 11, 27 and 32% for the respective doses. In comparison, atorvastatin at doses 10 times higher (3 and 10 mg/kg) decreased these levels by 25 and 39%, respectively. LDL clearance was also improved with NK-104 treatment (24% with 1 mg/kg NK-104 *vs.* 47% with 10 mg/kg atorvastatin). LDL composition also improved with NK-104 treatment (6).

A preferential effect on triglyceride-rich lipoproteins and an antiatherosclerotic effect were seen for NK-104 in Watanabe heritable hyperlipidemic (WHHL) rabbits. In these experiments, the product was administered in the drinking water at a concentration approximately equal to 0.5 mg/kg/day for 26 weeks starting from 12 weeks of age. Total plasma cholesterol and triglyceride levels were reduced 7-20% and 16-39%, respectively, due to significant decreases in VLDL cholesterol (61-62%), intermediate-density lipoprotein (IDL) cholesterol (49-60%), VLDL triglycerides (40-53%) and IDL triglycerides (29-59%), while no effect was seen on LDL cholesterol. NK-104 treatment also reduced the lesion area in the aortic arch, where the most advanced lesions were seen, by 23.1% and increased the percentage of smooth muscle cells in the media of the thoracic aorta by 69.9%, indicating the ability to suppress the degeneration of the media. It is concluded that the antiatherosclerotic effects of NK-104 in this model are due mainly to a decrease in triglyceride-rich lipoproteins, although a direct effect on macrophages may also be involved (7).

The pharmacology of NK-104 was reported in a study using mice, rats and dogs with results showing that the agent did not cause any serious acute adverse events. NK-104 (3-30 mg/kg) did not affect gross behavior, spontaneous locomotor activity, hexobarbital-induced anesthesia, electroshock seizure, pentylenetetrazol-induced convulsions or muscle relaxation in mice or body temperature in rats. In mice, the agent (10-30 mg/kg) inhibited acetic acid writhing but showed no effects on the tail pinch response. In isolated guinea pig ileum, NK-104 (100 μM) significantly inhibited acetylcholine-, histamine- and barium chloride-induced contractions. When administered to anesthetized dogs, the agent (0.3-3 mg/kg i.v.) had no effects on respiration, blood pressure, heart rate, ECG, femoral blood flow, acetylcholine-induced depressor response or norepinephrine-induced pressor responses. NK-104 did not affect intestinal propulsion in mice or gastric and bile secretion in rats nor did it cause gastric lesions. The lithogenic index of bile was unaffected in guinea pigs after multiple dosing (3 mg/kg/day p.o. for 15 days). $Na^+$ and $Cl^-$ excretion and urinary volume were decreased with doses of 10 and 30 mg/kg. No effects of the agent were observed on coagulation of platelet aggregation (8).

The proposed international nonproprietary name for NK-104 has been changed to pitavastatin calcium (9).

SkyePharma has signed a contract with Kowa for the scale-up and manufacturing of phase III clinical batches of Kowa's NK-104. Under the terms of the agreement, SkyePharma will be responsible for providing materials for the European and U.S. clinical trials at its FDA-inspected production facility near Lyon, France. A marketing application for NK-104 has been filed in Japan. Phase II trials have been completed in Europe and are expected to begin in the U.S. in the spring. Once approved, the product will be copromoted by Sankyo in the U.S. and in Europe by a Kowa affiliate and Negma (10).

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8. Yoshinaka, Y., Suzuki, H., Tamaki, T., Sato, F., Wada, Y. *General pharmacological study of an anti-hyperlipidemic agent, NK-104.* Jpn Pharmacol Ther 2001, 29(1): 59.

9. *Proposed international nonproprietary names (Prop. INN): List 83.* WHO Drug Inf 2000, 14(2): 132.

10. *SkyePharma to manufacture NK-104 for Kowa.* DailyDrugNews.com (Daily Essentials) Feb 13, 2001.

*Original monograph* - Drugs Fut 1998, 23: 847.

**Additional References**

Fujino, H. et al. *Simultaneous determination of taxol and its metabolites in microsomal samples by a simple thin-layer chromatography radioactivity assay - inhibitory effect of NK-104, a new inhibitor of HMG-CoA reductase.* J Chromatogr B - Biomed Sci Appl 2001, 757(1): 143.

Mutsukado, M., Suzuki, M. *A new HMG-CoA reductase inhibitor, NK-104: QSAR studies.* 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PA-143.

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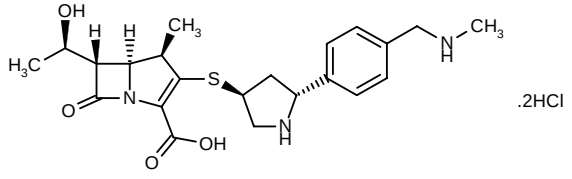
## J-111225

*Carbapenem Antibiotic*

EN: 268243




$C_{22}H_{29}N_3O_4S.2HCl$ **Banyu**

A new practical synthesis of J-111225 has been reported: Reduction of the chiral benzaldehyde (I) with $NaBH_4$ in methanol gives the benzyl alcohol (II), which is treated with MsCl and TEA in dichloromethane to yield the mesylate (III). The reaction of compound (III) with methylamine in methanol affords the benzylamine (IV), which is treated with $Boc_2O$ in dioxane/water to provide the carbamate (V). The deprotection of compound (V) with TBAF in THF gives the pyrrolidinol (VI), which is treated with potassium thioacetate in hot DMF to provide the thioester (VII). Hydrolysis of (VII) with HCl in refluxing methanol affords the mercaptan (VIII), which is condensed with the penem phosphate (IX) by means of DIEA and TEA in DMF, providing the phosphate (X). Finally, the *p*-nitrobenzyl ester of (X) is hydrogenated with $H_2$ over Pd/C in DMF/THF to yield J-111225 (1). Scheme 1.

1. Imamura, H., Shimizu, A., Sato, H., Sugimoto, Y., Sakuraba, S., Yamada, K., Morishima, H. *Practical synthesis of a 1b-methylcarbapenem, J-111,225, using 4-mercapto-2-[4-(N-methylaminomethyl)phenyl]pyrrolidine as a precursor.* Chem Pharm Bull 2001, 49(4): 476.

*Original monograph* - Drugs Fut 2000, 25: 833.

**Additional Reference**

Imamura, H. et al. *Discovery of novel trans-3,5-disubstituted pyrrolidinylthio-1β-methylcarbapenems.* Bioorg Med Chem 2000, 8(8): 1969.

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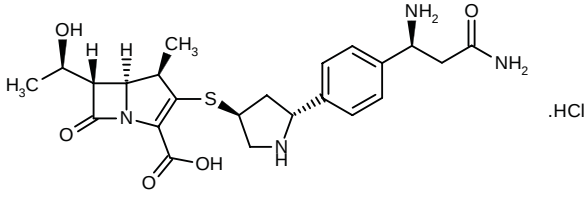
## J-114870

*Carbapenem Antibiotic*

EN: 268244

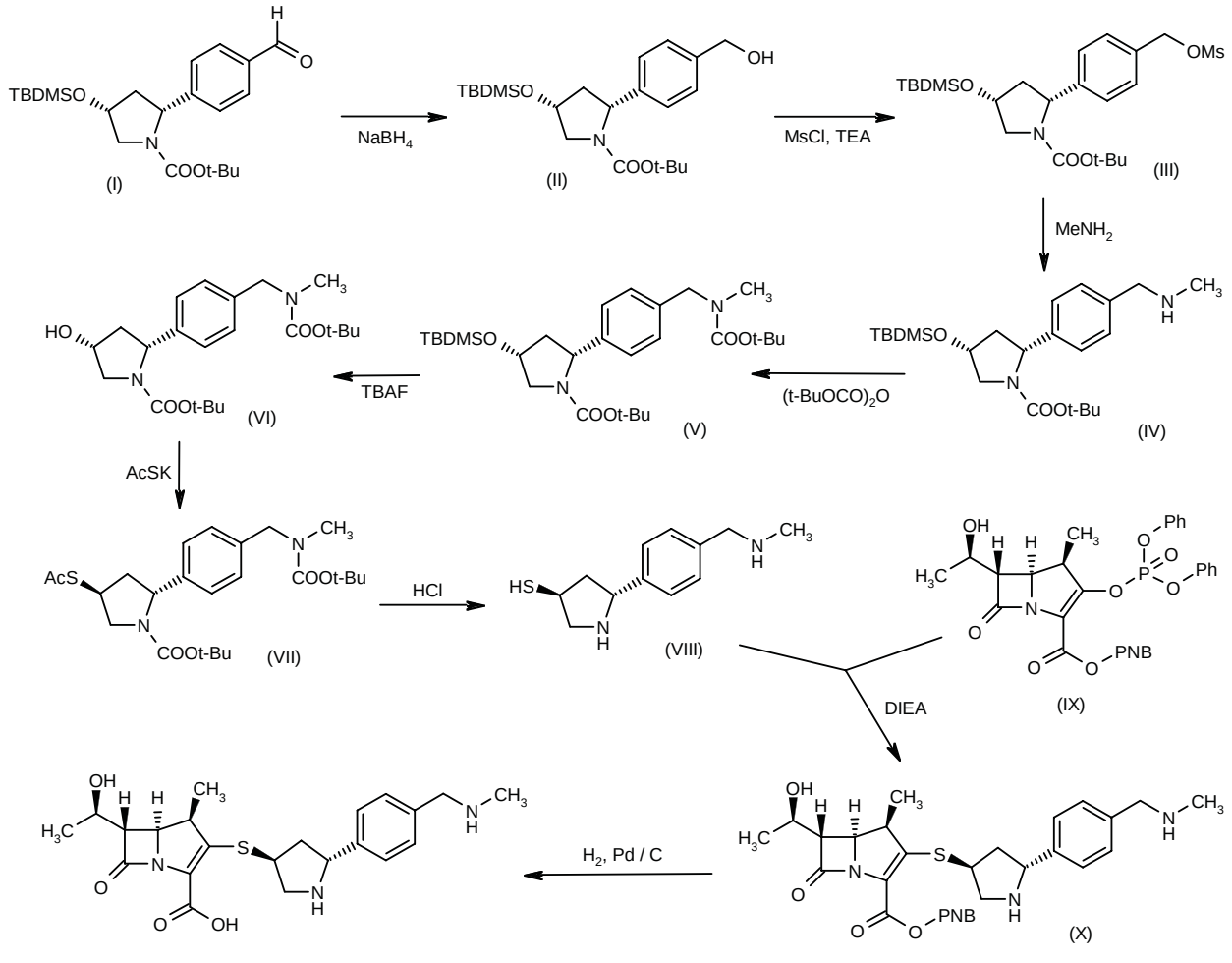



$C_{23}H_{30}N_4O_5S.HCl$ **Banyu**

A new stereoselective synthesis of J-114870 has been described: Silylation of 4(*R*)-hydroxy-2-pyrrolidone (I) with TBDMS-Cl and imidazole in DMF gives the silyl ether (II), which is protected at the NH group with $Boc_2O$, TEA and DMAP in acetonitrile to yield the protected pyrrolidone derivative (III). Reaction of pyrrolidone (III) with the Grignard reagent (IV) in THF affords the 2-hydroxypyrrolidine adduct (V) in equilibrium with an open-chain form (VI). Reduction of the ketonic group of (VI) with $NaBH_4$ in methanol in the same vessel provides the alcohol (VII), which is cyclized by means of MsCl and TEA in dichloromethane and then treated with TsOH in $THF/H_2O$ to furnish the pyrrolidine-benzaldehyde (VIII). The Wittig condensation of the aldehyde group of (VIII) with the phosphonate (IX) by means of NaH in THF gives the cinnamic ester derivative (X), which is desilylated with TBAF in THF to yield the hydroxy pyrrolidine (XI). Stereocontrolled condensation of (XI) with the chiral amine (XII) by means of BuLi in THF affords the *N*-alkylated β-amino ester (XIII), which is debenzylated with $H_2$ over $Pd(OH)_2/C$ in AcOH/methanol to provide the free amino ester (XIV). The protection of the $NH_2$ group of (XIV) with $Boc_2O$ and TEA in dioxane/water gives the *N*-protected amino ester (XV), which is hydrolyzed with NaOH in hot ethanol to afford the carboxylic acid (XVI). Reaction of the carboxylic acid (XVI) with MsCl and TEA in THF yields the fully protected mixed anhydride (XVII). The chemo-selective ammonolysis of anhydride (XVII) gives amide (XVIII), which by displacement of the mesyloxy group with potassium thioacetate in hot DMF yields the thioacetate (XIX). Removal of the Boc protecting groups of (XIX) with HCl in ethyl acetate affords compound (XX), which is

**Scheme 1: Synthesis of J-111225**




reprotected with allyl chloroformate (XXI) and TEA in dichloromethane to provide the bis(allyloxycarbonyl) compound (XXII). Hydrolysis of the thioacetate group of (XXII) with NaOH in methanol gives the thiol compound (XXIII), which is condensed with the carbapenem diphenyl phosphate (XXIV) by means of DIEA in acetonitrile to provide the expected adduct (XXV). Finally, this compound is deprotected by a treatment with $Bu_3SnH$ and $PdCl_2(PPh_3)_2$ in dichloromethane/water (1). Scheme 2.

