Drugs of the Future 2001, 26(11): 1093-1131

CCC: 0377-8282/2001

Information Update

Volume 1-25, Number 11

Estimated developmental phase for this month's updated products:

Preclinical

Epibatidine (analgesic; Dept. Health Human Services, CytoMed)
GM-237354 (antifungal; GlaxoSmithKline)

Phase I

Ibogaine (narcotics antagonist; NDA Int., OmniChem)
TOP-53 (oncolytic; Taiho)

Phase II

AGM-1470 (oncolytic, angiogenesis inhibitor; TAP, Takeda)
CI-994 (oncolytic; Pfizer)
DA-5018 (analgesic; Korea Res. Inst. Chem. Technol., Dong-A, Stiefel)
Ecteinascidin 743 (oncolytic; PharmaMar, Ortho Biotech)
Entecavir (anti-HBV; Bristol-Myers Squibb)
FR-901228 (oncolytic; Fujisawa, Natl. Cancer Inst.)
N-0923 (antiparkinsonian; Discovery Therapeutics, Schwartz)
NCX-4016 (nitric oxide donor; NicOx)
Renzapride hydrochloride (treatment of IBS; Alizyme)
Retigabine (antiepileptic; Arzneimmittelwerk Dresden, Asta Medica, Wyeth-Ayerst)

Phase III

Cariporide mesilate (treatment of myocardial infarction, Na^+/H^+ exchange inhibitor; Aventis Pharma)
Conivaptan hydrochloride (treatment of heart failure; Yamanouchi, Pfizer)
Rufinamide (antiepileptic, treatment of neurogenic pain; Novartis)
Seocalcitol (oncolytic; Leo)
Vapreotide (oncolytic; Tulane Univ., Debiopharm)

Preregistered

Gemifloxacin mesilate (naphthyridine antibacterial; LG Chem, GlaxoSmithKline)
Israpafant (antiallergy/antiasthmatic; Welfide)
Olmesartan medoxomil (antihypertensive; Sankyo, Recordati, Menarini)
Sivelestat sodium hydrate (treatment of ARDS; Ono, Lilly)

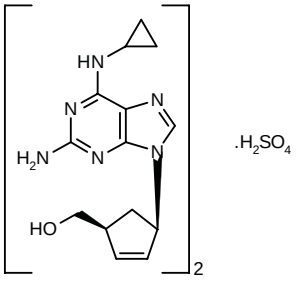
Launched/Year

Abacavir sulfate (anti-HIV, reverse transcriptase inhibitor; GlaxoSmithKline)/1999
Argatroban monohydrate (antithrombocytopenic, treatment of ischemic stroke; Mitsubishi-Tokyo Pharm., Texas Biotechnology, GlaxoSmithKline)/1990
Atosiban (tocolytic, oxytocin antagonist; Ferring, Johnson & Johnson)/2000
Beraprost sodium (treatment of peripheral vascular disease, treatment of pulmonary hypertension; Toray, United Therapeutics)/1992
Eptaplatin (oncolytic; SK Chemicals)/1999
Esomeprazole magnesium (antiulcer, treatment of GERD; AstraZeneca)/2000
Iloprost (treatment of peripheral vascular disease, treatment of pulmonary hypertension; Berlex, Schering AG, Eisai)/1992
Linezolid (oxazolidinone antibacterial; Pharmacia)/2000
Lisinopril (antihypertensive, treatment of heart failure; Merck & Co., AstraZeneca)/1987
Orlistat (antiobesity, antidiabetic; Roche)/1998
Oseltamivir phosphate (antiinfluenza virus; Roche, Gilead, Shionogi)/1999
Pamidronate sodium (treatment of Paget's disease, treatment of hypercalcemia; Gador, Henkel, Novartis)/1987
Pioglitazone hydrochloride (antidiabetic; Takeda, Lilly, Abbott, Novo Nordisk)/1999

Abacavir Sulfate
Ziagen®

Anti-HIV
Reverse Transcriptase Inhibitor

EN: 173602



$C_{14}H_{18}N_6O.H_2O_4S$ **GlaxoSmithKline**

An efficient asymmetric synthesis of abacavir has been reported: Acylation of the chiral oxazolidinone (I) with the mixed anhydride (II) by means of BuLi in THF gives the *N*-pentenoyloxazolidinone (III), which by condensation with acrolein (IV) catalyzed by $TiCl_4$ and (–)-spartein in dichloromethane yields the chiral adduct (V). The ring-closing metathesis of adduct (V) by means of the ruthenium catalyst $(Cy_3P)Cl_2Ru{=}CHPh$ in dichloromethane affords the chiral cyclopentenol (VI), which is reduced to 5(*R*)-(hydroxymethyl)-2-cyclopenten-1(*R*)-ol (VII) by means of $LiBH_4$ in THF. Reaction of diol (VII) with a) Ac_2O, TEA and DMAP, b) methyl chloroformate, TEA and DMAP or c) methyl chloroformate, pyridine and DMAP gives a) the diacetate (VIII), b) the cyclic carbonate (IX) or c) the dicarbonate (X), respectively. The condensation of diacetate (VIII), cyclic carbonate (IX) or dicarbonate (X) with 2-amino-6-chloropurine (XI) by means of $Pd(PPh_3)_4$ yields the carbocyclic purines (XII), (XIII) or (XIV), respectively. Treatment of these chloropurines (XII), (XIII) and (XIV) with cyclopropylamine (XV) in hot DMSO provides the corresponding cyclopropylaminopurine carbonate (XVI), abacavir or cyclopropylaminopurine acetate (XVII), respectively. Finally, the protecting groups of purines (XVI) and (XVII) are hydrolyzed with aqueous NaOH (1). Scheme 1.

Alternatively, 2-amino-6-chloropurine (XI) is treated with cyclopropylamine (XV) in hot DMSO to give 2-amino-6-(cyclopropylamino)purine (XVIII), which is condensed with the chiral diacetate (VIII) by means of $Pd(PPh_3)_4$ to yield the carbocyclic purine acetate (XVI). Finally, purine (XVI) is deprotected by hydrolysis with aqueous NaOH (1). Scheme 2.

Alternatively, 5(*R*)-(hydroxymethyl)-2-cyclopenten-1(*R*)-ol (VII) can also be obtained as follows: Acylation of the chiral oxazolidinethione (XIX) with the mixed anhydride (II) by means of BuLi in THF gives the *N*-pentenoyloxazolidinethione (XX), which by condensation with crotonaldehyde (XXI) catalyzed by $TiCl_4$ and (–)-spartein in dichloromethane yields the chiral adduct (XXII). The ring-closing metathesis of (XXII) by means of the ruthenium catalyst in dichloromethane affords the chiral cyclopentenol derivative (XXIII), which is reduced to the target diol (VII) by means of $LiBH_4$ in THF (1). Scheme 3.

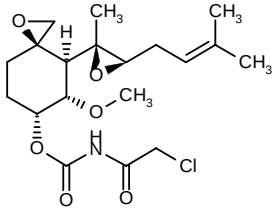
1. Crimmins, M.T., King, B.W., Zuercher, W.J., Choy, A.L. *An efficient, general asymmetric synthesis of carbocyclic nucleosides: Application of an asymmetric aldol/ring-closing metathesis strategy.* J Org Chem 2000, 65(25): 8499.

Original monograph – Drugs Fut 1998, 23: 1155.

AGM-1470
TNP-470

Oncolytic
Angiogenesis Inhibitor

EN: 161076



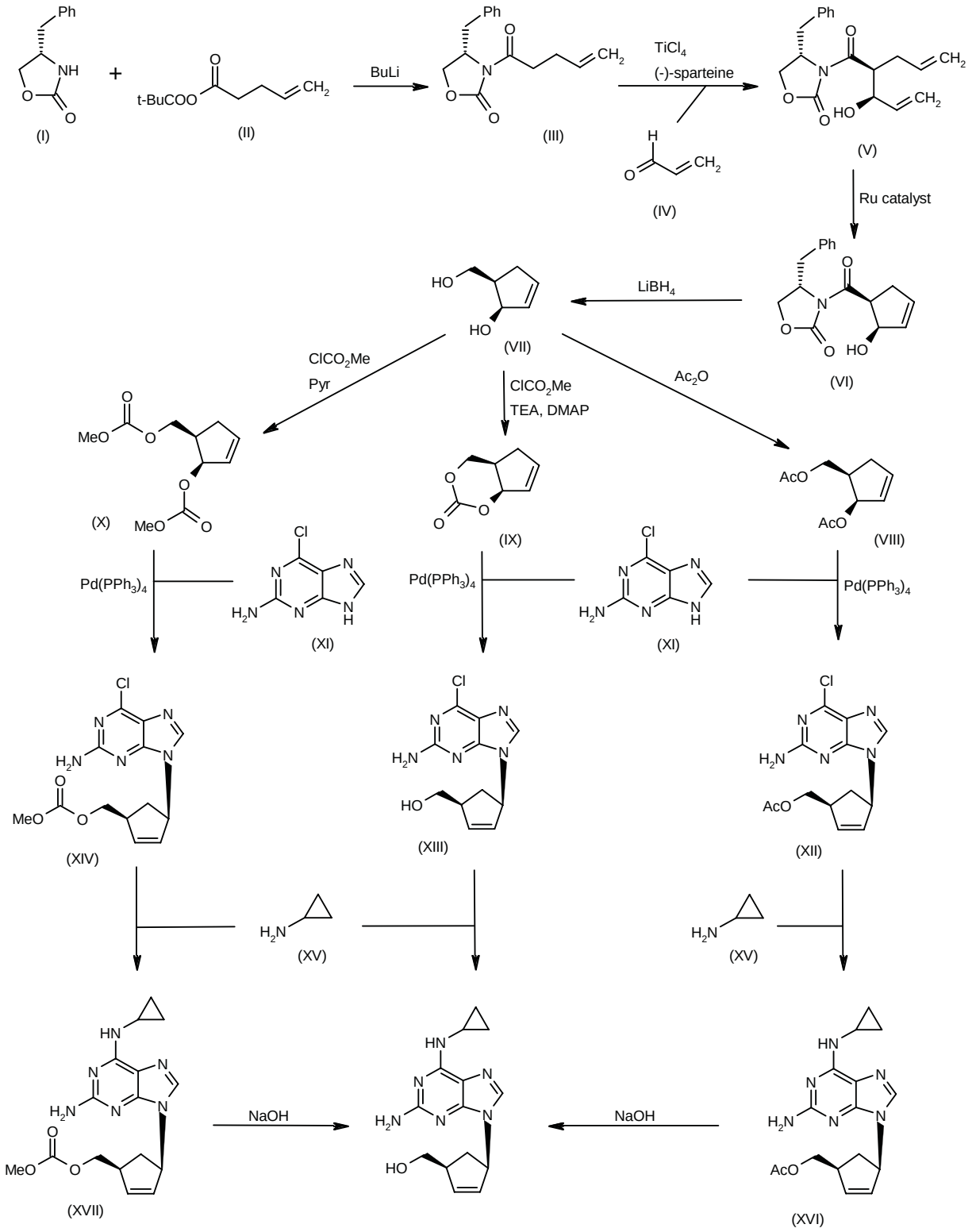
$C_{19}H_{28}ClNO_6$ **TAP; Takeda**

TNP-470 (100 mg/kg s.c. 3 times/week or continuous infusion) was shown to be a potent inhibitor of human neuroblastoma growth rate and tumorigenicity in mouse models of clinically evident and minimal disease. The results of the study suggest that the drug may be useful as adjuvant therapy for high-risk neuroblastoma patients with minimal disease status (1).

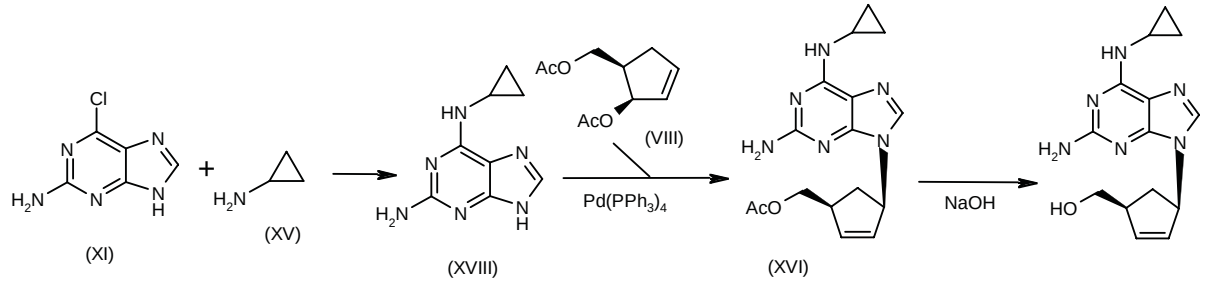
A mouse model of stem cell transplant was developed to test the use of TNP-470 during the period of posttransplant hematopoietic engraftment. In lethally irradiated mice rescued with stem cells, reliable multilineage engraftment and normal lymphoid maturation were observed in both TNP-470-treated mice and those given placebo. No excess mortality was seen in the group treated with TNP-470 (2).

The antitumor and antimetastatic effects of the angiogenesis inhibitor TNP-470 have been examined in a murine model of transitional cell bladder carcinoma. In this study, highly metastatic human bladder transitional cell carcinoma cells were transplanted into athymic nude mice, which were treated for 3 weeks with TNP-470 at doses of 15, 35 or 105 mg/kg s.c. for 7 days/week, 35 mg/kg s.c. for 3 days/week or 105 mg/kg s.c. once weekly starting 3 days after tumor cell inoculation. Dose-dependent inhibition of tumor growth and neovascularization, as well as of the expression of angiogenesis factors and MMP-9 (gelatinase B), was seen in TNP-470-treated animals. The optimal dose as regards activity and toxicity appeared to be 15 mg/kg/day for 3 weeks (3).

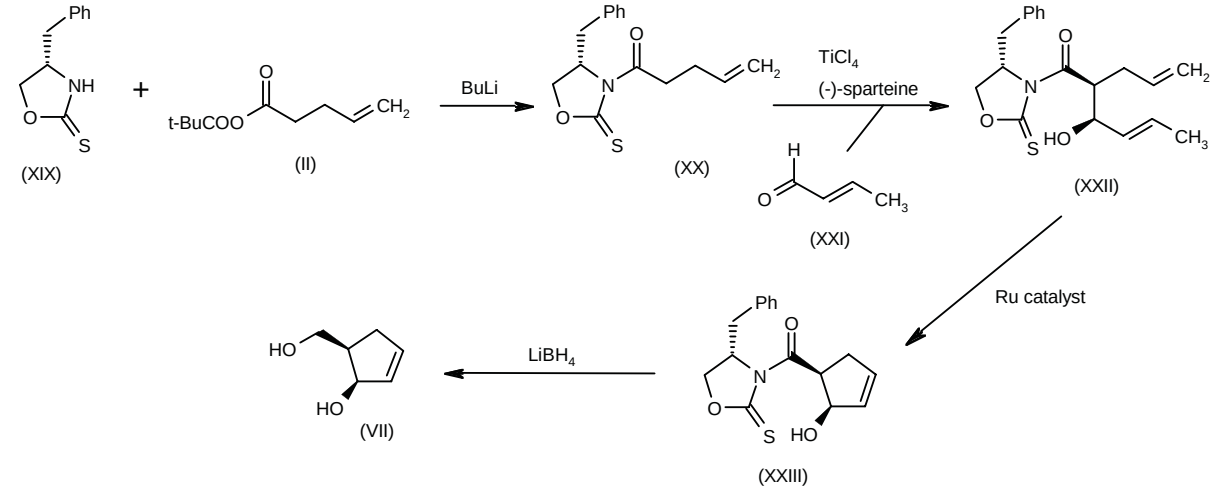
Scheme 1: Synthesis of Abacavir



Scheme 2: Synthesis of Abacavir



Scheme 3: Synthesis of Intermediate (VII) of Abacavir



Results from a study in a rat bladder carcinogenesis model were reported. Rats were given BBN in the drinking water for 12 weeks and treated or not with TNP-470 at a dose of 30 mg/kg i.p. every other day. The bladder hyperplasia and increased microvascular density seen in BBN-treated animals were both markedly decreased at 4, 8 and 12 weeks by TNP-470. Thus, the beneficial effects of TNP-470 in the early stage of bladder carcinogenesis appear to involve antiangiogenic effects (4).

A study using an intracerebral xenograft model (human glioma cells overexpressing VEGF implanted in the right cortex of nude male rats) demonstrated that TNP-470 (30 mg/kg s.c. every other day for 5 doses starting 3-4 weeks after animals became symptomatic) reduced brain tumor uptake of temozolomide (starting 24 h after the last TNP-470 dose at doses to achieve steady-state plasma concentration of 20 μg/ml). Temozolomide plasma concentrations were similar in both controls and TNP-470-treated animals. However, concentrations of unbound temozolomide in brain tumors were significantly lower in TNP-470-treated animals as compared to controls (4.4 ± 0.37 *vs.* 9.9 ± 0.99 μg/ml). TNP-470-treated animals exhibited a 2-fold decrease in steady-state C_{tumor}/C_p ratios as compared to controls (0.21 ± 0.039 *vs.* 0.42 ± 0.037). TNP-470 inhibited temozolomide brain tumor uptake via the agent's action on capillary permeability (5).

A subrenal capsule assay was used to evaluate treatment of implanted renal tumors in nude mice with thalidomide (200 mg/kg/day i.p.) or TNP-470 (30 ml/kg/day s.c.) for 7 days. When tumors were excised on day 8, TNP-470 was found to significantly lower tumor weight compared to thalidomide (p <0.05). The expression of murine KDR gene was also lower in TNP-470-treated animals as compared to animals in the control and thalidomide-treated groups (6).

Antiangiogenic therapy with TNP-470, angiostatin and endostatin was evaluated in superficial and invasive bladder carcinoma cell lines subcutaneously injected in mice. The agents inhibited superficial and invasive bladder

carcinoma growth by 60-89% and 65-74%, respectively. All three agents significantly reduced the vascular density of the tumors compared with controls. Angiostatin and endostatin were particularly effective against slow growing, poorly vascularized tumors. The results may encourage further study of antiangiogenic therapy in patients with disseminated bladder cancer (7).

Using human neuroblastoma xenograft models, researchers have shown that TNP-470 inhibits human neuroblastoma growth both when given alone and in combination with chemotherapy, and therefore may be useful as adjunctive treatment in patients with high-risk neuroblastoma disease (8).

In evaluations of TNP-470 (30 or 50 mg/kg s.c. 3 or 5 times) in subcutaneous rhabdomyosarcomas of various sizes in rats, tumor volume and dose were correlated with treatment outcomes. The study findings support the exploration of angiogenesis inhibition for the treatment of progressive tumor growth and large tumors (9).

In a phase I dose-escalation trial of TNP-470 in 33 patients with metastatic and androgen-independent prostate cancer, TNP-470 demonstrated no obvious antitumor activity, although in some patients transient stimulation of the serum prostate-specific antigen concentration was observed. A dose of 47.25 mg/m^2 i.v. given on alternate days was recommended for future studies (10).

1. Shusterman, S., Grupp, S.A., Barr, R., Carpentiere, D., Zhao, H.Q., Maris, J.M. *The angiogenesis inhibitor TNP-470 effectively inhibits human neuroblastoma xenograft growth, especially in the setting of subclinical disease.* Clin Cancer Res 2001, 7(4): 977.