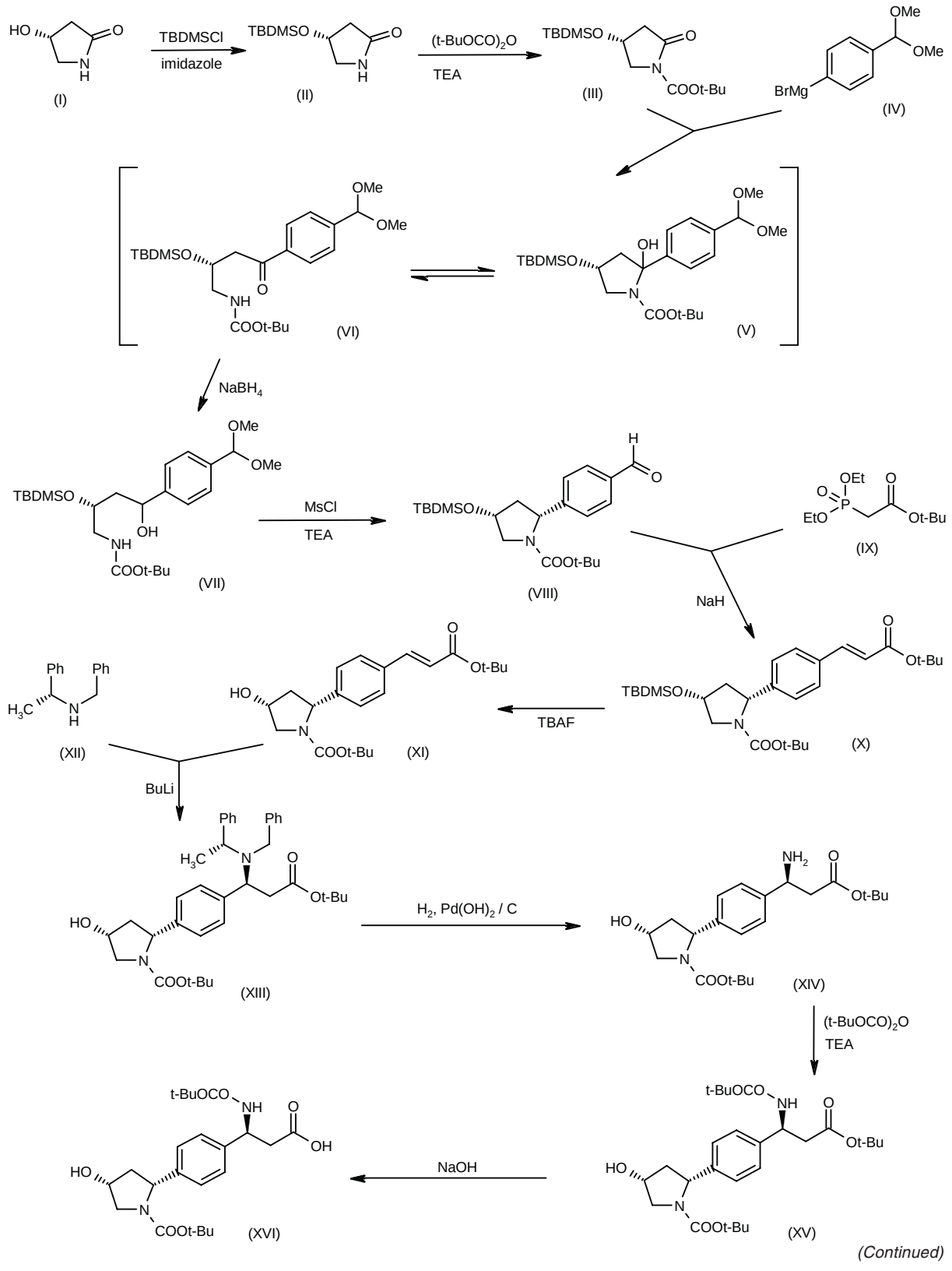
The efficacy of J-114870 was examined in a study using a mouse model of septicemia (infection with methicillin-resistant *Staphylococcus aureus* [MSRA], *Pseudomonas aeruginosa*, *Streptococcus pneumoniae* or mixed infection). The $ED_{50}$ values for J-114870, imipenem and vancomycin were 5.49, 74.35 and 4.25 mg/kg, respectively, against MSRA infections and 0.16, 0.32 and > 100 mg/kg, respectively, against *P. aeruginosa* infections. J-114870 ($ED_{50}$ = 3.56 mg/kg) also showed good activity against mixed infections which was comparable to that seen with combination vancomycin + imipenem ($ED_{50}$ = 8.93 mg/kg). The $ED_{50}$ values for J-114870, imipenem, meropenem and penicillin G against *S. pneumoniae* infection were 0.12, 0.15, 0.29 and 5.85 mg/kg, respectively (2).

1. Imamura, H., Shimizu, A., Sato, H., Sugimoto, Y., Sakuraba, S., Nakajima, S., Abe, S., Miura, K., Nishimura, I., Yamada, K., Morishima, H. *Stereoselective synthesis of a broad spectrum 1β-methylcarbapenem, J-114,870.* Tetrahedron 2000, 56(39): 7705.

2. Shibata, K., Nagano, R., Hashizume, T., Yamada, K., Imamura, H., Morishima, H. *Activity of new 1β-methylcarbapenem J-114,870 with unusual antibacterial spectrum including methicillin-resistant Staphylococcus aureus (MRSA) and pseudomonas aeruginosa.* 40th Interscience Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1235.

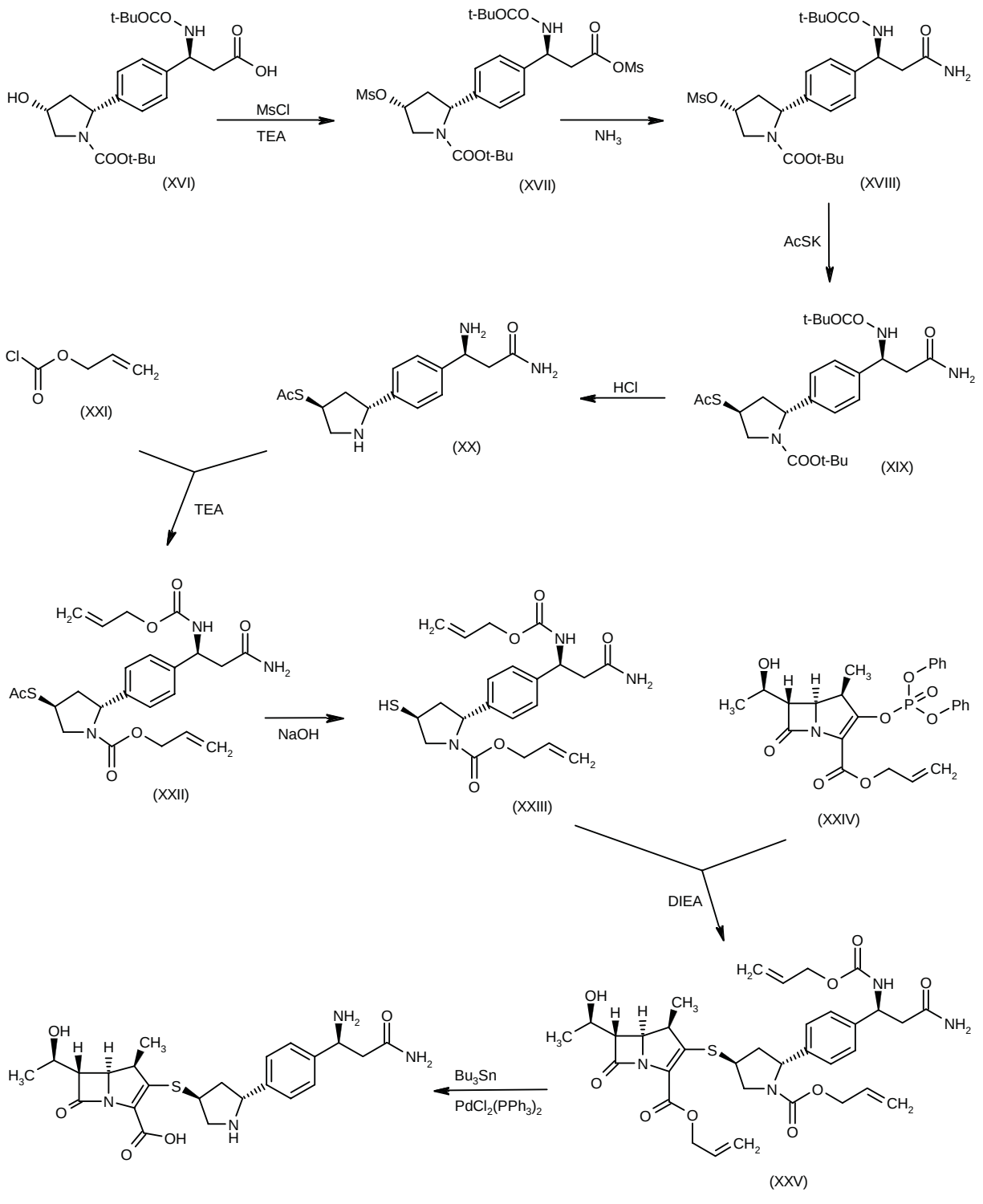
*Original monograph* - Drugs Fut 2000, 25: 833.

**Scheme 2: Synthesis of J-114870**



**Scheme 2: Synthesis of J-114870 (Cont.)**

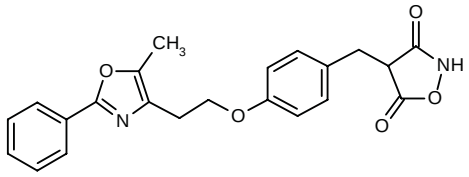


## JTT-501
## PNU-182716
## Reglitazar

*Antidiabetic*

EN: 226594



$C_{22}H_{20}N_2O_5$ **Japan Tobacco; Pharmacia**

Results from a study using alloxan-diabetic dogs showed that JTT-501 (30 mg/kg p.o. for 10 days) enhanced hepatic and peripheral insulin sensitivity. Results obtained following hyperinsulinemic (intraportal administration of 18 pmol/kg/min insulin)-hyperglycemic (portal infusion of 22.2 μmol/kg/min glucose) clamps showed that the agent significantly increased insulin-stimulated glucose utilization and glucose production. It was concluded that JTT-501 may show efficacy as a treatment for type 2 diabetes (1).

Reglitazar in the proposed international nonproprietary name for JTT-501 (2).

1. Niwa, M., Rashid, S., Shum, K., Mathoo, J.M.R., Chan, O., Tchipashvili, V., Kawamori, R., Vranic, M., Giacca, A. *Effect of JTT-501 on net hepatic glucose balance and peripheral glucose uptake in alloxan-induced diabetic dogs.* Metab Clin Exp 2000, 49(7): 862.

2. *Proposed international nonproprietary names (Prop. INN): List 84.* WHO Drug Inf 2000, 14(4): 266.

*Original monograph* - Drugs Fut 1999, 24: 893.

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Tang, Y. et al. *Adipocyte-specific reduction of phosphodiesterase 3B gene expression and its restoration by JTT-501 in the obese, diabetic KKAy mouse.* Eur J Endocrinol 2001, 145(1): 93.

Wulff, E.M. et al. *Characterisation of a future generation insulin sensitizer in vitro and in vivo.* Diabetes 2001, 50(Suppl. 2): Abst 2210-PO.

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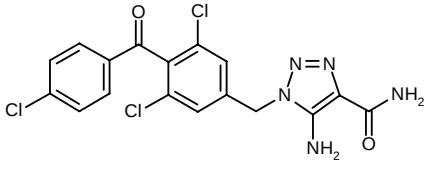
## L-651582
## CAI

*Oncolytic*

EN: 113265



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

The combination of CAI and paclitaxel for the treatment of relapsed solid tumors has been evaluated in a phase I preclinical and clinical study. In preclinical experiments using A2780 human ovarian cancer cell lines, the combination was found to be additive when subtherapeutic paclitaxel doses were administered after 1 or 5 μM CAI. Paclitaxel resistance was not altered by CAI and CAI resistance was observed in paclitaxel-resistant cells. No additive toxicity was seen with the combination in nude mice. In the clinical study, 39 patients were administered CAI in PEG-400 (50-100 mg/m$^2$) or micronized CAI (250 mg/m$^2$) for 8 days. CAI treatment was followed by a 3-h infusion of paclitaxel 110-250 mg/m$^2$ every 21 days. Paclitaxel dose-dependently increased circulating CAI concentrations. The combination was well tolerated and did not result in additive toxicity. Grade 3 nonhematological toxicity occurred infrequently. There were 3 partial and 2 minor responses (1).

An implantable device has been constructed and tested for the sustained-release delivery of CAI into the vitreous to treat ocular neovascularization. Three designs were tested: A) 10 mg CAI pellets coated with 0.7 mm of polydimethylsiloxane, B) 10 mg CAI pellets coated with 10% polyvinyl alcohol heated at 110 °C for 3 h and C) 20 mg CAI pellets coated with 10% polyvinyl alcohol heated at 110 °C for 3 h. All devices were placed in 20 ml PBS at 37 °C for 30 min. Steady-state drug release rates, determined by assaying drug levels over time, were 12.80 ± 0.99, 19.56 ± 6.74 and 5.92 ± 1.29 μg/day for designs A, B and C, respectively. According to pharmacokinetic modeling, the implants would achieve steady-state concentrations in the vitreous of 0.58-1.93 μM. Design B devices implanted in the vitreous of the right eye of 6 rabbits were well tolerated over a 7-month period and serial ERGs remained normal. The lifespan of the various implants ranges from 1.3-9 years (2).

1. Kohn, E.C., Reed, E., Sarosy, G.A. et al. *A phase I trial of carboxyamido-triazole and paclitaxel for relapsed solid tumors: Potential efficacy of the combination and demonstration of pharmacokinetic interaction.* Clin Cancer Res 2001, 7(6): 1600.

2. Robinson, M.R., Ross, M.L., Lutz, R.J., King, B.A., Yuan, P., Gogolak, L., Whitcup, S.M. *Sustained-release intraocular device for carboxyamide-amino-imidazole: A novel angiostatic agent.* Invest Ophthalmol Visual Sci 2000, 41(4): Abst 4085.

*Original monograph* - Drugs Fut 1991, 16: 717.

### Additional References

Capiod, T., Colosetti, P. *Carboxyamidotriazole (CAI) and SK&F 96365 (SKF) increase the NAD(P)H fluorescence in suspensions of rat hepatocytes.* Mitochondrial Dysfunct Pathogenesis (Jan 15-20, Santa Fe) 2000, Abst 110.

Hicklin, D.J. et al. *Monoclonal antibody strategies to block angiogenesis.* Drug Discov Today 2001, 6(10): 517.

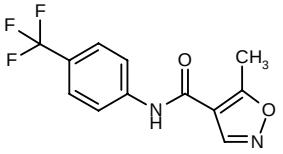
Kruger, E.A., Figg, W.D. *Protein binding alters the activity of suramin, carboxyamidotriazole, and UCN-01 in an ex vivo rat aortic ring angiogenesis assay.* Proc Amer Assoc Cancer Res 2001, 42: Abst 3145.

  CCC: 0377-8282/2001 

## Leflunomide
## Arava®

*Antiarthritic*
*Oncolytic*

EN: 116061



$C_{12}H_9F_3N_2O_2$ **Aventis Pharma; Sugen; Kyorin**

Aventis has issued a letter to healthcare professionals regarding reports of liver injury and isolated cases of fatalities in patients taking leflunomide (Arava®) for the treatment of rheumatoid arthritis. The company urges that patients showing symptoms such as nausea, vomiting, stomach pain or swelling, jaundice, dark urine or unusual tiredness report to their doctor immediately (1).

1. *Aventis warns of potential liver injury on Arava.* DailyDrugNews.com (Daily Essentials) May 9, 2001.

*Original monograph* - Drugs Fut 1998, 23: 827.

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## Lepirudin
## Refludan®

*Anticoagulant*

EN: 199872

**Aventis Pharma**

In May 2000, Aventis received a nonapprovable letter from the FDA concerning its application for regulatory approval of lepirudin (Refludan®) as an anticoagulant in adults suffering from acute coronary syndrome. Aventis maintains an open dialogue with the FDA to assess its next steps. The company also withdrew a similar application in the E.U. (1).

1. *Aventis updates 2000 achievements and highlights emerging pipeline products.* DailyDrugNews.com (Daily Essentials) March 20, 2001.

*Original monograph* - Drugs Fut 1994, 19: 734.

### Additional References

Dager, W.E., White, R.H. *Use of lepirudin in patients with heparin-induced thrombocytopenia and renal failure requiring hemodialysis.* Ann Pharmacother 2001, 35(7-8): 885.

Farner, B. et al. *A comparison of danaparoid and lepirudin in heparin-induced thrombocytopenia.* Thromb Haemost 2001, 85(6): 950.

Farner, B. et al. *A first approach to compare efficacy and safety of danaparoid and lepirudin in patients with heparin-induced thrombocytopenia.* Thromb Haemost 2001, (Suppl.): Abst P1241.

Greinacher, A., Lubenow, N. *Recombinant hirudin in clinical practice. Focus on lepirudin.* Circulation 2001, 103(10): 1479.

Piquet, P. et al. *Biological follow up of lepirudin (Refludan®) treatment. Comparison of a new chromogenic test (S-2366, biogenic) with APTT and ecarin clotting time (ECT).* Thromb Haemost 2001, (Suppl.): Abst P692.

Sun, Y. et al. *The use of lepirudin for anticoagulation in patients with heparin-induced thrombocytopenia during major vascular surgery.* Anesth Analg 2001, 92(2): 344.

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## Lidamycin
## C-1027

*Antineoplastic Antibiotic*

EN: 149075

**Chin. Acad. Med. Sci.; Taiho**

An *in vitro* study using human fibroblasts from a healthy (GM00637H [ATM+/+]) patient and a patient with ataxia-telangiectasia (GM05849C [ATM–/–]) examined the mechanism of C-1027 (10 nM)-induced DNA damage and compared it to damage with bleomycin (50 μg/ml) and ionizing radiation (55 Gy). While both cell types were sensitive to C-1027 ($EC_{50}$ ratio = 1.5), differential sensitivities were observed with bleomycin ($EC_{50}$ ratio = 3.2) and radiation ($EC_{50}$ ratio = 5.5). C-1027 was capable of inhibiting DNA repair in both cell types while radiation and bleomycin were only effective in inhibiting DNA replication in cells with inactive ATM. Thus, C-1027-induced activation of DNA damage in human cells was via an ATM-independent mechanism (1).

An *in vitro* study using human hepatoma (BEL-7402) cells and breast cancer cells (MCF-7) examined the mechanism of cytotoxic action of C-1027. Results showed that the potent activity of the agent was due to an interaction between direct breaking of DNA strands and induction of an apoptotic signal pathway (2).

1. Dziegielewski, J., Beerman, T.A. *C-1027-induces activation of DNA-damage responses is ATM-independent.* Proc Amer Assoc Cancer Res 2001, 42: Abst 1068.

2. He, Q., Li, D. *Interaction of direct breaking DNA strands and initiating of apoptotic pathway contributed to high potent cytotoxicities of enediyne antibiotic lidamycin (C1027) to human tumor cells.* Proc Amer Assoc Cancer Res 2001, 42: Abst 3461.

*Original monograph* - Drugs Fut 1999, 24: 847.

### Additional Reference

Sasaki, T. et al. *Synthetic studies toward C-1027 chromophore: Construction of a highly unsaturated macrocycle.* Tetrahedron Lett 2001, 42(31): 5299.

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## Liposomal NDDP Aroplatin®

*Oncolytic*
*Platinum Complex*

EN: 146897

**Aronex; M.D. Anderson Cancer Center**

Aronex and Sumitomo have signed a license agreement granting Aronex exclusive rights in the U.S. to a particular class of DACH platinum compounds. Aroplatin™, a liposomal formulation of a novel platinum compound from this class of drugs, is currently under development by Aronex. This compound has been designed to overcome the toxicity and drug resistance that currently limit the usefulness of other platinum drugs, which are widely used as chemotherapeutic agents in the treatment of solid tumors. Under the terms of the license agreement, Sumitomo will receive an upfront payment, subsequent milestone payments based on regulatory filings, approval and sales of Aroplatin™ and royalties on the sales of Aroplatin™ in the U.S. Except for the treatment of hepatica, the license agreement gives Aronex the exclusive right to make, use, develop, import and sell Aroplatin™ in the U.S. (1).

1. *Sumitomo licenses class of DACH platinum compounds to Aronex.* DailyDrugNews.com (Daily Essentials) Dec 29, 2000.

*Original monograph* - Drugs Fut 1989, 14: 765.

**Additional References**

Clark, P. et al. *A normal phase stability indicating HPLC method for neo-decanoato diamino-cyclohexane platinum (II) (NDDP) and other Pt-DACH complexes.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 2547.

Nouraldeen, A.M. et al. *Selective reversed phase HPLC separation of cis-bis (neodecanoato)(trans-(R,R)-1,2-diaminocyclohexane)platinum (II)[NDDP] from its major biological degradation product di-chloro(trans-(R,R)-1,2-diaminocyclohexane platinum (II) [DACH-Pt-C12].* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 1046.

Shuttlewoth, J., Desai, S.D. *A reverse-phase HPLC assay for stability of NDDP (a cisplatin analogue).* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 2542.

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## Liposomal Nystatin Nyotran®

*Antifungal*

EN: 211301

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

The *in vitro* activity of liposomal nystatin was examined against 215 opportunistic fungal pathogens including 155 yeast and 60 filamentous fungi isolates. Activity of the agent was compared to the activities of nystatin, amphotericin B, liposomal amphotericin B, flucytosine, fluconazole and itraconazole. The $MIC_{90}$s of liposomal nystatin ranged from 0.5-4 μg/ml against yeasts and from 4-16 μg/ml against molds. The MFCs of liposomal nystatin against yeasts and molds were 1-16 and 4->16 μg/ml, respectively (1).

1. Quindos, G., Carrillo-Muñoz, A.J., Ruesga, M.T. et al. *In vitro activity of a new liposomal nystatin formulation against opportunistic fungal pathogens.* Eur J Clin Microbiol Infect Dis 2000, 19(8): 645.

*Original monograph* - Drugs Fut 1994, 19: 724.

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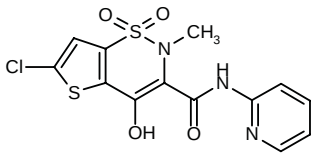
## Lornoxicam Xefo®

*Antiarthritic*
*Analgesic*

EN: 120668



$C_{13}H_{10}ClN_3O_4S_2$ **Nycomed Amersham; CeNeS**

Xefo™ (lornoxicam) was recently introduced in the U.K. by CeNeS, under license from Nycomed Pharma, for the short-term treatment of moderate postoperative pain, pain associated with acute lumbar sciatica and the symptomatic treatment of pain and inflammation in osteoarthritis and rheumatoid arthritis. Lornoxicam is a potent oxicam nonsteroidal antiinflammatory drug (NSAID) for both parenteral (pain) and oral (pain and arthritis) administration, presented as tablets and powder in vials for injection containing 4 or 8 mg drug (1).

1. *Xefo introduced by CeNeS in U.K.* DailyDrugNews.com (Daily Essentials) Sept 7, 2001.

*Original monograph* - Drugs Fut 1992, 17: 683.

**Additional References**

Bianchi, M. et al. *Anti-hyperalgesic effects of lornoxicam, piroxicam, meloxicam, ketorolac, and aspirin in rats.* Br J Pharmacol 2001, 133(Suppl.): Abst 51P.

Mizushima, Y. et al. *Clinical evaluation of TS-110 against rheumatoid arthritis - A long term administration study.* Inflamm Regen 2001, 21(3): 273.

Mizushima, Y. et al. *Clinical evaluations of TS-110 against rheumatoid arthritis - Double blind comparative study using indomethacin as a control.* Inflamm Regen 2001, 21(3): 243.

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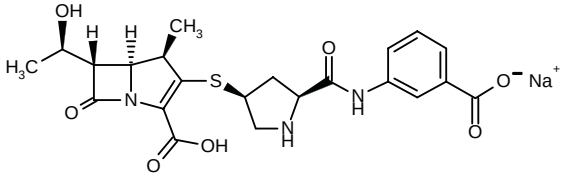
**MK-0826** *Carbapenem Antibiotic*
**L-749345**
**ZD-4433**
**MK-826**
**Ertapenem Sodium**
**Invanz®**

EN: 236885



$C_{22}H_{24}N_3NaO_7S$ **AstraZeneca; Merck & Co.**

Of 67 specimens from skin and soft tissue infections such as diabetic lower extremity infections, perineal cellulitis/abscesses, deep soft tissue abscesses and complicated cellulitis, 50.7% contained anaerobic isolates including *Peptostreptococcus*, *Porphyromonas*, *Prevotella* and *Bacteroides* spp. All isolates were fully susceptible to both ertapenem and imipenem (MIC = ≤ 2 μg/ml), as well as to chloramphenicol, and 99.2, 95.9, 96.7 and 98.4%, respectively, were susceptible to piperacillin/tazobactam, ticarcillin/clavulanate, metronidazole and ampicillin/sulbactam (1).

The *in vitro* activity of ertapenem was compared to activities of imipenem, cefepime, ceftriaxone and piperacillin-tazobactam against 3478 recent clinical isolates from Europe and Australia. Ertapenem was the most active agent against *Enterobacteriaceae* ($MIC_{90}$ = ≥ 1 μg/ml) and was more active than imipenem against fastidious Gram-negative bacteria and *Moraxella* spp. However, imipenem was slightly more active than ertapenem against streptococci, methicillin-susceptible staphylococci and anaerobes; the $MIC_{90}$ for ertapenem for these groups was still ≤ 0.5 μg/ml. While *Acinetobacter* spp. and *Pseudomonas aeruginosa* were also less susceptible to ertapenem as compared to imipenem, the majority of *Enterococcus faecalis* strains tested were resistant. Resistance to ertapenem was also seen in 3 strains of *Enterobacter aerogenes* and 2 (*Bacteriodes fragilis* and *Clostridium difficile* strains) of 135 anaerobes. The MICs of ertapenem for 2 and 1 of the 234 *Streptococcus pneumoniae* strains were 2 and 4 μg/ml, respectively, and of the 67 non-*Streptococcus pyogenes*, ertapenem had MICs of 2 and 16 mcg/ml against 2 non-*S. pneumoniae* streptococci strains which also exhibited decreased susceptibility to other β-lactams and imipenem (2).