2. Stern, J.W., Fang, J.J., Shusterman, S., Pierson, G., Barr, R., Pawel, B., Diller, L., Grupp, S.A. *Angiogenesis inhibitor TNP-470 during bone marrow transplant: Safety in a preclinical model.* Clin Cancer Res 2001, 7(4): 1026.

3. Inoue, K., Fukada, S., Chikazawa, N., Yoshikawa, C., Shuin, T. *Antitumor and antimetastatic effects of TNP-470, a neovascularization inhibitor, against transitional cell bladder carcinoma.* Jpn J Urol 2001, 92(2): Abst MP-89.

4. Cho, S., Yamashita, M., Kuwata, Y., Takenaka, I. *Involvement of angiogenesis and efficacy of TNP-470 in the early stage of rat bladder carcinogenesis.* Jpn J Urol 2001, 92(2): Abst MP-90.

5. Ma, J., Li, S., Gallo, J.M. *Reduction of temozolomide (TMZ) brain-tumor uptake by the antiagiogenic agent TNP-470 (TNP) in an intracerebral xenograft model.* Proc Am Assoc Cancer Res 2001, 42: Abst 3513.

6. Sato, K., Iinuma, M., Abe, A., Wang, L., Tsuchiya, N., Satoh, S., Habuchi, T., Kato, T. *Evaluation of efficacy of antiangiogenic drugs by subrenal capsule assay.* Jpn J Cancer Res 2000, 91(Suppl.): Abst 2797.

7. Beecken, W.-D., Jones, J., Shing, Y., Folkman, J. *Antiangiogenic therapy of superficial and invasive bladder carcinoma models in mice.* Eur Urol 2001, 39(Suppl. 5): Abst 675.

8. Shusterman, S., Grupp, S.A., Maris, J.M. *Inhibition of tumor growth in a human neuroblastoma xenograft model with TNP-470.* Med Pediatr Oncol 2000, 35(6): 673.

9. Landuyt, W., Theys, J., Nuyts, S. et al. *Effect of TNP-470 (AGM-1470) on the growth of rat rhabdomyosarcoma tumors of different sizes.* Cancer Invest 2001, 19(1): 35.

10. Logothetis, C.J., Wu, K.K., Finn, L.D., Daliani, D., Digg, W., Ghaddar, H., Gutterman, J.U. *Phase I trial of the angiogenesis inhibitor TNP-470 for progressive androgen-independent prostate cancer.* Clin Cancer Res 2001, 7(5): 1198.

Original monograph - Drugs Fut 1994, 19: 981.

Additional References

Blumenschein, G.R. et al. *A phase I study of continuous infusion of TNP-470 alone or in combination with paclitaxel and carboplatin in adult patients with solid tumors.* AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Oct 29-Nov 2, Miami Beach) 2001, Abst 30.

Burke, P.A., DeNardo, S.J. *Antiangiogenic agents and their promising potential in combined therapy.* Crit Rev Oncol Hematol 2001, 39(1-2): 155.

Dixon, S.C. et al. *The control of prostate-specific antigen expression and gene regulation by pharmacological agents.* Pharmacol Rev 2001, 53(1): 73.

Dossi, R. et al. *Sensitivity to anti-angiogenic compounds of endothelial cells derived from human tumors and normal tissues.* Haemostasis 2001, 31(Suppl. 1): Abst PO 08.

Inoue, K. et al. *Docetaxel enhances the effect of therapy of metastatic human transitional cell carcinoma with the angiogenesis inhibitor TNP-470 (AGM-1470).* Jpn J Cancer Res 2001, 92(Suppl.): Abst 418.

Matsumoto, G. et al. *Combined therapy using immune and anti-angiogenesis drugs demonstrates novel anti-tumor effect against hepatic metastases of hamster pancreatic cancer.* Jpn J Cancer Res 2001, 92(Suppl.): Abst 686.

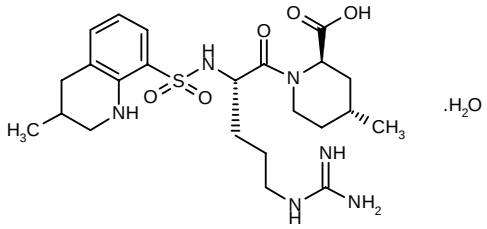
Matsusaka, S. et al. *Inhibition by angiogenesis inhibitor, TNP-470, of growth of human hepatoblastoma heterotransplanted into nude mice.* Dig Surg 2000, 17(Suppl. 1): Abst P235.

Mysliwski, A. et al. *Synergistic effect of the angiogenesis inhibitor TNP-470 and tumor necrosis factor (TNF) on Bomirski Ab melanoma in hamsters.* Anticancer Res 2000, 20(6B): 4643.

Tran, H.T. et al. *Phase I study of the angiogenesis inhibitor TNP-470 in combination with paclitaxel (P) and carboplatin (CPt) in patients with solid tumors.* Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 394.

Argatroban Monohydrate *Antithrombocytopenic*
Novastan® *Treatment of Ischemic Stroke*
Slonnon®

EN: 090744

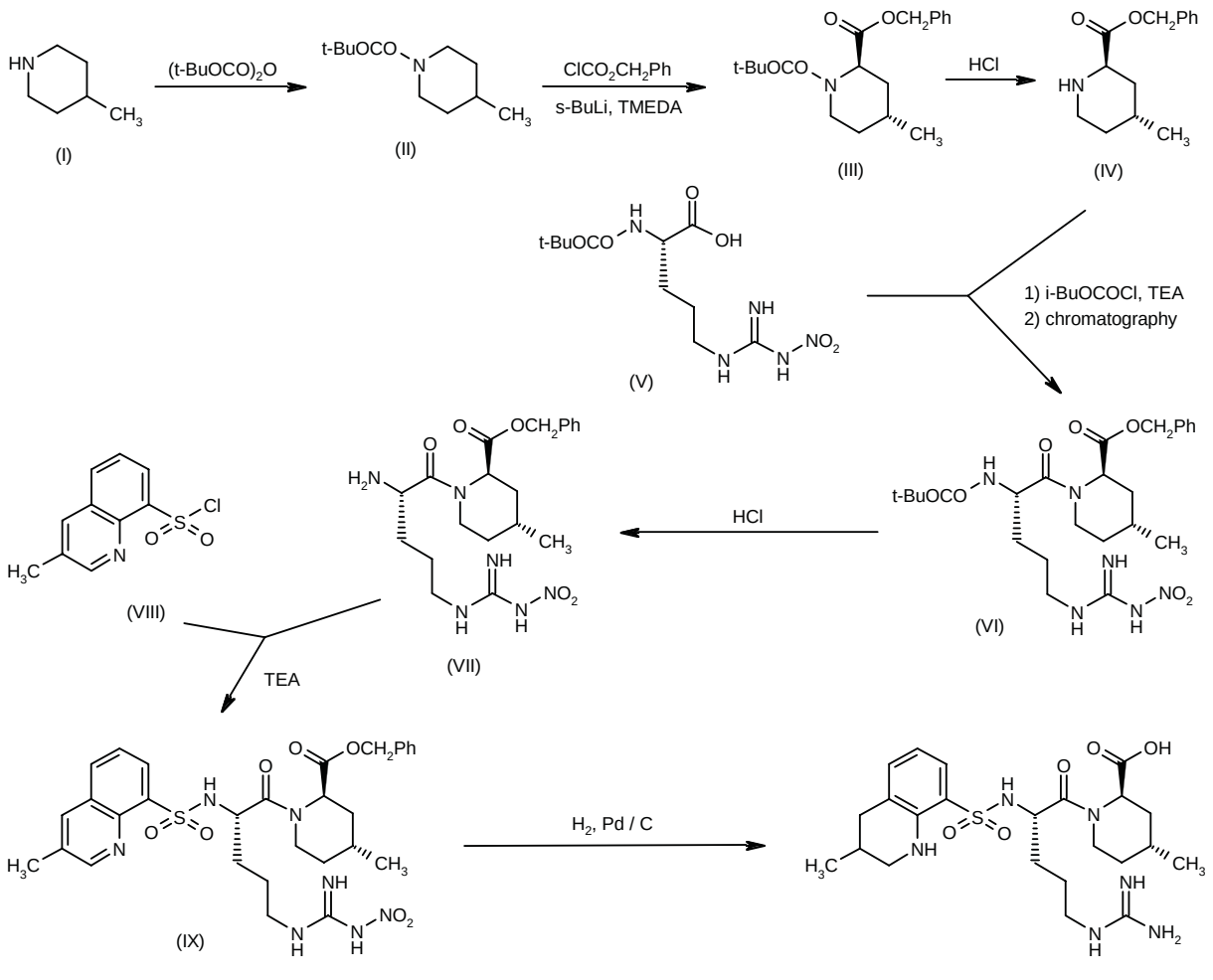


$C_{23}H_{36}N_6O_5S.H_2O$ **Mitsubishi-Tokyo Pharm.; Texas Biotechnology; GlaxoSmithKline**

A new short synthesis of argatroban has been reported: The protection of 4-methylpiperidine (I) with $(Boc)_2O$ gives the carbamate (II), which is condensed with benzyl chloroformate by means of *sec*-butyl lithium and TMEDA in ethyl ether to yield (±)-*trans*-1-(*tert*-butoxycarbonyl)-4-methylpiperidine-2-carboxylic acid benzyl ester (III). Deprotection of the NH group of (III) with HCl in ethyl acetate affords (±)-*trans*-4-methylpiperidine-2-carboxylic acid benzyl ester (IV), which is condensed with the protected arginine derivative (V) by means of isobutyl chloroformate and TEA to provide the corresponding amide as a diastereomeric mixture. Resolution of this mixture by flash chromatography furnishes the desired diastereomer (VI), which is treated with HCl in ethyl acetate in order to remove the Boc-protecting group to yield compound (VII). Condensation of compound (VII) with 3-methylquinoline-8-sulfonyl chloride (VIII) by means of TEA in dichloromethane affords the expected sulfonamide (IX). Finally, this compound is submitted to hydrogenation with H_2 over Pd/C in AcOH/ethanol in order to produce debenzylation, cleavage of the NO_2 group and hydrogenation of the pyridine ring to yield argatroban (1). Scheme 4.