The *in vitro* activity of ertapenem was compared to activities of imipenem, amoxicillin-clavulanate and ciprofloxacin against 5558 recent clinical isolates. Ertapenem was more active than imipenem against *Enterobacteriaceae*. However, imipenem was more effective against pseudomonads and Gram-positive bacteria (3).

The *in vitro* activity of MK-0826 was examined against 309 strains from the *B. fragilis* group and compared to that of 11 other β-lactams and 5 non-β-lactam antimicrobials. MK-0826 exhibited activity similar to imipenem and meropenem (MIC ≤ 0.006-4 μg/ml). The $MIC_{90}$s for cefotoxin and piperacillin were 32 and > 256 μg/ml, respectively. Of the β-lactam-β-lactamase combination examined, piperacillin/tazobactam was the most active. Metronidazole and chloramphenicol showed activity against all strains and moxifloxacin and trovafloxacin had good activity ($MIC_{90}$ = 2 and 4 μg/ml, respectively). Resistance to clindamycin was seen in 38.8% of the strains tested (4).

The *in vitro* activity of MK-0826 was compared to imipenem, meropenem, ceftriaxone, piperacillin/tazobactam, clindamycin and metronidazole against 178 anaerobes isolated from patients with intraabdominal infections and 120 other recent isolates. Of all the isolates tested, 95.6% were susceptible to MK-0826 at a proposed breakpoint of ≤ 4 μg/ml. The MICs of imipenem and meropenem were generally similar to those of MK-0826. MK-0826 at the MIC (0.25, 0.5 and 0.06 μg/ml for the respective strains) and above was bactericidal (3 $\log_{10}$ killing or more after 48 h) against a strain of *B. fragilis*, *Bacteroides thetaiotaomicron* and *Clostridium perfingens*. The other agents were bactericidal against these strains at and 2 times above the MIC after 48 h (5).

The *in vitro* activity of MK-0826 was examined against 224 pneumococci including 109 penicillin-susceptible, 37 penicillin-intermediate and 78 penicillin-resistant strains, and was compared to that of 9 other antimicrobials. Imipenem had the lowest MICs followed by MK-0826 and meropenem, ceftriaxone and cefepime, amoxicillin ± clavulanate and cefuroxime. Resistance to clarithromycin was seen in all groups, particularly the penicillin-intermediate and -resistant strains. MK-0826 was active against all strains at a proposed breakpoint concentration of < 2 μg/ml (6).

The *in vitro* activity of MK-0826 was examined against *Klebsiellae* isolates with and without extended spectrum β-lactamases (ESBLs), plasmid AmpC enzymes or hyperproduced KI enzymes, *Escherichia coli* transconjugants with β-lactamases and EBSLs, and AmpC β-lactamase expression mutants. The activity of the agent was compared to that of imipenem, cefepime, ceftazidime, piperacillin and piperacillin/tazobactam. MK-0826 displayed the lowest $MIC_{90}$s against ESBL producers (0.06 mg/l); the $MIC_{90}$s against these strains for imipenem, cefepime and the other agents were 0.5, 16 and > 128 mg/l, respectively. The MICs of MK-0826 for AmpC-depressed enterobacteria and a KI enzyme hyperpro-ducing strain of *Klebsiellae oxytoca* were 0.015-0.25 mg/l as compared to 0.25-1 mg/l for imipenem and 0.5-4 mg/l for cefepime. From the results obtained, it was concluded that MK-0826 had good activity against β-lactamase producers with the exception of those attacking other carbapenems. ESBL-producing and AmpC

enzyme-hyperproducing strains were slightly less susceptible to MK-0826 (7).

The *in vitro* activity of MK-0826 was examined against cephalosporin-resistant *Enterobacteriaceae* isolates including strains bearing extended spectrum β-lactamases (ESBLs) and AmpC β-lactamase. Isolates were obtained from patients with UTI and intraabdominal infections. The most common EBSLs detected were SHV2, SHV5 and Tem-10 β-lactamases. MK-0826 showed good activity against the isolates tested (MIC ≤ 0.5 μg/ml (8).

Clinical trials are now ongoing to confirm the results of a study of the *in vitro* antimicrobial activity of ertapenem against 1001 clinical isolates from human intraabdominal infections. Researchers collected anaerobes from 17 countries around the world and used an agar dilution method for the study, which found that ertapenem was active at ≤ 8 μg/ml against all of the anaerobes, including those of the *B. fragilis* group, except 12 of 61 *Bilophila wadsworthia* isolates, 3 isolates of *Lactobacillus* spp. and 1 isolate of *Acidaminococcus fermentans*. Susceptibilities of the anaerobes to ertapenem were similar across geographic regions (9).

A randomized, 4-period, crossover study conducted in 16 male and female healthy volunteers examined the pharmacokinetics of single-dose MK-0826 (0.5, 1 and 2 g infused in 50 ml saline and 3 g in 150 ml saline over 2 h). For the 0.5-2 g dose ranges, the AUC value was nearly dose-proportional. The AUC of total MK-0826 was slightly less than dose proportional, particularly with the 3 g dose. The mean apparent plasma clearance of total MK-0826 was 27.6, 29.5, 33.4 and 36.3 ml/min for the 0.5, 1, 2 and 3 g doses, respectively. The apparent $t_{1/2}$ and steady-state volume of distribution were about 3.5-4 h and 8 l, respectively. No significant differences were observed between the pharmacokinetics of men and women (10).

The antianaerobic activity of ertapenem has been assessed using specimens obtained during international clinical studies in patients with acute pelvic infections or complicated skin and soft tissue infections. Of 185 specimens from pelvic infections, including postpartum endometritis, pelvic cellulitis, adnexitis and septic abortion, 81.2% grew anaerobic bacteria, including *Prevotella*, *Peptostreptococcus*, *Porphyromonas*, *Fusobacterium*, *Bacteroides* and *Clostridium* spp. Ertapenem was active against 99.8% of all anaerobic bacteria with an MIC of ≤ 4 μg/ml. Imipenem exhibited a similar spectrum of activity and 99.6, 96.6, 99.4, 95.6 and 98.6% of strains, respectively, were susceptible to piperacillin/tazobactam, cefoxitin, chloramphenicol, metronidazole and ampicillin/sulbactam (11).

Ertapenem sodium is the U.S. adopted name and the proposed international nonproprietary name for MK-0826 (12, 13).

An NDA for FDA approval was submitted for ertapenem sodium (Invanz®) in November 2000 (14).

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2. Livermore, D.M., Carter, M.W., Bagel, S. et al. *In vitro activities of ertapenem (MK-0826) against recent clinical bacteria collected in Europe and Australia.* Antimicrob Agents Chemother 2001, 45(6): 1860.

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7. Livermore, D.M., Warner, M., Oakton, K. *Activity of MK-0826 versus β-lactamase producers.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst E-385.

8. Overbye, K.M., Kong, L., Mordekhay, D., Suber, D., Dorso, K., Pelak, B.A., Rosen, H. *Activity of MK-0826 against clinical strains of cephalosporin resistant Enterobacteriaceae, including strains bearing extended spectrum β-lactamases (ESBL).* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst E-380.

9. Goldstein, E.J.C., Citron, D.M., Merriam, C.V., Warren, Y., Tyrrell, K.L. *Comparative in vitro activities of ertapenem (MK-0826) against 1,001 anaerobes isolated from human intraabdominal infections.* Antimicrob Agents Chemother 2000, 44(9): 2389.

10. Majumdar, A.K., Birk, K.L., Neway, W. et al. *Single-dose pharmacokinetics and dose-proportionality of MK-0826, a once-daily carbapenem antibiotic, in healthy male and female volunteers.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst A-491.

11. Citron, D.M., Merriam, C.V., Warren, Y.A., Tyrell, K.L., Goldstein, E.J.C. *Comparative in vitro activity of ertapenem (MK-0826) against 498 anaerobes isolated from acute pelvic infections in hospitalized women.* Int J Antimicrob Agents 2001, 17(Suppl. 1): Abst P19.030.

12. *USAN Council. List No. 432.* Clin Pharmacol Ther 2000, 68(5): 580.

13. *Proposed international nonproprietary names (Prop. INN): List 84.* WHO Drug Inf 2000, 14(4): 256.

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  CCC: 0377-8282/2001 

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Thomson, K.S. et al. *Standard and high inoculum MICs of MK-0826 in tests with ESBL, plasmid-mediated AmpC and multiple β-lactamase producing Enterobacteriaceae.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst E-383.

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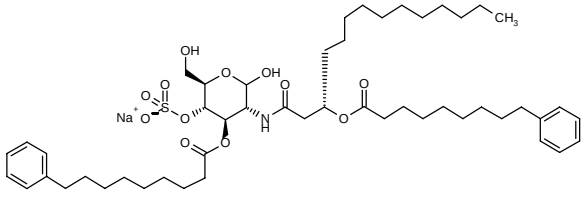
## Ono-4007

*Oncolytic*
*Immunomodulator*

EN: 193855



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

A study has examined the effects of Ono-4007 on antigen-specific IgE production *in vivo* using ovalbumin-sensitized BALB/c mice. Treatment with the agent inhibited ovalbumin-induced total IgE and $IgG_1$ production but had no effect on $IgG_{2a}$ production. *In vitro* studies using a coculture of dendritic cells and T cells showed that the agent inhibited IL-4 production of naive CD4+ T cells (1).

Ono-4007 (1-2 mg/site s.c.) was shown to dose-dependently increase vascular permeability of mouse skin through mechanisms involving TNF-α, IL-1α and constitutive nitric oxide synthase (NOS)-derived NO; neither prostaglandins nor histamine were involved. Effects of the agent were seen 120 min postdosing. Pretreatment with anti-TNF-α, anti-IL-1α and L-NAME (10 mg/kg) significantly decreased Ono-4007-induced permeability while indomethacin, diphenhydramine and aminoguanidine had no effect. Ono-4007 also increased the permeability of skin of inducible nitric oxide synthase (iNOS)-deficient mice. In addition, the agent dilated phenylalanine-contracted rat thoracic aortic rings, an effect blocked by L-NAME treatment (2).

1. Iio, J., Ohmura, K., Meguro, T., Yatsuno, T., Katamura, K., Nakahata, T. *Effects of the lipid A derivative ONO-4007 on antigen-specific IgE production.* Jpn J Allergol 2000, 49(9-10): Abst 79.

2. Ishida, H., Fujii, E., Irie, K., Yoshioka, T., Muraki, T., Ogawa, R. *Role of inflammatory mediators in lipid A analogue (ONO-4007)-induced vascular permeability change in mouse skin.* Br J Pharmacol 2000, 130(6): 1235.

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## Oral Heparin

*Anticoagulant*

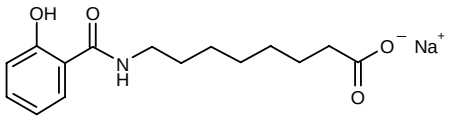
EN: 273032

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

## SNAC

*Absorption Promoter*

EN:245771



$C_{15}H_{20}NNaO_4$ **Emisphere; DuPont Pharm.**

A phase I trial in healthy volunteers examined the effects of a SNAC/heparin oral capsule formulation. Treatment resulted in dose-dependent increases in clotting time (aPTT) up to 3 times baseline values. Peak effects were seen between 0.5-1.5 h after dosing, after which levels returned to normal by 6 h. Treatment was well tolerated. The adverse events seen with treatment were mainly gastrointestinal. No serious changes in vital signs, physical exams, ECGs or laboratory parameters were seen (1).

1. Leone-Bay, A., Rivera-Schaub, T., Agarwall, R., Majuru, S., Tanner, T., Rees, J., Febbrato, S., Baughman, R.A. *Phase I studies assessing the oral delivery of capsules containing heparin in combination with a delivery agent, SNAC.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 3292.

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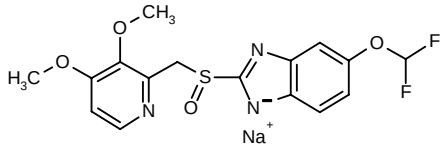
## Pantoprazole Sodium
## Pantoloc®
## Protonix®

*Treatment of GERD*

EN: 163674



$C_{16}H_{14}NaF_2N_3O_4S$

**Byk Gulden; Solvay; American Home Products**

Byk Canada and Solvay have announced that pantoprazole sodium (Pantoloc®) was recently approved by Health Canada for the treatment of symptomatic gastroesophageal reflux disease (GERD), also known as heartburn. A Canadian trial which randomized patients to either pantoprazole or nizatidine was pivotal in the approval for the symptomatic GERD indication. This trial, developed by the Canadian Pantoprazole GERD Study Group, compared symptomatic relief of heartburn on pantoprazole once daily to nizatidine twice daily in patients with endoscopy-negative reflux disease and in patients with esophagitis. The study was a 4-week, randomized, double-blind, multicenter study in 220 patients from across Canada. Patients were randomized to either pantoprazole 40 mg once daily or nizatidine 150 mg twice daily. Pantoprazole treatment resulted in a significantly greater relief of heartburn symptoms in a higher proportion of patients at 7 days than nizatidine at 28 days. Pantoloc®, available in tablet form, works by reducing acid secretion in the stomach by inhibiting both basal and stimulated gastric secretion (1).

American Home Products has launched Protonix® I.V. in the U.S. following the March approval by the FDA for the short-term treatment (7-10 days) of GERD as an alternative to oral therapy in patients who are unable to continue taking Protonix® delayed-release tablets. Protonix® is the first and only intravenous proton pump inhibitor available in the U.S. (2).

The FDA has approved the long-term use of Protonix® delayed-release tablets. Protonix® was initially approved in the U.S. for the short-term treatment (up to 16 weeks) of erosive esophagitis associated with GERD. Protonix® is marketed by Wyeth-Ayerst, the pharmaceutical division of American Home Products. Supporting the regulatory application filed for this extended indication for Protonix® were results from 2 double-blind studies in which Protonix® effectively maintained healing of erosive esophagitis in 86% of patients at 12 months. Protonix® 40 mg provided relief from daytime and nighttime heartburn 90% of the time. In addition, it was shown that Protonix® 40 mg was superior to ranitidine 150 mg b.i.d. in reducing the number of daytime and nighttime heartburn episodes from the first month through the twelfth month of treatment (3).

1. *Health Canada approves Pantoloc for treatment of heartburn.* DailyDrugNews.com (Daily Essentials) April 3, 2001.

2. *Protonix I.V. now available in the U.S. for GERD.* DailyDrugNews.com (Daily Essentials) May 18, 2001.

3. *FDA approves extended indication for delayed-release Protonix.* DailyDrugNews.com (Daily Essentials) June 18, 2001.

*Original monograph* - Drugs Fut 1990, 15: 801.

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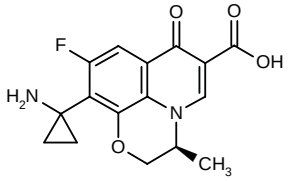
## Pazufloxacin
## Pasil®
## Pazucross®

*Quinolone Antibacterial*

EN: 166473



$C_{16}H_{15}FN_2O_4$

**Toyama; Welfide**

From the results of a pharmacokinetic study in 10 elderly volunteers administered pazufloxacin (500 mg i.v. drip over 30 min), it was concluded that older patients should be monitored to avoid reductions in renal function. In subjects who were 75 years or older, peak $C_{max}$ and AUC values were higher and systemic and renal clearance and steady-state distribution were lower as compared to 65-74 year old subjects; however, elimination $t_{1/2}$ values were not longer. The mean urinary excretion rate was 83.5% at 24 h; renal clearance was the predominant route of elimination. Accumulation of the agent was not detected after multiple dosing (500 mg b.i.d. or t.i.d. for 7 days). No adverse events were reported (1).

Results from a study conducted in patients with reduced renal function showed that the pharmacokinetics of pazufloxacin (300 mg i.v. drip over 30 min) were altered in patients with severe renal dysfunction. Elimination $t_{1/2}$ and $AUC_{0-\infty}$ values increased with the degree of renal dysfunction; the $t_{1/2\beta}$ values were 20 h longer in patients receiving hemodialysis. Renal clearance was also decreased, indicating a delay in urinary excretion in patients with reduced renal function. The apparent $t_{1/2}$ of the agent during hemodialysis was 2.78-4 h which was one-sixth of the $t_{1/2}$ obtained during nonhemodialysis periods. No dose adjustments were required in patients with creatinine clearance of 44.7 and 23.6 ml/min. However, patients receiving hemodialysis with creatinine clearance of zero required modifications of the dosing interval (2).

A clinical study conducted in 10 patients undergoing radical hysterectomy and 49 patients with adnexitis, parametritis or pelvic peritonitis, showed the efficacy and safe-

  CCC: 0377-8282/2001 

ty of pazufloxacin (300 or 500 mg i.v. drip over 30 min). Pazufloxacin concentrations in uterine artery blood and peripheral vein blood at 0.83 h in patients undergoing hysterectomy treated with 300 mg were 6.72 and 6.21 μg/ml, respectively. Peak pazufloxacin concentrations in the portio vaginalis, cervix uteri, endometrium, myometrium, oviduct and ovaries of these patients were 5, 7.79, 13.9, 12.9, 9.34 and 5.65 μg/g. Serum concentrations of the agent peaked (7.83 μg/ml) at 0.25-0.5 h. Efficacy results from the 42 evaluable patients with gynecological infections showed excellent, good and poor responses in 4, 33 and 5 patients, respectively; the overall clinical efficacy rate was 88.1%. Efficacy rates according to infection type were 95.2, 80 and 81.8% for adnexitis, parametritis and pelvic peritonitis, respectively. Bacteriological efficacy rates evaluated in 30 patients were 83.3 and 88.9% for monomicrobial and polymicrobial infections, respectively. The eradication rates for 60 isolated strains, Gram-positive species, Gram-negative species and anaerobes were 60, 85.2, 94.1 and 93.8%, respectively. Adverse events were reported in 5/48 patients and included mild to moderate diarrhea, rash and elevated transaminases (3).

The efficacy and safety of pazufloxacin were examined in a study conducted in 9 patients with sepsis, empyema or endocarditis. Clinical efficacy responses for sepsis and empyema were seen in 2/2 and 3/5 patients, respectively. The 2 cases of sepsis were caused by *Escherichia coli* and a polymicrobial infection of *E. coli* and *Enterococcus faecalis*, respectively; the monomicrobial infection was eradicated with treatment but the outcome of the polymicrobial infection was unknown. One case of empyema was caused by *Streptococcus intermedius* which was not eradicated by treatment. Adverse events were observed in 3/8 patients and consisted of 1 case each of delirium, eosinophilia and elevated Al-P levels (4).

1. Takagi, K., Yajima, Y., Yoshizawa, H. *Pharmacokinetics of pazufloxacin mesilate in elderly subjects.* Jpn J Chemother 2000, 48(8): 633.

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*Original monograph* - Drugs Fut 1993, 18: 717.

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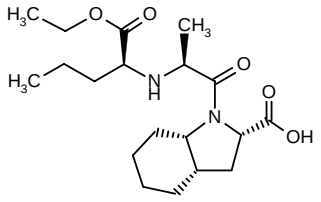
## Perindopril
## Aceon®

*Antihypertensive*
*ACE Inhibitor*

EN: 102331



$C_{19}H_{32}N_2O_5$ **Servier**

Results of a landmark study indicated that over 500,000 strokes or transient ischemic attacks (TIAs) could be prevented by using a combination of the antihypertensive ACE inhibitor perindopril and the diuretic indapamide. A series of trials involving 6000 patients, referred to as the PROGRESS (Perindopril Protection Against Recurrent Stroke Study) trials, demonstrated that the incidence of secondary stroke was reduced by as much as 50% when a regimen of perindopril and a diuretic was followed. PROGRESS, a double-blind, placebo-controlled, randomized trial in both hypertensive and normotensive patients, took place in 10 countries over a period of 5 years. Patients were assigned to receive combination therapy or perindopril alone, or matching placebos. Notably, there was a 38% reduction in fatal strokes in patients using the perindopril-based therapy. Furthermore, there was up to a 50% reduction in stroke-related dementia and serious cognitive impairment for TIA patients who went on to experience a recurrent stroke. The trial also indicated that the perindopril/diuretic therapy would be beneficial in patients with normal blood pressure. At present, perindopril is approved by the FDA for use as an antihypertensive medication (1).

1. Chalmers, J., MacMahon, S. *PROGRESS – Perindopril Protection Against Recurrent Stroke Study: Main results.* J Hypertens 2001, 19(Suppl. 2): Abst 40.

*Original monograph* - Drugs Fut 1985, 10: 636.

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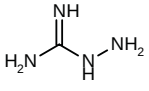
## Pimagedine
## Aminoguanidine

*Treatment of Diabetic Retinopathy*

EN: 182590



$CH_6N_4$ **Alteon; Yamanouchi**

STZ-induced diabetic rats with proteinuria and increased urinary heparan sulphate excretion were

treated with aminoguanidine to see how the drug affected these parameters. A high incorporation of heparan sulphate-associated charge into glomerular basement membrane was indicated by reduced urinary heparan sulphate levels observed in aminoguanidine-treated rats. Proteinuria was also relatively improved in these animals. The beneficial effects of aminoguanidine may therefore be related to the restoration of prediabetes renal basement membrane heparan sulphate levels (1).

A rat model of ischemia was used to evaluate the role of nitric oxide (NO) production in the impairment of learning behavior and hippocampal long-term potentiation after transient ischemia. Rats were given aminoguanidine (10 mg/kg i. p.) 30 min prior to a 10-min occlusion of the common carotid arteries and then every 24 h for 4 days. The agent inhibited increases in NO production seen on days 1 and 4. The Y-maze test and contextual fear conditioning revealed that aminoguanidine ameliorated learning behavior impaired by 4-vessel occlusion. Pretreatment with the agent prevented the inhibition of long-term potentiation in perforant path-dentate gyrus, but not in Schaffer collateral-CA1 synapses. Increased NO production by NO synthase appeared to impair learning behavior, and an association between behavioral performance and long-term potentiation formation in perforant path-dentate gyrus synapses was found (2).

Aminoguanidine showed potential for the treatment and prevention of pulmonary fibrosis in a study in rats. Animals were grouped to receive either 10 IU/kg intratracheal bleomycin, 10 IU/kg intratracheal bleomycin plus 4 weeks of aminoguanidine (50 mg/kg/day) or controls. Bleomycin was administered to induce a fibrotic response. Analysis revealed that aminoguanidine significantly reduced the total hydroxyproline content of the lungs and promoted a significant reduction of the area occupied by collagen in the axial and septal zones (3).

The effects of aminoguanidine (100 mg/kg) and desferrioxamine (50 mg/kg) were evaluated in normal and STZ-induced hyperglycemic rats. Both agents were administered i.p. once daily for 14 days. In normal rats, aminoguanidine reduced the response of aortae to phenylephrine and increased body weight but had no effect on biochemical parameters related to oxidative stress. In hyperglycemic rats, aminoguanidine normalized the aortic response to phenylephrine which was elevated by hyperglycemia. Biochemical changes resulting from hyperglycemia were also modulated. Plasma glucose levels were not affected. In normal rats, desferrioxamine treatment reduced the aortic response to phenylephrine and decreased body weight without affecting biochemical markers. In hyperglycemic animals, desferrioxamine had no effect on body weight loss or elevation in plasma glucose levels while the aortic responsiveness to phenylephrine was attenuated. Desferrioxamine also normalized elevated plasma total thiol levels and had a modulatory effect on superoxide dismutase and glutathione peroxidase activities and lipid peroxide levels (4).

A study investigated the effect of aminoguanidine on ocular infection related to the herpes simplex virus. Balb/c mice with herpes simplex virus were treated topically with aminoguanidine 0.5, 0.1 and 0.05 mg, resulting in a dose-dependent increase in ocular disease. Ocular washings from aminoguanidine-treated mice were higher in viral titers as compared to controls. Three days postinfection, the corneas from treated mice showed an infiltrate consisting largely of neutrophils, compared with few inflammatory cells in corneas from controls. Treated mice also died in greater number and earlier than controls. The results indicate that NO, which is inhibited by aminoguanidine, has an inhibitory effect on herpes simplex virus ocular infection (5).

A study was conducted to evaluate aminoguanidine treatment in rats with experimental autoimmune encephalomyelitis. Treatment with the drug was found to delay the onset of the disease although recovery was impaired. This was associated with proinflammatory cytokine production and persistent inflammation in the central nervous system. Aminoguanidine decreased the percentage of V $\beta$ 8.2(+) T lymphocytes undergoing early apoptosis in the periphery but not in the spinal cord. The drug also increased T lymphocyte proliferation against myelin basic protein in the periphery. Aminoguanidine, therefore, appeared to prolong the survival of circulating encephalitogenic cells, thus allowing a longer time of entry of the cells into the nervous system (6).

A 5-year study in diabetic dogs has examined the effects of aminoguanidine and aspirin on the development of retinopathy. Alloxan-diabetic animals were randomly assigned to an untreated control group or treatment at the onset of diabetes with aminoguanidine or aspirin at doses of 20-25 mg/kg/day, and comparable levels of glycemia were maintained in all groups. Aminoguanidine resulted in practically total inhibition of the development of retinopathy despite continued hyperglycemia, with significant attenuation of regional microaneurysms, acellular capillaries and pericyte ghosts, a significant decrease in the severity of sudanophilia and marked inhibition of retinal hemorrhages. Aspirin, on the other hand, only provided significant inhibition of retinal hemorrhages, capillary sudanophilia and acellular capillaries, other effects not reaching statistical significance. No effect on the increased levels of advanced glycation end products was seen for aminoguanidine, although it did inhibit the increased nitration of a retinal protein. Neither aminoguanidine nor aspirin had a significant effect on the increased albumin excretion or changes in renal structure associated with diabetes. A modest beneficial effect was seen for aminoguanidine, but not aspirin, on the decrease in ulnar nerve conduction velocity (7).

A multicenter, randomized, double-blind, placebo-controlled trial examined the efficacy of pimagedine (150 or 300 mg b.i.d.) on diabetes complications. The trial was conducted in a total of 690 patients with type 1 diabetes mellitus with proteinuria > 500 mg/day, creatinine clearance of 40-90 cc/min and retinopathy. Treatment significantly decreased UprV with peak effects observed at 36 months. Treatment also significantly improved

progression of retinopathy and significantly lowered total cholesterol and LDL-cholesterol levels. Adverse events associated with the drug were flu-like symptoms, anemia and an induction of ANA and ANCA antibodies. Incidence of adverse events were similar in the low-dose and placebo groups (8).