The effects of argatroban (6.25 μg/kg/min for 48 h), human recombinant tPA (10 mg/kg over 30 min following

Scheme 4: Synthesis of Argatroban



an initial 10% bolus) and combination of the agents, given via the femoral vein starting 4 h after middle cerebral artery occlusion, have been examined in a rat model of embolic focal cerebral ischemia. Compared to untreated controls, argatroban- and tPA-treated animals which showed respective mean ischemic lesion sizes of 35.3, 36.5 and 43.4%, lesion size in the rats treated with the combination was significantly reduced to 17.1%. Importantly, gross cerebral hemorrhage was not increased (20, 17, 33 and 17%, respectively, in control, argatroban, tPA and argatroban + tPA groups). These findings indicate that combination of argatroban with tPA in acute stroke may widen the therapeutic window for the safe administration of tPA (2).

Texas Biotechnology has initiated a multicenter, placebo-controlled phase II trial (ARGIS-I) to evaluate the safety and efficacy of intravenous infusion of argatroban in patients with acute ischemic stroke. The trial, the first of its kind in the U.S. to evaluate the use of a direct thrombin inhibitor as a treatment for ischemic stroke, is expected to include 180 ischemic stroke patients at over 30 sites in North America. The treatment window under evaluation in ARGIS-I is within 12 h of onset of symptoms, with data being evaluated in 2 groups: 0-6 h and 6-12 h. Patients who present within the 0-3 h window and who are not candidates for tPA, the only approved product for ischemic stroke, will also be eligible to participate in the trial. Neurological assessments will be made using the Modified Rankin Scale (mRS), the Barthel Index (BI) and the National Institute of Health Stroke Scale (NIHSS). These measures will be evaluated at 30, 60 and 90 days. Safety, the primary endpoint of this study, will be assessed in terms of incidence of major bleeding. Argatroban was approved by the FDA late last year for the prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT). The drug has been approved as a treatment for ischemic stroke since 1996 in Japan, where it is marketed by Mitsubishi-Tokyo Pharmaceuticals. GlaxoSmithKline is responsible for marketing argatroban in HIT, whereas Texas Biotechnology and Mitsubishi are funding the phase II ARGIS-I trial (3).

Texas Biotechnology has announced that the Canadian Therapeutics Products Program has issued approval of argatroban, an anticoagulant therapy in patients with heparin-induced thrombocytopenia syndrome (HIT). Argatroban is also approved by the U.S. Food and Drug Administration (FDA) for the prophylaxis or treatment of thrombosis in patients with HIT and is currently marketed in the U.S. by GlaxoSmithKline. In addition, clinical trials are under way designed to establish the use of argatroban as a treatment for ischemic stroke and in combination with gpIIb/IIIa inhibitors for patients undergoing percutaneous coronary intervention (PCI) (4).

1. Cossy, J., Belotti, D. *A short synthesis of argatroban: A potent selective thrombin inhibitor.* Bioorg Med Chem Lett 2001, 11(15): 1989.

2. Morris, D.C., Zhang, L., Zhang, Z.G., Berens, K.L., Brown, P.M., Chopp, M. *Opening the window of opportunity for treatment of stroke with argatroban and tPA.* Acad Emerg Med 2001, 8(5): 541.

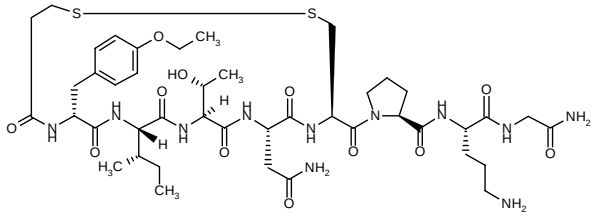
3. *Argatroban enters phase II for ischemic stroke.* DailyDrugNews.com (Daily Essentials) March 16, 2001.

4. *Texas Biotechnology announces approval of argatroban in Canada.* DailyDrugNews.com (Daily Essentials) Aug 3, 2001.

Original monograph - Drugs Fut 1982, 7: 810.

Atosiban
Tractocile® *Tocolytic*
Antocin® *Oxytocin Antagonist*

EN: 140299



$C_{43}H_{67}N_{11}O_{12}S_2$ **Ferring; Johnson & Johnson**

Atosiban, at concentrations as low as 1 μg/ml, demonstrated significant, dose-dependent inhibition of oxytocin-induced contractions of human myometrium *in vitro* (2).

1. Buscher, U., Chen, F.C.K., Riesenkampff, E., vonDehn, D., David, M., Dudenhausen, J.W. *Effects of oxytocin receptor antagonist atosiban on pregnant myometrium in vitro.* Obstet Gynecol 2001, 98(1): 117.

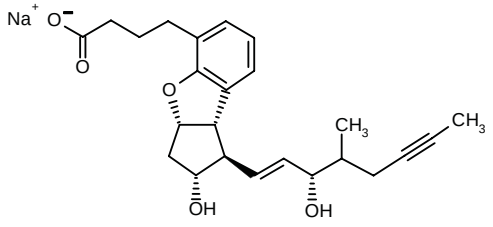
Original monograph - Drugs Fut 1994, 19: 985.

Additional Reference

Husslein, P. et al. *Treatment with the oxytocin receptor antagonist atosiban (Tractocile®) in patients at risk of preterm delivery - The Vienna experience.* J Perinat Med 2001, 29(Suppl. I): 174.

Beraprost Sodium
Procylin® *Treatment of Peripheral Vascular Disease*
Dorner® *Treatment of Pulmonary Hypertension*

EN: 116067



$C_{24}H_{29}NaO_5$ **Toray; United Therapeutics**

United Therapeutics has completed patient enrollment in its randomized, double-blind, placebo-controlled phase III study of oral beraprost in patients with moderate pulmonary hypertension. The objective of the study, involving approximately 116 patients at 10 U.S. centers, is to assess the effects of beraprost on exercise performance, cardiopulmonary hemodynamics, signs and symptoms of disease and quality of life in patients over a 12-month period. Traditionally, patients with advanced pulmonary hypertension are treated with a chronic intravenous infusion of prostacyclin, the only currently approved therapy. The invasive nature of this treatment has made it less attractive to patients with moderate or early-stage disease. As an orally active prostacyclin analogue, beraprost is formulated as a tablet and may therefore be better accepted by patients with early disease. Beraprost is approved in Japan for the treatment of patients with primary pulmonary hypertension. The drug was exclusively licensed to United Therapeutics by Toray for North America (1).

United Therapeutics has announced the preliminary results of a phase III clinical trial investigating oral beraprost sodium for the treatment of intermittent claudication resulting from peripheral vascular disease. Beraprost was studied in approximately 750 patients at 60 centers in the U.S. in a trial that was designed to confirm the significant efficacy results of the first phase III trial of beraprost in 422 patients. While the preliminary data confirmed a trend for fewer critical cardiovascular events, the study did not confirm the positive results of the European phase III trial and statistical significance was not achieved in the study's endpoints relating to exercise. Based on these results, United Therapeutics expects to discontinue development of beraprost for intermittent claudication (2).

1. *Patient enrollment complete in phase III trial of oral treatment for pulmonary hypertension.* DailyDrugNews.com (Daily Essentials) Feb 27, 2001.

2. *Development of beraprost for intermittent claudication expected to be dropped.* DailyDrugNews.com (Daily Essentials) Oct 17, 2001.

Original monograph - Drugs Fut 1986, 11: 956.

Additional References

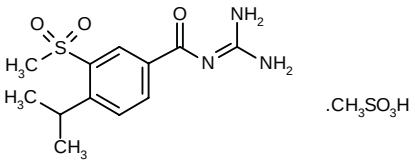
Abe, Y. et al. *Effects of inhaled prostacyclin analogue on chronic hypoxic pulmonary hypertension.* J Cardiovasc Pharmacol 2001, 37(3): 239.

Ono, F. et al. *Oral administration of beraprost sodium improves survival in patients with chronic thromboembolic pulmonary hypertension.* Circulation 2001, 104(17, Suppl. 2): Abst 3593.

Cariporide Mesilate

Na^+/H^+ Exchange Inhibitor
Treatment of Myocardial Infarction

EN: 215949



$C_{12}H_{17}N_3O_3S.CH_4O_3S$ **Aventis Pharma**

Cariporide has been tested for potential antifibrotic effects in the liver. Initial *in vitro* studies demonstrated significant inhibition of PDGF-induced proliferation of rat hepatic stellate cells at concentrations of 100 nM or more, with a maximal effect at 10 μM. This effect appeared to be due to selective inhibition of PDGF-induced activation of Na^+/H^+ exchange, which also reached a maximum at 10 μM. Cariporide given in the diet during treatment with dimethylnitrosamine was not associated with toxicity in rats and reduced liver injury as assessed by ALT levels, as well as hepatic stellate cell proliferation and collagen deposition. These findings thus confirm that selective inhibition of Na^+/H^+ exchange may be useful for preventing or reducing liver fibrosis (1).