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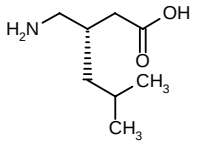
## Pregabalin

*Antiepileptic*
*Treatment of Diabetic Neuropathy*

EN: 194644




$C_8H_{17}NO_2$ **Pfizer**

Scientists have described a method to modulate substance P by using GABA analogs, in particular gabapentin or pregabalin. These compounds are thus useful for the treatment of substance P-related diseases such as headache, migraine, neurogenic inflammation, emesis, cough, bronchitis, obesity, asthma, allergy, hemorrhoids, *etc.* (1).

Pregabalin has been reported to be endowed with anticonvulsant, anxiolytic and analgesic effects and has been shown to have high affinity for the $\alpha_2\delta$ subunit of the L-type $Ca^{2+}$ channel. Its effects in a recently developed rat model of endotoxin-induced delayed visceral hyperalgesia, mimicking the major symptom seen in patients with irritable bowel syndrome, have now been examined. In this model, i.p. lipopolysaccharide (LPS) is used to produce a delayed lowering threshold of abdominal contractions in response to rectal distension. This rectal allodynic effect of LPS was blocked by systemic morphine sulfate (0.3 mg/kg s.c.), an effect which was antagonized by naloxone. Likewise, oral pretreatment with pregabalin (1, 3, 10 and 30 mg/kg) produced a dose-dependent reduction in the LPS-enhanced abdominal response to rectal distension, and it was also effective following a single i.p. dose of 30 mg/kg. In contrast to morphine, the antiallodynic effect of pregabalin could not be blocked by pretreatment with naloxone or the GABA-A receptor antagonist bicuculline, suggesting that it does not act via GABA-A or opiate receptors. It was concluded that pregabalin may be a therapeutic candidate for the treatment of gut hypersensitivity (2).

A study using the rat conflict and elevated X-maze tests of anxiety demonstrated the efficacy of pregabalin. The agent was found to selectively bind with high affinity to the $\alpha_2\delta$ subunit of voltage-dependent calcium channels (VDCC); its (*R*)-enantiomer, (*R*)-isobutylgaba, displayed an approximate 10-fold weaker affinity. Pregabalin induced anxiolytic-like effects in both the rat conflict test (MED = 3 mg/kg) and elevated X-maze test

(MED 10 mg/kg) in contrast to (*R*)-isobutylgaba which only induced effects in the conflict test at a concentration of 100 mg/kg (3).

Intracolonic (i.c.) glutamate and intrathecal (i.t.) glutamate were evaluated for their effect on pain by assessing their influence on the spontaneous occurrence of abdominal contractions in rats. The same study evaluated antagonism by orally and intrathecally administered pregabalin on i.c. and i.t. glutamate-induced abdominal cramps. Electrodes were implanted in the abdomen and neck muscles of 6 groups of 10 adult male Wistar rats, which were also equipped with i.c. and i.t. catheters. In one set of experiments, i.c. glutamate (4 mg/kg) was administered to rats treated with pregabalin and its vehicle either p.o. (30 mg/kg) 1 h before or i.t. (300 μg/kg) 10 min after glutamate. From 1-2 h after i.c. glutamate administration, abdominal spike bursts were increased significantly. In a second set of experiments, administration of pregabalin (either p.o. 30 mg/kg or i.t. 300 μg/kg) was followed by i.t. administration of glutamate (40 μg/kg). Glutamate administered i.t. resulted in an 86% increase in abdominal spike bursts lasting longer than 2 h, although neck muscle was unaffected. Both p.o. and i.t. pregabalin inhibited the effects of i.c. and i.t. glutamate. Neither i.t. nor p.o. pregabalin affected the basal number of abdominal cramps noted after vehicle administered i.t. or i.c (4).

A study which investigated the effect of pregabalin on visceral pain has been reported. Electrodes were implanted or not on the external abdominal muscle of male SD rats. After 2 weeks, pregabalin 30 mg/kg or water was administered, and a latex balloon was inserted through the anus into the rectocolic segment of the animals. Pregabalin was found to reduce the number of abdominal contractions in response to the first and second colorectal distensions as compared with controls. Pregabalin also reduced the heightened AUC during the second distention by 13% in comparison to controls. In addition to inhibiting visceral pain from repeated colorectal distention and inhibiting visceral hypersensitivity, pregabalin blunted L6-S1 spinal cord neuronal activation induced by repeated colorectal distention (5).

A study conducted in 7 healthy subjects showed that pregabalin is well absorbed in the proximal colon but poorly absorbed in the distal colon. Subjects were administered a pregabalin 100 mg solution orally or perfused via a nasoenteric tube over 4 h in specific regions of the colon. Oral administration resulted in rapid absorption with a mean $t_{max}$, $C_{max}$ and $t_{1/2}$ of 0.75 h, 3.34 μg/ml and 5.4 h, respectively. The $t_{max}$ following intracolonic perfusion was 4 h or more. The $C_{max}$, $t_{1/2}$ and relative bioavailability following perfusion into the proximal colon were 1.41 μg/ml, 6.8 h and 56.2%, respectively, and 0.105 mg/ml, 26.9 h and 11.7%, respectively, after perfusion into the distal colon (6).

The results from 3 recently completed double-blind, randomized, placebo-controlled studies of pregabalin in patients with generalized anxiety disorder (GAD) were discussed. In these trials, patients received placebo, pregabalin 150 or 600 mg/day or lorazepam 6 mg/day for 4 weeks, followed by tapering off of dose over 1 week. In 2 studies enrolling 276 and 271 patients, the higher dose of pregabalin was superior to placebo in reducing symptoms of GAD as assessed on the Hamilton Anxiety Rating Scale (HAM-A), and a significant effect for the lower dose of pregabalin *versus* placebo was also seen in the trial in 276 patients. Lorazepam was also superior to placebo in reducing HAM-A scores in these trials. The third study (n = 282) showed no significant differences among groups on the HAM-A, but in all 3 studies pregabalin 600 mg/day was significantly superior to placebo in reducing scores on the Hamilton Depression Rating Scale (HAM-D); lorazepam significantly reduced scores on the HAM-D in only 1 trial. Somnolence and dizziness were the most common adverse events reported on pregabalin (7).

The results from a double-blind, randomized, placebo-controlled trial of low- and high-dose pregabalin in 135 patients with social phobia have been reported. Patients received placebo or pregabalin 150 or 600 mg/day over 11 weeks. According to intent-to-treat analysis, high-dose pregabalin was significantly superior to placebo in reducing total scores on the Liebowitz Social Anxiety Scale (LSAS), as well as on some secondary measures such as certain LSAS subscales and the fear subscale of the Brief Social Phobia Scale (BSPS). In contrast, the lower dose of pregabalin was not statistically significantly superior to placebo on any measure. Patients not suffering from other psychiatric disorders appeared to have a better response to pregabalin 600 mg/day than those with comorbidity. Tolerance was generally good, the most frequent adverse event being somnolence (8).

Two double-blind, parallel-group studies conducted in 557 diabetic patients with neuropathic pain examined the relationship between pregabalin exposure (dose and concentration) and response following multiple dosing (75-600 mg/day). Data were best described by an $E_{max}$ model. Compared to placebo, 300 mg/day of pregabalin decreased the pain score by approximately 1 point. When increasing the dose up to 600 mg, the pain score decreased by approximately 40% (9).

Three double-blind, parallel-group studies in a total of 1042 patients with refractory partial seizures determined the relationship between pregabalin exposure and response over 3 months following multiple dosing (50-600 mg/day). Data were best described by a mixed effect model. A dose-dependent and asymptotic reduction in seizure frequency was observed in 75% of patients: the maximum decrease was 100% in women and 80% in men. In responsive patients, the expected decrease in the baseline seizure rate was 50% of maximum following administration of 180 mg. The dose-response relationship seen was not influenced by age, race or menopausal status of women (10).

The efficacy and safety of pregabalin (300 and 600 mg/day) were shown in 2 randomized, double-blind, placebo-controlled studies conducted in a total of 584 patients with painful diabetic peripheral neuropathy

(duration of 1-5 years). Patients were administered either the placebo or pregabalin (75, 150, 300 and 600 mg/day) 3 times daily. A significant decrease in endpoint weekly mean pain scores was observed with pregabalin doses of 300 and 600 mg/day as compared to placebo. Improvements were also seen with these doses in sleep interference scores from patient diaries and subscales of the SF-McGill Pain Questionnaire (SFMPQ) at 1 week; these improvements were sustained throughout the study. Treatment with 300 and 600 mg/day pregabalin also resulted in significantly better Clinical and Patient Global Impressions of Change (CGIC, PGIC) scores and a better responder rate (number of patients with a 50% or greater decrease in pain as compared to baseline) as compared to placebo. The most common adverse events included mild to moderate somnolence and dizziness. The study was completed by 89% of the patients, of whom most continued in a subsequent open-label phase; the withdrawal rate of 5.3% was due to adverse events (11).

A study conducted in 6 healthy male volunteers showed that pregabalin was predominantly eliminated by renal excretion and its metabolism was negligible. Following p.o. administration of [$^{14}$C]-pregabalin (100 mg), total radioactivity was mainly recovered in urine (92% *vs.* < 0.1% for feces). In urine collected during the first 48 h postdose, radioactivity was mainly due to unchanged pregabalin (89.9%). Minor components detected included the *N*-methylated metabolite (0.9%) and an unidentified agent (0.4%). Similarly, unchanged pregabalin was primarily determined in plasma (12).

Results from 2 multicenter, randomized, double-blind, placebo-controlled, parallel-group studies in a total of 661 patients with chronic lower back pain failed to show any significant effects of pregabalin in reducing pain. Neither endpoint mean pain scores nor secondary efficacy parameters for pregabalin-treated patients were significantly different from placebo. However, treatment was well tolerated with the most common adverse events being somnolence and dizziness (13).

Pfizer has restricted the use of pregabalin for certain patients in clinical trials following discussions with the FDA. The restriction is the result of the FDA's analysis of previously submitted results from a lifetime mouse study that showed an increased incidence of a specific tumor type. It is not known whether these results are applicable to humans, since pregabalin is not a chemical mutagen and not genotoxic in preclinical studies. A similar lifetime dosing study in rats did not show increases in any tumor type, nor were negative results seen in any other toxicological screen or study. Pregabalin is under development for the treatment of neuropathic pain, epilepsy, a variety of anxiety disorders and chronic pain conditions for which there are only limited treatment options. The submission of an NDA seeking FDA approval for pregabalin for the treatment of neuropathic pain and epilepsy is expected to proceed as planned. Pfizer continues to work closely with the FDA to resolve the recently surfaced issue (14).

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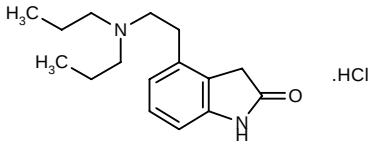
## Ropinirole Hydrochloride
## ReQuip®

*Antiparkinsonian*
*Treatment of RLS*

EN: 100359



$C_{16}H_{24}N_2O.HCl$ **GlaxoSmithKline; SkyePharma**

The results of an open-label and double-blind, placebo-controlled study of ropinirole *versus* placebo have been reported. In the open-label phase, 30 patients with idiopathic restless legs syndrome (RLS) were started on 0.25 mg of ropinirole, which was then titrated until benefit over 2 weeks to a maximum of 6 mg/day. Twenty-five patients completed the 2-week open-label phase and 68% showed moderate to marked improvement in the RLS disability score, with a group mean reduction of 44%. Minor side effects such as headache, nausea and drowsiness were frequent and 2 patients withdrew because of side effects (1).

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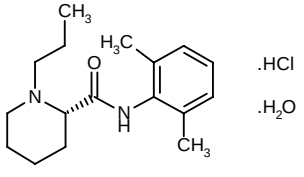
*Original monograph* - Drugs Fut 1989, 14: 781.

## Ropivacaine Hydrochloride
## Naropin®

*Anesthetic*

EN: 150269



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

AstraZeneca has submitted an sNDA for a single-dose administration of Naropin® (ropivacaine hydrochloride) injection for regional anesthesia in pediatric patients. The company is seeking approval of the drug for acute pain management in children aged 1-12 years. In November, AstraZeneca received FDA approval for 72-h infusion of Naropin® 2.0 mg/ml for postoperative pain management. An additional concentration of Naropin®, 7.5 mg/ml, was approved for major nerve block. Naropin® is a long-acting anesthetic indicated for the production of local or regional anesthesia for surgery, postoperative pain management and for obstetrical procedures (1).

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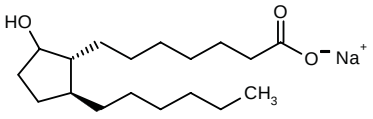
## Rosaprostol Sodium
## Rosal®

*Antiulcer*

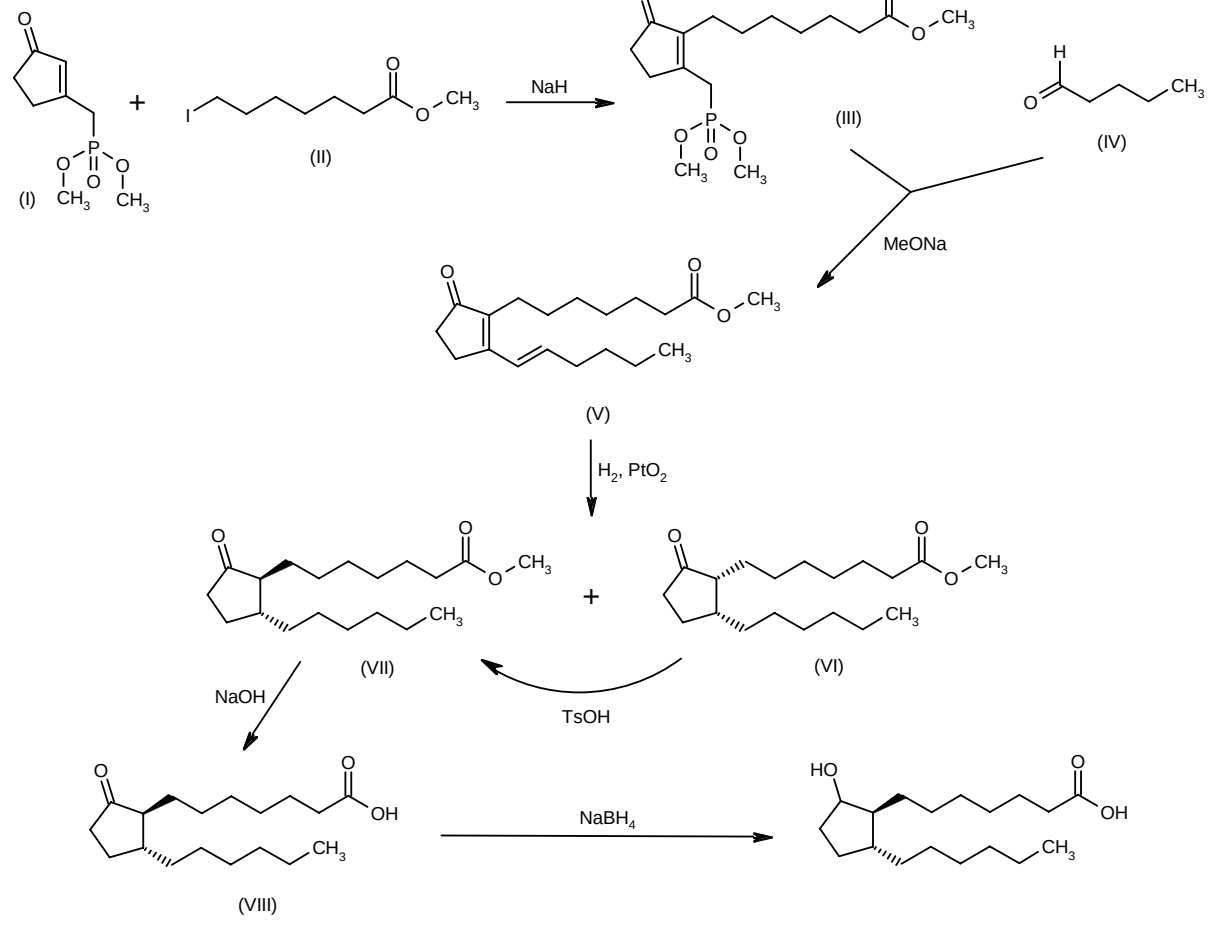
EN: 090454



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

**Scheme 3: Synthesis of Rosaprostol**




A new synthesis of rosaprostol has been developed: Reaction of 3-(dimethoxyphosphorylmethyl)-2-cyclopenten-1-one (I) with 7-iodoheptanoic acid methyl ester (II) by means of NaH in DMSO gives the C-2 alkylated cyclopentenone (III), which is condensed with pentanal (IV) by means of NaOMe in methanol to yield the dienone (V). Reduction of the double bonds of (V) with $H_2$ over $PtO_2$ in acetic acid affords a mixture of the *cis*- and *trans*-cyclopentanones (VI) and (VII) which, without isolation, is submitted to epimerization with TsOH in methanol to furnish almost quantitatively the desired *trans*-isomer (VII). The hydrolysis of the methyl ester of (VII) with NaOH in dioxane/water gives the corresponding carboxylic acid (VIII), which is finally hydrogenated with $NaBH_4$ in methanol (1). Scheme 3.

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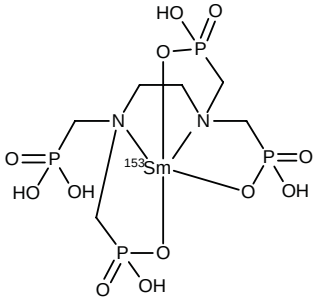
## Samarium ($^{153}$Sm) Lexidronam Quadramet®

*Analgesic*
*Antiarthritic*

EN: 135050



$C_6H_{17}N_2O_{12}P_4Sm$ **Aventis Pharma; Cytogen; Berlex**

A study conducted in 29 patients undergoing radionuclide therapy for palliation of bone pain used a new scintigraphic quantification technique to separately measure

bone uptake and soft tissue retention of Sm-153-EDTMP (37 MBq) and Re-186-HEDP (1295 MBq). The mean bone uptake at 3 and 24 h after injection of Re-186-HEDP was 13.7 ± 8.6 and 21.8 ± 9% of initial whole body activity, respectively, and 29.2 ± 15.5 and 47.7 ± 11.2%, respectively, after injection of Sm-153-EDTMP. Soft tissue activity at 3 and 24 h following Re-186-HEDP injection was 49.4 ± 16.9 and 12.8 ± 5.4%, respectively, and 38.4 ± 14.5 and 12.7 ± 4.7%, respectively, for Sm-153-EDTMP. Urinary excretion for Re-186-HEDP was 36.9 ± 14.4% at 3 h and 65.3 ± 12.8% at 24 h postinjection; these values for Sm-153-EDTMP were 32.3 ± 12.9 and 39.5 ± 13.8%, respectively. It was concluded that results obtained using this method, which measures the region of interest, correlated well with conventional 24-h whole-body retention measurements. The new method offers the advantage that bone uptake and soft tissue retention can be calculated separately (1).

Clinical evidence for beneficial therapeutic effects over and above the established pain-relieving effect of Sm-153-EDTMP in prostate cancer patients with multiple painful bone lesions was reported. Eight patients were treated with 30 mCi Sm-153-EDTMP at 3-month intervals for 5 doses. After the third therapy, all but 1 patient had a significant decrease in the number and uptake intensity of bone lesions and a significant reduction in pain subsequent to decreases in PSA (prostate-specific antigen) levels (2).

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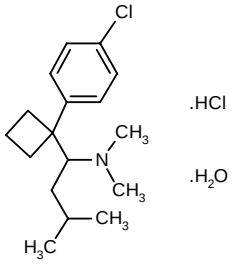
## Sibutramine Hydrochloride Monohydrate

**Reductil®** *Antiobesity*

**Meridia®**

EN: 125655




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

Synergistic effects are achieved when combining the antiobesity agents sibutramine hydrochloride hydrate and orlistat, a lipase inhibitor. Preferably, sibutramine is administered at a dose of 20 or 30 mg once daily and orlistat is given at a dose of 120 mg 3 times daily. Pharmaceutical compositions incorporating both compounds are also described (1).

The results from the STORM (Sibutramine Trial of Obesity Reduction and Maintenance) study demonstrate that obese subjects managed with a weight reduction regimen including sibutramine hydrochloride are able to lose weight and maintain significant weight loss over 2 years. Sibutramine has proved to induce dose-dependent weight loss and to enhance the effects of a low-calorie diet over 1 year, and its longer term efficacy was thus examined in this randomized, placebo-controlled, double-blind, parallel-group trial with an open run-in phase. The STORM trial enrolled 605 obese patients with a body mass index of 30-45 $kg/m^2$ who received sibutramine (10 mg/day) and an individualized diet/exercise program for 6 months. Patients showing weight loss of over 5% of their body weight were then randomized to receive sibutramine (10-20 mg/day) or placebo for 18 months. During the 6-month run-in period, patients lost an average of 25 pounds, or 11% of body weight, on sibutramine, 77% achieving a weight loss of at least 5%. Of 204 sibutramine-treated patients completing the trial, 89 (43%) achieved the primary outcome measure of maintenance of at least 80% of the weight loss achieved during the first 6 months, compared to only 9 (16%) of the 57 placebo patients. Almost 70% of those in the sibutramine group maintained a 5% weight loss for 2 years, compared to 44% in the placebo group, 46% maintained a 10% weight loss, compared to only 21% in the placebo group, and 27% maintained their full initial weight loss on sibutramine over 18 months. Furthermore, sibutramine patients showed a 20.7% increase in HDL levels (*vs.* 11.7% on placebo), and improvement was also seen *versus* placebo in triglycerides, VLDL cholesterol, insulin C-peptide and uric acid. The treatment was well tolerated, only 3% of those on sibutramine withdrawing due to hypertension. In this regard, it is suggested that any potential increase in cardiovascular risk due to the increases in blood pressure seen with sibutramine would likely be counteracted by its beneficial effects on lipid and other metabolic parameters (2).

Following its recent European Commission approval, sibutramine hydrochloride has been launched in the U.K. as Reductil® as adjunctive therapy within a weight management program for patients with obesity. Sibutramine acts by inhibiting 5-HT and noradrenaline reuptake, which enhances satiety. Knoll (now part of Abbott) developed sibutramine and markets the drug in the U.K. as capsules containing sibutramine hydrochloride monohydrate, 10 and 15 mg (3).

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  CCC: 0377-8282/2001 

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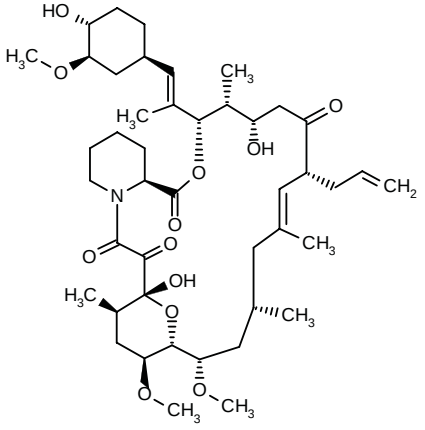
## Tacrolimus
## Protopic®
## Prograf®

*Treatment of Atopic Dermatitis*
*Treatment of Transplant Rejection*

EN: 124071



$C_{44}H_{69}NO_{12}$ **Fujisawa**

Analysis of results from 3 double-blind, vehicle-controlled, 12-week trials (1 pediatric and 2 adult trials) and 1 open-label, long-term (1-year) pediatric study conducted in a total of 1238 patients with atopic dermatitis showed that treatment with tacrolimus (0.03 and 0.1%) generally did not increase the incidence of cutaneous infections (*e.g.*, skin infection, fungal dermatitis, herpes simplex, warts). However, significantly more patients treated with 0.03 and 0.1% tacrolimus developed folliculitis (4.7 and 3%, respectively, *vs.* 0.3% in vehicle) (1).

The safety and efficacy of tacrolimus as a treatment for eyelid dermatitis was demonstrated in a study in which patients were treated twice daily for up to 8 weeks (2).

Analysis of results from 3 randomized, 3-arm, double-blind, vehicle-controlled studies conducted in a total of 983 adult (16 years or older) and pediatric (2-15 years old) patients with moderate to severe atopic dermatitis of whom 913 were examined separately as black (27%) and white (68%) populations, showed that tacrolimus ointment (0.03 and 0.1% b.i.d. for up to 12 weeks) was safe and effective regardless of race. The majority of black (63%) and white (72%) populations experienced a moderate or better improvement from baseline with treatment as compared to vehicle (25 and 22%, respectively). Both black and white children and adults had significantly greater improvement with treatment as compared to the vehicle. Black adults were found to have significantly more benefit when treated with the 0.1% formulation (3).

Results from 3 double-blind, vehicle-controlled 12-week trials (1 pediatric and 2 adult trials) and 1 open-label, long-term (1-year) pediatric study conducted in a total of 1238 patients with atopic dermatitis showed that facial application of tacrolimus (0.03 and 0.1%) was safe and effective. Of all the patients participating in the 3 controlled trials, 86% presented lesions of atopic dermatitis on the head and neck and the efficacy of tacrolimus on these areas was similar to results obtained for overall body sites. Adverse event incidence ratios of facial to nonfacial site application were 0.9 for both formulations. Like other body sites, the most common adverse event on the face was skin burning which resolved within the first days of treatment (4).

Fujisawa has received approval from Health Canada to market Protopic® (tacrolimus ointment) for the treatment of moderate to severe atopic dermatitis, or eczema. Protopic® was approved in Japan in June 1999 and in the U.S. in December 2000. The product is expected to be launched in Canada in the fall of 2001 (5).

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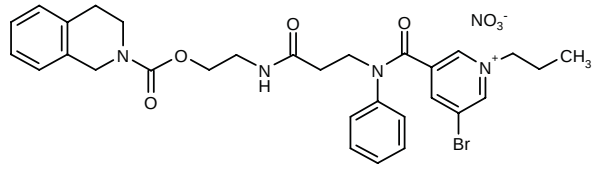
## TCV-309

*Treatment of Septic Shock*
*PAF Antagonist*

EN: 164606




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

A double-blind, randomized, placebo-controlled trial has investigated the effects of TCV-309 on organ dysfunction, morbidity and mortality in patients fulfilling the criteria for severe SIRS (systemic inflammatory response syndrome) or sepsis. A total of 97 patients, receiving placebo or TCV-309 at a dose of 1.0 mg/kg i.v. b.i.d. for 14 days, were available for intention-to-treat analysis. TCV-309 had no significant effect on overall survival at day 56 (51.0% *vs.* 41.7% on placebo), but the PAF antagonist did significantly reduce organ dysfunction (11.9% failed organs *vs.* 25.1% on placebo) and improve clinical severity, as seen by a significant reduction in the APACHE-II score compared to placebo patients. Also, significantly more TCV-309-treated patients recovered from shock after 14 days (9 of 29 patients *vs.* 2 of 32 patients on placebo). The beneficial effects of TCV-309 on organ dysfunction and morbidity were not associated with an increased frequency or severity of adverse effects compared to placebo. Based on these and previous findings with single-agent therapy, as well as the known complexity of the inflammatory cascade in sepsis, it is suggested that TCV-309 and other PAF antagonists may be useful as part of multidrug therapy in the treatment of sepsis (1).