An isolated working rat heart study used 6 experimental protocols to evaluate the presence or absence of DNA fragmentation using ss-DNA antibody and to assess the effects of cariporide on DNA fragmentation appearance and recovery of cardiac function. The groups were as follows. Group 1: no ischemia, 20-min perfusion only (control); group 2: 20-min normothermic ischemia followed by 20-min working perfusion; group 3: 35-min reperfusion followed by 20-min ischemia; group 4: 1-h reperfusion followed by 20-min ischemia; group 5: 5-h reperfusion followed by 20-min ischemia; and group 6: cariporide (10 μmol/l) administered for 3 min before ischemia and reperfused for 1 h. DNA fragmentation was seen in group 2 and increased DNA fragmentation appearance was seen in group 4. Postischemic recovery of cardiac output was increased from 24.9 ± 7.9% to 48.9 ± 7.2% by cariporide infusion, which also suppressed the appearance of DNA fragmentation from 14.8 ± 1.8% to 8.58 ± 0.88%. It was concluded that inhibition of the Na^+/H^+ exchange system may impact DNA fragmentation and improve myocardial protection (2).

In rat hearts with left ventricular hypertrophy, cariporide (1 μM) treatment reduced peak ischemic contracture and reperfusion contracture, demonstrating that the cardioprotective effects of the drug can be produced in clinically relevant models as well as in normal hearts (3).

Normotensive rats (n = 90) given lifelong treatment with cariporide (0.3% in the chow) had a significant extension in life span (39 *vs.* 30 months for the cariporide and placebo groups, respectively). This finding was correlated

  CCC: 0377-8282/2001

with a delayed occurrence of cancer as well as prevention of left ventricular hypertrophy, cardiac and vascular dysfunction and changes in organs related to aging (4).

In postischemic rat hearts, cariporide and eniporide similarly reduced Ca^{2+} overload and improved contractile recovery. Treatment also reduced ischemic Na^+ overload and prolonged acidosis, which accounted for lower postischemic diastolic $[Ca^{2+}]_i$ and lower end diastolic pressure (5).

The mechanisms involved in the occurrence of atrial contractile dysfunction following restoration of sinus rhythm were investigated in 23 anesthetized dogs. Inhibition of the Na^+/H^+ exchanger with cariporide significantly blunted the decline in left atrial mechanical function from rapid atrial rates as compared to control and nifedipine-treated animals (6).

Inflammatory cytokines were measured in 40 patients with unstable angina who were treated with placebo or cariporide (3 x 20, 80 or 120 mg for 2-3 days) and PTCA. Monocyte chemoattractant protein-1 and interleukin-6 appeared to be involved in the pathogenesis of acute coronary syndrome. Cariporide demonstrated antiinflammatory as well as antiischemic effects (7).

Cariporide (20, 80 or 120 mg as 1-h infusion every 8 h) was evaluated in a randomized, placebo-controlled, phase II/III trial for its potential to prevent myocardial cell necrosis in patients with unstable angina or non-ST-elevation myocardial infarction or patients undergoing high-risk percutaneous or surgical revascularization. Although cariporide failed to demonstrate benefit over placebo on the primary endpoint of death or MI, the drug was safe and results indicated that inhibition of the Na^+/H^+ exchanger may prevent cell necrosis in the setting of ischemia-reperfusion (8).

1. Di Sario, A., Bendia, E., Baroni, G.S., Marzioni, M., Ridolfi, F., Schindler, U., Trozzi, L., Benedetti, A. *Cariporide, a selective Na^+/H^+ exchange inhibitor, decreases liver fibrosis in the rat.* J Hepatol 2001, 34(Suppl. 1): 81.

2. Kagaya, S., Yamamoto, F., Sekine, S. et al. *Cardioprotective effect of Na^+-H^+ exchange inhibitor (HOE642) and its role in preventing the myocardial DNA fragmentation.* J Mol Cell Cardiol 2000, 32(11): Abst P87.

3. Kevelaitis, E., Kevelaitiene, S., Mouas, C., Marotte, F., Menasche, P. *Sodium-hydrogen exchange inhibition by cariporide improves postischaemic recovery of hypertrophied myocardium.* Eur Heart J 2001, 22(Suppl.): Abst P391.

4. Linz, W., Weichert, A., Albus, U. *Long-term treatment with the NHE-1 inhibitor cariporide extends the normal lifespan of Wistar Kyoto rats.* Eur Heart J 2001, 22(Suppl.): Abst P936.

5. ten Hove, M., Van Emous, J.G., Van Echteld, C.J.A. *Na^+/H^+ exchanger blockers cariporide and eniporide reduce postischaemic Ca^{2+}-overload.* Eur Heart J 2001, 22(Suppl.): Abst P2825.

6. Altemose, G.T., Zipes, D.P., Weksler, J., Miller, J.M., Olgin, J.E. *Inhibition of the Na^+/H^+ exchanger delays the development of rapid pacing-induced atrial contractile dysfunction.* Circulation 2001, 103(5): 762.

7. Ries, M., Buerke, M., Lusch, A., Rupprecht H.-J., Meyer, J. *Sodium/H^+ exchange inhibitor (cariporide) reduces proinflammatory markers following PCTA in patients with unstable angina.* Eur Heart J 2001, 22(Suppl.): Abst P1597.

8. Théroux, P., Chaitman, B.R., Erhardt, L., Meinertz, T., Schroeder, J.S., Tognoni, G., White, H.D., Willerson, J.T., Jessel, A. *Inhibition of the sodium-hydrogen exchanger with cariporide to prevent myocardial infarction in high-risk ischemic situations. Main results of the GUARDIAN trial.* Circulation 2000, 102(25): 3032.

Original monograph - Drugs Fut 1997, 22: 1197.

Additional References

Buerke, M. et al. *Sodium/H^+ exchange inhibitor (cariporide) reduces soluble adhesion molecule expression following PTCA in patients with unstable angina.* Eur Heart J 2001, 22(Suppl.): Abst P449.

Fukuhiro, Y. et al. *Cardioplegic strategies for calcium control. Low Ca^{2+}, high Mg^{2+}, citrate, or Na^+/H^+ exchange inhibitor HOE-642.* Circulation 2000, 102(19, Suppl. 3): III-319.

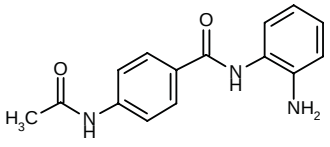
Hashimoto, K. et al. *Effects of Na^+/H^+ and Na^+/Ca^{2+} exchange inhibitors on cardiac arrhythmias.* Jpn J Pharmacol 2001, 85(Suppl. I): Abst S10-5.

Portman, M.A. et al. *HOE-642 (cariporide) alters pH(I) and diastolic function after ischemia during reperfusion in pig hearts in situ.* Am J Physiol - Heart Circ Physiol 2001, 280(2): H830.

CI-994

Oncolytic

EN: 137584



$C_{15}H_{15}N_3O_2$ **Pfizer**

A study in 53 patients with solid tumors determined the recommended phase II starting dose of CI-994 to be 8 mg/m^2/day for 8 weeks with a 2-week period between cycles (1).

1. Prakash, S., Foster, B.J., Meyer, M., Wozniak, A., Heilbrun, L.K., Flaherty, L., Zalupski, M., Radulovic, L., Valdivieso, M., LoRusso, P.M. *Chronic oral administration of CI-994: A phase 1 study.* Invest New Drugs 2001, 19(1): 1.

Original monograph - Drugs Fut 1997, 22: 1201.

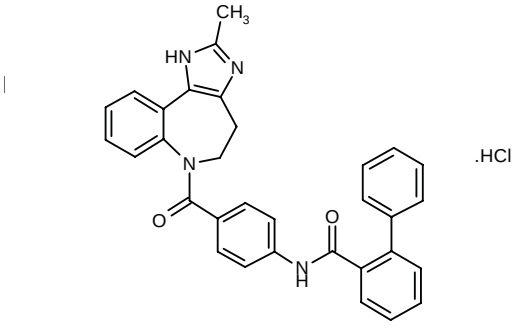
Additional References

Graziano, M.J. et al. *CI-994, a histone deacetylase inhibitor, induces apoptosis but is not clastogenic to CHO cells in vitro.* AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Oct 29-Nov 2, Miami Beach) 2001, Abst 267.

Kimmel, K.A. et al. *Phase I dose-finding study of CI-994 in combination with capecitabine in patients with advanced solid tumors.* Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 345.

Olivares, J. et al. *Phase I pharmacokinetic (PK) study of CI-994 in combination with carboplatin (C) and paclitaxel (T) in patients (pts) with advanced solid tumors.* Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 346.

Conivaptan Hydrochloride
YM-087 *Treatment of Heart Failure*
CI-1025



$C_{32}H_{26}N_4O_2.HCl$ **Yamanouchi; Pfizer**

Mixed effects modeling of data from syndrome of inappropriate antidiuretic hormone secretion (SIADH) and congestive heart failure (CHF) patients has been used to characterize the pharmacokinetics and pharmacodynamics of conivaptan and its effect on serum sodium. A two-compartment model was used to describe the pharmacokinetics of conivaptan. Typical value of intrinsic clearance V_{max}/k_m was 16.1 and 7.1 l/h in SIADH and CHF patients, respectively, and the typical value of oral bioavailability was 58%. Post hoc Bayesian feedback estimations of individual pharmacokinetic parameters were similar in SIADH patients and healthy volunteers. According to the indirect response model used to describe the effect of conivaptan on serum sodium concentrations, the IC_{50} was 18.8 ± 15.4 ng/ml and K_{out} was 0.021 ± 0.006 hr^{-1}. I_{max} was about 2-fold larger in SIADH than in CHF patients and higher in patients having lower serum sodium at baseline (1).

A randomized, double-blind, multicenter, placebo-controlled trial of 142 heart failure patients was designed to evaluate the efficacy and safety of conivaptan 10, 20 and 40 mg in single i.v. doses. Treatment was well tolerated and significantly decreased pulmonary capillary wedge pressure and right atrial pressure without having significant effects on systemic blood pressure or heart rate (2).

Conivaptan (10, 20 and 40 mg) increased urine output, effective water clearance and free water clearance and had no significant effect on urine or plasma sodium and potassium in a randomized, double-blind, multicenter, placebo-controlled study in 142 heart failure patients. This evidence suggests that the drug antagonizes vasopressin effects on renal V_2 receptors (3).