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*Original monograph* - Drugs Fut 1993, 18: 721.

## Teriparatide
## rhPTH(1-34)
## LY-333334
## Forteo®

*Treatment of Osteoporosis*
*Parathyroid Hormone*

EN: 253969

H-Ser-Val-Ser-Glu-Ile-Gln-Leu-Met-His-Asn-Leu-Gly-Lys-His-Leu-Asn-Ser-Met-Glu-Arg-Val-Glu-Trp-Leu-Arg-Lys-Lys-Leu-Gln-Asp-Val-His-Asn-Phe-OH

$C_{181}H_{291}N_{55}O_{51}S_2$ **Lilly; Inhale; Emisphere**

Parathyroid hormone has been found to reduce the risk of cancer, particularly breast, skin, bladder and gastric carcinomas, preferably breast carcinoma, including subjects with relatively low risk or high risk of osteoporosis. The preferred hormone is human PTH(1-34) or its recombinant form, teriparatide (1).

An *in vivo* study performed in ovariectomized rats showed the efficacy of combination LY-333334 (30 μg/kg/day) and 17β-estradiol (10 μg/kg/day) treatment for 30 days in increasing cortical porosity and improving cancellous bone volume and cortical width (2).

The effects of LY-333334 on bone mass, remodeling and strength were examined in cortical bone of rabbits treated *in vivo* with the agent (10 μg/kg s.c.) for 30 or 70 days. Treatment significantly increased the intracortical activation frequency of cortical bone in the tibial midshaft at 35 days. Animals treated for 30 or 70 days also displayed significantly greater cortical area and bone strength. No changes in porosity were observed with treatment (3).

The population pharmacokinetics of injectable LY-333334 (20 or 40 μg/day) were determined from 1757 blood samples taken in a randomized, multiple-dose trial involving 404 postmenopausal women with osteoporosis. A one-compartment model influenced by clearance (CL/F), volume of distribution (V/F) and absorption rate constant ($K_a$) best fit the parameters obtained. The estimates for CL/F, V/F and Ka were 69.7 l/h, 112 l and 10.4 1/h, respectively. The interpatient variability was 51% for CL/F and 46% for V/F. The predicted bioavailability of the 40 μg dose was 80% of the 20 μg dose. Although body weight and injection site influenced LY-333334 distribution, it was concluded that the variability was clinically insignificant (4).

A study measured and compared the levels of circulating osteoprotegerin (OPG) in 18 healthy subjects, 16 healthy postmenopausal women (PMW), 18 postmenopausal women with osteoporosis (OpPMW) of whom 15 were treated with LY-333334 (10 nmol/kg/h for 24 h followed by 48 mcg/day s.c. for 4 weeks) and 15 patients with Paget's disease. OPG levels were similar in healthy women, PMW and OpPMW. However, significantly lower levels were found in patients with Paget's disease. LY-333334-treated PMW displayed a drop in OPG levels from 0.68 ± 0.064 ng/ml to 0.48 ± 0.049 and 0.51 ± 0.06 ng/ml at 12 and 24 h postinfusion, respectively. With subsequent LY-333334 s.c. treatment, OPG levels were 0.46 ± 0.04, 0.49 ± 0.06 and 0.49 ± 0.05 ng/ml after 4, 14 and 28 days, respectively (5).

A pilot study has evaluated the effects of LY-333334 treatment on cortical bone thickness and area using peripheral quantitative computed tomography (pQCT). pQCT was performed on women randomized to placebo or 20 or 40 μg of LY-333334 once daily as part of a large, multicenter study. LY-333334-treated patients were found to have greater periosteal circumference and cortical area, similar bone mineral content and lower bone density than those given placebo. LY-333334-treated patients had greater polar and axial moments of inertia and torsional bone strength index. The greater periosteal distribution of cortical bone detected by pQCT may, in part, explain the reduction in nonvertebral fractures seen with LY-333334 treatment (6).

Analysis of pooled total lumbar spine and femoral neck bone mineral density (BMD) measurements from 1637 postmenopausal women participating in a randomized, placebo-controlled phase 3 study involving treatment with LY-333334 (20 or 40 μg/day) showed that biochemical markers (procollagen 1 carboxy-terminal propeptide [PICP], bone specific alkaline phosphatase and urinary *N*-telopeptide excretion) of bone formation and resorption at 1 month and patient age were significant indicators of treatment response. PICP at 1 month was found to be the most significant predicator of femoral neck and lumbar spine BMD responses to LY-333334 treatment. Marked responses in total lumbar spine BMD were observed in those patients over 50 years of age with increases in PICP of more than 100 pM at 1 month (7).

Digital X-ray radiogrammetry (DXR) was used in a pilot study to measure changes in cortical thickness associated with LY-333334 treatment in women with osteoporosis. DXR was performed on the radius, ulna and three middle metacarpals at baseline and at 1 year on 40 patients from a large, double-blind, randomized study who received either placebo or LY-333334 20 or 40 mcg once daily. The combined measurements showed that LY-333334 increased the outer diameter and decreased the inner diameter compared to placebo. Cortical thickness tended to decrease in the placebo group and increase in the LY-333334-treated groups. The outer and inner bone diameters expanded, however, in patients with hyperparathyroidism. It was concluded that increases in cortical thickness due to LY-333334 treatment could be detected by the technique and may be useful in assessing bone strength independent of bone mineral density (8).

A randomized, placebo-controlled, double-blind study of LY-333334 was carried out in 1637 postmenopausal women with osteoporosis to assess the relationship between radiographic vertebral fracture grade and clinical sequelae of fracture. Patients were treated with either placebo or 20 or 40 μg injections of LY-333334 once daily in addition to receiving supplemental calcium and vitamin D. After a median follow-up of 21 months, it was found that the risks relative to placebo for vertebral fracture in the LY-333334 20 and 40 μg groups were 0.35 and 0.31, respectively. For women with one or more moderate or severe fractures, the fracture risk as compared with placebo was 0.10 and 0.22 for the 20 and 40 mcg groups, respectively. Significantly fewer LY-333334-treated patients had new moderate or severe vertebral fractures. The incidence and severity of clinical sequelae were also reduced in the LY-333334 treatment groups (9).

The efficacy and safety of LY-333334 (400 IU) were examined in a randomized, double-blind, placebo-controlled study involving 23 men with idiopathic osteoporosis. After 18 months of treatment, patients receiving the placebo were crossed over to open-label LY-333334 while LY-333334-treated patients continued. Eighteen months of LY-333334 treatment resulted in increases in bone mineral density at the lumbar spine (11.3 ± 1.6%), femoral neck (3.6 ± 0.9%) and total hip (1.9 ± 0.5%). T scores also significantly improved in these areas. No significant alterations in serum calcium, phosphorous, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D or urinary calcium were observed after 18 months of treatment. A significant increase in bone turnover markers such as osteocalcin, BSAP, *N*-telopeptide and free pyridinoline were also noted after 18 months of treatment. Those patients treated with LY-333334 and continuing for up to 30 months also displayed increases in BMD in the lumbar spine (15.1 ± 0.3%), femoral neck (4.2 ± 0.1%) and total hip (4.6 ± 0.2%) as compared to baseline. Bone turnover markers decreased to baseline levels in these patients (10).

Treatment with LY-333334 was found to reduce the risk of nonvertebral fractures in a randomized, double-blind, placebo-controlled study in 1637 women with postmenopausal osteoporosis. Women with at least 1 vertebral fracture received supplemental calcium and vitamin D and were randomized to LY-333334 (20 or 40 μg) or placebo. Women receiving 20 and 40 mcg of the agent had relative risks for overall nonvertebral fractures of 0.65 and 0.60, respectively, as compared with placebo. The relative risks for fragility fractures were 0.47 and 0.46 for the 20- and 40-μg groups, respectively, as compared with placebo. The effect of LY-333334 treatment was evident earlier for fragility fractures than for overall nonvertebral fractures, as revealed by analysis of time to first event (11).

A randomized, placebo-controlled, double-blind study conducted in 1637 postmenopausal women with

osteoporosis and 1 or more prevalent vertebral fractures, examined the efficacy of LY-333334 (20 or 40 μg/day) in combination with calcium and vitamin D supplementation. After a follow-up of up to 21 months, patients treated with LY-333334 (20 and 40 μg, respectively) displayed an increase in vertebral (8.6 and 12.6%) and femoral neck (3.6 and 4.6%) bone mineral density (BMD) and a decrease in the rate of new vertebral fractures (65 and 69%) and nontraumatic nonvertebral fractures (53 and 54%) as compared to placebo. The effects of the agent were independent of baseline vertebral BMD, age or number of prevalent vertebral fractures (12).

Emisphere received payments from Lilly related to ongoing development efforts for oral formulations of a recombinant parathyroid hormone (PTH) for osteoporosis. A phase I study of a capsule formulation of oral PTH is scheduled to begin in the third quarter of 2001 (13).

Lilly reinitiated its development project with Inhale for an inhalable formulation of teriparatide, a bone-forming agent being developed by Lilly as a treatment for osteoporosis (14).

New clinical data for teriparatide injection were presented at the IBMS/ECTS 2001 meeting. Results from a pivotal phase III study of teriparatide showed that it significantly reduced the risk of spinal and nonspinal fractures and improved cortical bone strength among postmenopausal women with a history of osteoporosis-related fractures. Lilly anticipates submitting the product to the European Medicines Evaluation Agency for review this year as the first in a new class of drugs known as bone formation agents (15).

Teriparatide injection (Forteo®) has been recommended for approval by the FDA's Endocrinologic and Metabolic Drugs Advisory Committee as a treatment for osteoporosis in postmenopausal women. The committee also issued a 5-5 split vote on its recommendation of Forteo® to increase bone mass in men with osteoporosis. In contrast to currently approved osteoporosis therapies which slow or stop bone loss, Forteo® actually stimulates new bone formation by increasing the number and/or activity of osteoblasts (16).

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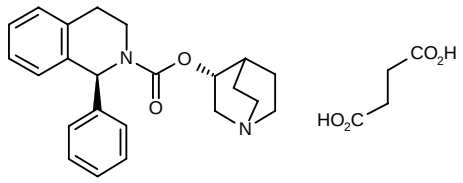
## YM-905

*Treatment of Urinary Incontinence*

EN: 249699



$C_{23}H_{26}N_2O_2.C_4H_6O_4$ **Yamanouchi**

The binding characteristics of YM-905 to muscarinic receptors were examined *ex vivo* following oral administration (30 and 100 mg/kg) to mice. A significant dose-dependent increase in the $K_d$ value for [$^3$H]-scopolamine was observed with little changes in the $B_{max}$ in the bladder, prostate, submaxillary gland, heart, colon and lung indicating competitive binding of YM-905 to receptors. The increased $K_d$ seen in the bladder, prostate, submaxillary gland and colon was sustained for 6 or 12 h (1).

YM-905 has entered phase III trials for pollakiuria and urinary incontinence in the U.S. and Europe (2).

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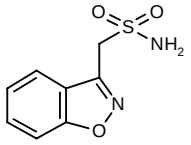
## Zonisamide
## Excegran®
## Zonegran®

*Antiepileptic*
*Antimigraine*

EN: 090354



$C_8H_8N_2O_3S$ **Dainippon Pharm.; Elan; Draxis Health**

A study tested the safety and efficacy of zonisamide, initially at 100 mg/day and increased up to 400 mg/day, in 34 patients with refractory migraine with and without aura. Patients continued abortive medications, but not analgesics. Zonisamide treatment was associated with a significant decrease in headache severity and reductions in frequency and duration of headache, except for 9 patients who discontinued due to lack of efficacy. Side effects included paresthesias, fatigue, anxiety and weight loss, which frequently resolved on treatment, as well as agitated dysphoria and difficulty concentrating, which led to withdrawal in 2 patients each (1).

In an open-label trial, 33 patients with refractory migraines and mixed headache disorders were treated with zonisamide as add-on therapy to other prophylactic agents. Zonisamide was initiated at 100 mg in the evening or at bedtime every third day, which was increased to every other day and then daily up to 600 mg/day. Of 23 evaluable patients, a reduction of at least 65% in frequency of migraine and other headaches was reported by 6 patients and 8 others experienced a 25-50% reduction in symptoms; the other 9 showed no response or were noncompliant and 4 of these withdrew due to adverse events (2).

Zonisamide has been assessed for its efficacy and safety in 16 patients with refractory chronic daily headache. At doses of 100-200 mg/day for 3 months, mean number of headache days/month was reduced by 34%, average duration of headache was reduced by 24%, total headache time was reduced by 50%, mean headache rating was reduced by 23% and mean disability rating was reduced by 24%. Adverse events included mild diarrhea in 2 patients and weight loss in 9 patients (3).

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2. Krusz, J.C. *Zonisamide in the treatment of headache disorders.* Cephalalgia 2001, 21(4): Abst P2-I16.

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