A randomized pilot study assessed treatment of 24 heart failure patients with furosemide (40 or 80 mg q.i.d.) for 6 days followed by concomitant conivaptan (20 or 40 mg q.i.d.) for 3 days. The drug combination effectively cleared free water, indicating that the combination could make hyponatremia and hypokalemia less likely in these patients. Furosemide plus conivaptan also partially antagonized renal excretion of sodium and potassium (4).

The effects of single i.v. doses of conivaptan (10, 20 or 40 mg) on pulmonary capillary wedge pressure (PCWP) and urine output in 142 heart failure patients were analyzed according to baseline serum sodium and plasma arginine vasopressin (AVP) levels. Treatment with conivaptan lowered PCWP and increased urine output in patients with normal AVP and sodium levels, indicating that AVP plays an important role in heart failure progression and that conivaptan may be useful in a broader population of heart failure patients (5).

1. Chanoine, F., Zegarac, E., Bakker-Arkema, R., Miller, R. *Population pharmacokinetic/pharmacodynamic analysis of conivaptan, a new vasopressin V_{1A}/V_2 antagonist, in patients with hyponatremia and congestive heart failure.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 2322.

2. Udelson, J., Smith, W.B., Hendrix, G., Painchaud, C., Ghazzi, M.M., Thomas, I., Ghali, J., Selaru, P., Pressler, M., Konstam, M. *Haemodynamic effects of conivaptan hydrochloride (YM087, CI-1025) a combined vasopressin V_{1A} and V_2 receptor antagonist, in patients with advanced heart failure.* Eur Heart J 2001, 22(Suppl.): Abst P2150.

3. Painchaud, C., Bichet, D., Udelson, J.E., Ghazzi, M.M., Selanu, P., Chartier, K. *Urinary water clearance after infusion of conivaptan, a combined vasopressin V_{1A} and V_2 receptor antagonist, in patients with NYHA class III/IV heart failure.* Eur Heart J 2001, 22(Suppl.): Abst P2151.

4. Tonkon, M., Russell, S., Ghali, J.K., Painchaud, C.A., Ghazzi, M.M., Konstam, M.A., Udelson, J.E., Selanu, P. *Interaction between furosemide and oral conivaptan (YM087) in patients with heart failure.* Eur Heart J 2001, 22(Suppl.): Abst P2915.

5. Smith, W.B., Russell, S., Ghali, J.K., Painchaud, C.A., Ghazzi, M.M., Konstam, M.A., Udelson, J.E., Selaru, P. *Conivaptan (CI-1025, YM087), a combined vasopressin V_{1A}/V_2 antagonist, reduces pulmonary capillary wedge pressure independent of baseline serum Na or vasopressin levels in heart failure.* Eur Heart J 2001, 22(Suppl.): Abst P2917.

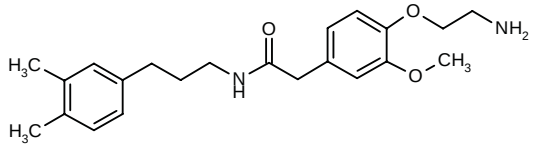
Original monograph - Drugs Fut 2000, 25: 1121.

Additional Reference
Decaux, G. *Long-term treatment of patients with inappropriate secretion of antidiuretic hormone by the vasopressin receptor antagonist conivaptan, urea, or furosemide.* Am J Med 2001, 110(7): 582.

DA-5018
Capsavanil
KR-25018

Analgesic

EN: 246619



$C_{22}H_{30}N_2O_3$ **Korea Res. Inst. Chem. Technol.; Dong-A; Stiefel**

Examination of vehicle systems allowing transdermal permeation of DA-5018 indicated that a binary system is the best approach, with the combination of ethoxydiglycol and isopropyl myristate yielding the maximum flux for DA-5018 across intact skin in mice (1).

Dong-A Pharmaceuticals is conducting phase II clinical studies with DA-5018 for the treatment of pain associated with osteoarthritis (2).

1. Cha, B.J., Lee, E.D., Kim, W.B., Chung, S.J., Lee, M.H., Shim, C.K. *Enhanced skin permeation of a new capsaicin derivative (DA-5018) from a binary vehicle system composed of isopropyl-myristate and ethoxydiglycol.* Arch Pharmacal Res 2001, 24(3): 224.

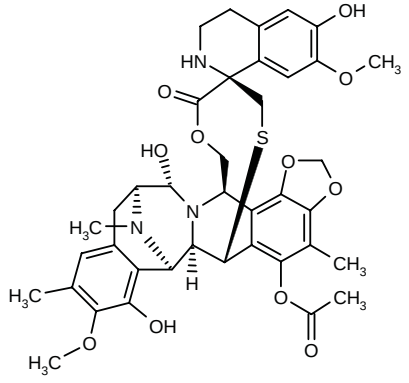
2. *DA-5018 development status.* Korea Research Institute of Chemical Technology Company Communication 2000, Nov 30.

Original monograph - Drugs Fut 2000, 25: 1131.

Ecteinascidin 743
ET-743

Oncolytic

EN: 139221



$C_{39}H_{43}N_3O_{11}S$ **PharmaMar; Ortho Biotech**

The metabolism of ET-743 was investigated *in vitro* in plasma/urine, human microsomes and incubations with uridine 5'-diphospho-glucuronyltransferase and *in vivo* in the bile, urine and plasma of treated patients. Screening revealed 8 products, with the main reaction products formed nonenzymatically with a major breakdown of the ET-743 molecule. Trace amounts of deacetylated drug were found in the plasma. Although not detected in the bile, urine or plasma of patients, glucuronidated ET-743 was synthesized *in vitro* (1).

Results from studies examining the mechanism of action of ET-743 in various cell systems with deficiencies in DNA repair mechanisms indicated that the drug appears to have a unique mechanism of interaction with DNA (2).

The combination of ET-743 (0.1 mg/kg i.v.) and doxorubicin (10 mg/kg i.v.) was studied in the murine fibrosarcoma UV2237, the mdr-resistant subline UV2237/ADR and the human rabdomyosarcoma xenograft TE671. Both drugs alone were active against UV2237 but neither was active alone against the other sarcomas. The combination of the drugs was active against all 3 sarcomas, with synergism being particularly marked in TE671 but independent of drug sequence or combination. Tumor weight inhibition was 46, 50, 77, 82 and 75% for ET-743 alone, doxorubicin alone, both drugs given simultaneously, ET-743 given 1 h before doxorubicin and ET-743 given 1 h after doxorubicin, respectively. Log_{10} cell kill values were 0.132, 0.33, 0.924, 1.12 and 0.85 for these same treatment regimens, respectively (3).

The cytotoxic potential of ET-743 to non-tumor cells has been assessed in an *in vitro* cytotoxicity assay, where the drug was found to affect liver (LD_{50} = 0.6 mM), kidney (LD_{50} = 1-2 mM), skeletal muscle (LD_{50} = 0.5 mM) and myelogenous (LD_{50} = 0.3 mM) cells. Less cytotoxicity was seen in cardiac cells (LD_{50} = 100 μM). Experiments using a fluorescent viability stain coupled with immunocytochemistry were conducted to evaluate the neurotoxicity seen with higher *in vitro* concentrations of ET-743. Approximately 1 mM ET-74 was found to be cytotoxic to brain cells, with a predilection for astrocytes. It was also cytotoxic to spinal cord motor neurons (LD_{50} = 4 mM), but not to substance P positive sensory neurons. Such motor neuron sensitivity may be responsible for weakness and fatigue in some patients (4).

The mechanism of action of ET-743 has been studied in a cancer cell line resistant to ET-743 which had defects in XPG, the gene implicated in the hereditary disease xeroderma pigmentosum. Sensitivity to ET-743 was restored when the activity of XPG was restored. In another ET-743-resistant cell line, restoration of the activity of cells deficient in DNA nucleotide excision repair (NER) genes with wild-type genes restored the ability of the genes to repair DNA damage from ultraviolet light and restored cell sensitivity to ET-743. Further experimentation with cells deficient in the XPG gene or in two genes implicated in Cockayne syndrome revealed that sensitivity to ET-743 relies on the transcription-coupled NER

pathway. The investigators concluded that ET-743 alters the machinery of NER to induce lethal DNA strand breaks in transcribed genes, resulting in cell death (5).

A study was performed to determine if proteins other than XPG gene involved in the nucleotide excision repair pathway played a part in the cytotoxicity of ET-743. XPA, XPD, XPF and XPG cells were found to be resistant to ET-743. Sensitivity to ET-743 was restored with complementation of XPA and XPD cells. Cells defective in transcription-coupled repair (CSA and CSB cells) demonstrated high-level resistance to ET-743. XPC cells with deficient global genome nucleotide excision repair but with normal transcription-coupled repair were as sensitive to ET-743 as XPC-complemented cells. Thus, the transcription-coupled repair pathway appeared to mediate the cytotoxicity of ET-743 (6).

A study of the relationship between P-glycoprotein/MDR1 and the activity of ET-743 found that ET-743 does not induce expression of P-glycoprotein in all ET-743-resistant cell lines, that P-glycoprotein expression alone does not confer resistance to ET-743 and that downregulation of P-glycoprotein by ET-743 may potentiate other chemotherapy agents (7).

ET-743, aplidine, kahalalide F and ES-285 were evaluated for their antiproliferative properties against various sarcoma cells *in vitro*. ET-743 induced apoptosis of chondrosarcoma (CHSA) cells in the nanomolar range and inhibited the growth of CHSA and osteosarcoma (OSA) cells equally. Aplidine was strongly cytotoxic to CHSA and OSA cells, with an IC_{50} in the picomolar range. Kahalalide F was cytotoxic to CHSA, OSA and hepatocellular and prostate carcinoma cells. ES-285 had no significant effect on CHSA and OSA cells. ET-743, aplidine and kahalalide F exhibited cytotoxic activity after 10 min of exposure and were suggested to be possible drugs for the treatment of CHSA and OSA (8).

The antitumor activity of ET-743 was evaluated in athymic mice with advanced stage xenografts of neuroblastoma and medulloblastoma. The xenografts were derived from primary human tumors. Five dose levels of the drug were administered every 4 days for 3 cycles. ET-743 was moderately effective against neuroblastoma: at 450 μg/kg (the maximum tolerated dose), significant delays in tumor growth were seen in IGR-N835 (8 days) and IGR-N91 (11 days) without tumor regression while there was no significant effect on IGR-NB8. ET-743 was highly active in 1 of 2 medulloblastomas: a significant tumor growth delay was seen in IGR-M34 (12 days) and the drug induced regressions with 9/10 tumor-free survivors in IGR-M57. Resistance to ET-743 was apparently not related to DNA mismatch repair deficiency and mdr overexpression (9).

The population pharmacokinetics of ET-743 (1.5 mg/m^2 as 24-h infusion every 3-4 weeks) in patients with advanced soft tissue sarcomas were determined from data from three phase II trials. Total body clearance was found to be lower in patients older than 50, resulting in higher mean C_{max} and AUC values for those patients. Patients with grade 3-4 toxicities also had a higher mean AUC. Severe toxicity was correlated to baseline SGOT and SGPT, and baseline alkaline phosphatase appeared to be an independent prognostic factor for grade 3-4 toxicity (10).

In a phase I study, ET-743 (1200 or 1800 μg/m^2) demonstrated activity in 29 previously treated advanced sarcoma patients, including partial responses in 2 soft tissue sarcoma patients and in 2 osteosarcoma patients (11).

A phase I pharmacokinetic study of ET-743 was performed in 52 patients with treatment-refractory solid tumors in order to determine the maximum tolerated dose (1800 μg/m^2 as a 24-h continuous infusion) and the recommended dose for phase II studies (1500 μg/m^2 as 24-h continuous infusion). Dose adjustments or delays in the recommended dose were indicated for patients with minor hepatobiliary function abnormalities at baseline, due to a greater likelihood of severe hematological toxicities (12).

A phase I study conducted in 21 adults with refractory solid tumors examined the tolerability and pharmacokinetics of treatment with a 72-h continuous i.v. infusion of ET-743 (600, 900, 1050 and 1200 μg/m^2 every 21 days). No dose-limiting toxicities were seen in the 6 patients receiving doses of 600 and 900 μg/m^2. Reversible grade 4 transaminitis in 2/9 patients and grade 4 rhabdomyolysis, renal failure requiring hemodialysis, grade 4 neutropenia and grade 3 thrombocytopenia in 1 patient were observed during the first cycle of treatment with 1200 μg/m^2; this dose was concluded to be the maximum tolerated dose (MTD). Six more patients were enrolled at the 1050 μg/m^2 dose which was determined to be the recommended dose for phase II studies. Toxicity was determined to be schedule-dependent since myelosuppression and hepatotoxicity were decreased when infusion duration was increased to 72 h from 3 or 24 h. No objective responses were seen although confirmed antitumor activity was seen in a patient with epithelioid mesothelioma. Pharmacokinetics were linear up to the 1200 mcg/m^2 dose and disposition of ET-743 was biexponential. The C_{max}, initial disposition phase $t_{1/2}$, terminal phase $t_{1/2}$ and total plasma clearance values with the 1050 μg/m^2 dose were 318 ± 147 pg/ml, 9 ± 10.3 min, 69 ± 56.7 h and 28.4 ± 22.5 l/h/m^2, respectively (13).

ET-743 (1500 μg/m^2 was every 3 weeks as a 24-h continuous infusion) was evaluated in a phase II study in 26 pretreated advanced/metastatic breast cancer patients. A median of 3 cycles were administered per patient. Grade 3-4 toxicities included neutropenia, 1 episode of febrile neutropenia, thrombocytopenia and reversible transaminitis. Grade 2-3 asthenia was reported as well. Partial responses were observed in 7 of 24 evaluable patients and disease stabilization lasting 2-11 months was seen in 11 patients (14).

A phase II study was conducted to assess the efficacy and tolerability of ET-743 in 47 patients with advanced soft tissue sarcoma. A dose of 1500 μg/m^2 was administered as a 24-h continuous infusion every 3 weeks. Toxicities observed included febrile neutropenia (11%), grade 3/4 neutropenia (38%) and thrombocytopenia (21%). Reversible, transient elevations of transaminases occurred in most cycles and reached grade 3/4 in 17 patients. Three deaths were related to toxicity and renal toxicity was observed in 3 patients. Severe toxicities were strongly correlated with abnormal alkaline phosphatase at baseline and a rise in alkaline phosphatase and/or bilirubin between cycles. Of 29 patients evaluated, there were 3 partial responses, 2 minor responses, 9 no change and 12 progressive disease. Toxicity was better controlled after the protocol was changed to require normal alkaline phosphatase and the ET-743 dose was reduced to 1200 μg/m^2 (15).

ET-743 (1500 μg/m^2 as continuous 24-h i.v. infusion every 3-4 weeks) was the focus of phase II clinical trials in 47 sarcoma patients with or without prior chemotherapy. Fatigue, myelosuppresion and temporary and asymptomatic transaminitis were observed, although tolerability was excellent when dexamethasone was used as pretreatment for antiemetic prophylaxis. Partial responses evolved from stable disease or minor responses over several cycles in 3 patients, and stable disease and minor responses were observed in 10 patients. Of 14 evaluable patients with gastrointestinal stromal tumors, 1 achieved stable disease (16).

ET-743 is currently in phase II/III clinical trials administered as a single infusion every 3 weeks. However, this schedule is associated with dose-limiting neutropenia, transaminitis and nausea and vomiting at doses above 1500 μg/m^2. Transaminitis appears to be related to peak plasma levels and in animals fractionation of the dose appeared to reduce the incidence of transaminitis. Thus, an ongoing study is examining ET-743 given as a 3-h i.v. infusion weekly for 3 weeks every 4 weeks in patients with advanced cancer. Sixteen patients have received doses of 300, 400, 525 and 650 μg/m^2/week. Dose-limiting neutropenia occurred in 1 heavily pretreated patient at the highest dose of ET-743, but no other clinically significant toxicity has been reported. A minor response was obtained in a heavily pretreated patient with metastatic liposarcoma and another patient with ovarian carcinoma has had prolonged disease stabilization. Pharmacokinetics appeared to be best described by a biexponential model with disposition and terminal half-lives of 0.18-0.34 h and 34-47 h, respectively. Further accrual at the highest dose level continues as the results so far indicate a potentially improved therapeutic index for this schedule. ET-743 was developed by Pharma Mar, a subsidiary of Zeltia, and was recently licensed to Ortho Biotech, a Johnson & Johnson company, for worldwide marketing, with the exception of Europe where Pharma Mar will market the compound (17).

1. Beijnen, J.H., Rosing, H., Sparidans, R., Hillebrand, M., Lopez-Lazaro, L., Jimeno, J., Cvitkovic, E., Van Oosterom, A., Schellens, J. *Search for metabolites of ecteinascidin-743 (ET-743), a novel marine derived anticancer agent.* Proc Amer Assoc Cancer Res 2001, 42: Abst 2929.

2. Damia, G., Silvestri, S., Carrassa, L., Filiberti, L., Faircloth, G.T., Liberi, G., Foiani, M., Dincalci, M. *Unique pattern of ET-743 activity in different cellular systems with defined deficiencies in DNA-repair pathways.* Int J Cancer 2001, 92(4): 583.

3. Riccardi, R., Colombo, T., Meco, D., Giavazzi, R., Ricardi, A., Faircloth, G.T., Jimeno, J., Erba, E., D'Incalci, M. *Effective combinations of ET-743 and doxorubicin for tumor growth inhibition against murine and human sarcomas in athymic mice.* Proc Amer Assoc Cancer Res 2001, 42: Abst 1132.

4. Luber-Narod, J., Smith, B., Grant, W., Jimeno, J., Lopez-Lazaro, L., Faircloth, G.T. *In vitro safety toxicology of ecteinascidin 743, a marine natural product with chemotherapeutic potential against solid tumors.* Proc Amer Assoc Cancer Res 2001, 42: Abst 1133.

5. Takebayashi, Y., Pourquier, P., Zimonjic, D.B. et al. *Antiproliferative activity of ecteinascidin 743 is dependent upon transcription-coupled nucleotide-excision repair.* Nat Med 2001, 7(8): 961.

6. Pourquier, P., Emmert, S., Ueda, T., Takabayashi, Y., Kraemer, K.H., Pommier, Y. *Nucleotide excision repair-mediated cytotoxicity of ecteinascidin 743, a novel anticancer agent in clinical trials.* Proc Am Assoc Cancer Res 2001, 42: Abst 2987.

7. Kanzaki, A., Takebayashi, Y., Fukumoto, M., Uchida, T., Pommier, Y. *Activity of ecteinascidin 743 and synergism with doxorubicin and vincristine in P-glycoprotein/MDR1 over-expression.* Proc Am Assoc Cancer Res 2001, 42: Abst 4354.

8. Shao, L., Weissbach, L., Faircloth, G.T., Chabner, B.A., Hornicek, F.J. *In vitro anti-proliferative effect on sarcoma cells by ET-743 and other marine chemotherapeutics.* Proc Am Assoc Cancer Res 2001, 42: Abst 1087.

9. Fontaniere, C., Terrier-Lacombe, M.-J., Santos, A., Aubert, G., Morizet, J., Jimeno, J.M., Faircloth, G., Vassal, G. *Antitumor activity of ET-743 (ecteinascidin-743) in neuroblastoma and medulloblastoma xenografts.* Proc Am Assoc Cancer Res 2001, 42: Abst 477.

10. Garcia-Carbonero, R., Demetri, G., Ryan, D. et al. *Population pharmacokinetics of ecteinascidin 743 in patients with advanced soft tissue sarcoma.* Clin Cancer Res 2000, 6(Suppl.): Abst 211.

11. Delaloge, S., Yovine, A., Taamma, A. et al. *Ecteinascidin-743: A marine-derived compound in advanced, pretreated sarcoma patients - Preliminary evidence of activity.* J Clin Oncol 2001, 19(5): 1248.

12. Taamma, A., Misset, J.L., Riofrio, M., Guzman, C., Brain, E., Lopez Lazaro, L., Rosing, H., Jimeno, J.M., Cvitkovic, E. *Phase I and pharmacokinetic study of ecteinascidin-743, a new marine compound, administered as a 24-hour continuous infusion in patients with solid tumors.* J Clin Oncol 2001, 19(5): 1256.

13. Ryan, D.P., Supko, J.G., Eder, J.P., Selden, M.V., Demetri, G., Lynch, T.J., Fischman, A.J., Davis, J., Jimeno, J., Clark, J.W. *Phase I and pharmacokinetic study of esteinascidin 743 administered as a 72-hour continuous intravenous infusion in patients with solid malignancies.* Clin Cancer Res 2001, 7(2): 231.

14. Zelek, L., Yovine, A., Brain, E., Turpin, F., Taamma, A., Riofrio, M., Spielmann, M., Jimeno, J., Cvitkovic, E., Misset, J.L. *Preliminary results of phase II study of ecteinascidin-743*

(ET-743) with the 24 hour (h) continuous infusion (CI) q3week schedule in pretreated advanced/metastatic breast cancer (A/MBC) patients (pts). Clin Cancer Res 2000, 6(Suppl.): Abst 212.

15. Le Cesne, A., Judson, I., Radford, J., Blay, J.-Y., Van Oosterom, A., Rodenhuis, S., Lorigan, P., Di Paola, E.D., Jimeno, J., Verweij, J. *Phase II study of ET-743 in advanced soft-tissue sarcoma (ASTS) in adults: A STBSG-EORTC trial.* Ann Oncol 2000, 11(Suppl. 4): Abst 574O.

16. Demetri, G., Garcia-Carbonero, R., Harmon, D., Seiden, M., Jimeno, J., Merriam, P., Waxman, A., Supko, J., Quigley, M.T., Ryan, D. *Ecteinascidin-743 (ET-743) induces objective responses and disease control in patients with advanced non-osseous sarcomas: Results from phase II trials.* Ann Oncol 2000, 11(Suppl. 4): Abst 573O.

17. Forouzesh, B. et al. *Phase I and pharmacokinetic study of ET-743, a minor groove DNA binder, administered weekly to patients with advanced cancer.* Eur J Cancer 2001, 37(Suppl. 6): Abst 106.

Original monograph - Drugs Fut 1996, 21: 1155.

Additional References

Curigliano, G. et al. *Ecteinascidin 743 (ET-743) in ovarian cancer: Activity in xenografts and preliminary results of an ongoing study in patients failing platinum-taxanes.* AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Oct 29-Nov 2, Miami Beach) 2001, Abst 380.

Demetri, G.D. et al. *Ecteinascidin-743 (ET-743) induces durable responses and promising 1-year survival rates in soft tissue sarcomas (STS): Final results of phase II and pharmacokinetic studies in the U.S.A.* Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 1406.

Donald, S. et al. *Modulation of the hepatotoxicity of ecteinascidin 743 (ET-743) in the rat.* AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Oct 29-Nov 2, Miami Beach) 2001, Abst 271.

Erba, E. et al. *Ecteinascidin-743 (ET-743), a natural marine compound, with a unique mechanism of action.* Eur J Cancer 2001, 37(1): 97.

Erba, E. et al. *ET-743 and cisplatin (DDP) show in vitro and in vivo synergy against human sarcoma and ovarian carcinoma cell lines.* AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Oct 29-Nov 2, Miami Beach) 2001, Abst 406.

Faircloth, G.T. et al. *In vivo combinations of chemotherapeutic agents with ecteinascidin 743 (ET-743) against solid tumors.* AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Oct 29-Nov 2, Miami Beach) 2001, Abst 387.

Forouzesh, B. et al. *Phase I and pharmacokinetic study of ET-743, a minor groove DNA binder administrated weekly to patients with advanced cancer.* Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 373.

Forouzesh, B. et al. *Phase I and pharmacokinetic study of the marine-derived DNA minor groove ET-743 on a weekly x3 every-4-week schedule in patients with advanced solid malignancies.* AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Oct 29-Nov 2, Miami Beach) 2001, Abst 209.

Gajate, C. et al. *Antitumor activity of ecteinascidin-743.* AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Oct 29-Nov 2, Miami Beach) 2001, Abst 352.

Le Cesne, A. et al. *ET-743 is an active drug in adult soft-tissue sarcoma (STS): A STBSG-EORTC phase II trial.* Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 1407.

Li, W.W. et al. *Sensitivity of soft tissue sarcoma cell lines to chemotherapeutic agents: Identification of ecteinascidin-743 as a potent cytotoxic agent.* Clin Cancer Res 2001, 7(9): 2908.

Maliepaard, M. et al. *Novel marine derived anticancer agents ET-743, aplidine, spisulosine (ES-285) and kahalalide F are not transported by the breast cancer resistance protein.* Proc Am Assoc Cancer Res 2001, 42: Abst 4352.

Mantovani, R. et al. *Differential effects of the marine compound ET743 on transcription of cell cycle regulated promoters.* Proc Am Assoc Cancer Res 2001, 42: Abst 4885.

Marchini, S. et al. *Gene expression profile of sensitive and resistant ovarian cancer cells treated with ET 743.* AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Oct 29-Nov 2, Miami Beach) 2001, Abst 403.

Marco, E. et al. *Structural similarity between zinc finger-DNA complexes and DNA complexes containing three tandemly bound ecteinascidin ET743 molecules.* AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Oct 29-Nov 2, Miami Beach) 2001, Abst 374.

Markenson, D. et al. *ET-743 inhibits SP1-mediated transcriptional activation of the p21 promoter.* Proc Am Assoc Cancer Res 2001, 42: Abst 1086.

Mathot, R. et al. *Population pharmacokinetics of the novel marine derived anti-cancer agent ecteinascidin 743 in two phase II studies using non-linear mixed effects modeling (NONMEM).* Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 372.

Riccardi, R. et al. *Preclinical activity and biodistribution of ecteinascidin 743 (ET-743) and doxorubicin (DOX) combination in human rhabdomyosarcoma.* AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Oct 29-Nov 2, Miami Beach) 2001, Abst 405.

Scotlandi, K. et al. *Effectiveness of the antineoplastic drug ecteinascidin 743 against sensitive and multidrug resistant sarcoma cells: A preclinical evaluation.* AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Oct 29-Nov 2, Miami Beach) 2001, Abst 383.

Scotto, K.W. et al. *Et-743, a novel marine-based anticancer agent that targets activated but not constitutive, transcription.* Mol Biol New Ther Strategies: Cancer Res 21st Century (Feb 12-16, Maui) 2001, C-76.

Shtil, A.A. et al. *Ecteinascidin 743, a novel natural cytotoxic compound, is potent for human neuroblastoma and rhabdomyosarcoma cell lines: Multiple mechanisms of cell kill.* Proc Am Assoc Cancer Res 2001, 42: Abst 4353.

Sparidans, R.W. et al. *Search for metabolites of ecteinascidin 743, a novel, marine-derived, anti-cancer agent, in man.* Anti-Cancer Drugs 2001, 12(8): 653.

Takebayashi, Y. et al. *Ecteinascidin 743 induces protein-linked DNA breaks in human colon carcinoma HCT116 cells and is cytotoxic independently of topoisomerase I expression.* Clin Cancer Res 2001, 7(1): 185.

Tolner, B. et al. *Effects of the DNA minor groove binding agent ecteinascidin (ET-743) on the topoisomerase IIalpha promoter.* AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Oct 29-Nov 2, Miami Beach) 2001, Abst 703.

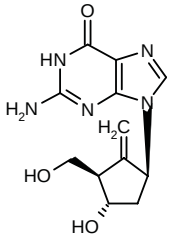
  CCC: 0377-8282/2001

Yovine, A. et al. *Ecteinascidin (ET-743) given as a 24 hour (H) intravenous continuous infusion (VCI) every 3 weeks: results of a phase II trial in patients(pts) with pretreated soft tissue sarcomas (PSTS).* Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 1449.

Entecavir
BMS-200475

Anti-HBV

EN: 182634



$C_{12}H_{15}N_5O_3$ **Bristol-Myers Squibb**

Antiviral combinations have been claimed for the treatment of hepatitis B virus (HBV) infections, including those caused by HBV mutants bearing resistance to nucleoside and non-nucleoside inhibitors of HBV replication. Preferred antiviral agents are lamivudine and BMS-200475 (1).

A double-blind, randomized trial compared entecavir (0.01, 0.1 and 0.5 mg q.d.) and lamivudine (100 mg q.d.) in 180 patients with chronic hepatitis B. Of 169 evaluable patients, 81% were HbeAg-positive and 22% had received prior interferon therapy. The two higher entecavir doses were more effective than the 0.01 mg dose and were superior to lamivudine; mean $\log_{10}$ reductions in HBV DNA were 4.3, 4.7 and 3.4 for entecavir 0.1 and 0.5 mg and lamivudine 100 mg, respectively, at week 22. HbeAg was lost by 4 entecavir-treated patients and 2 lamivudine-treated patients. Mild to moderate nervous system adverse events were seen more often in the entecavir 0.5 mg group than in the lamivudine-treated group. One subject receiving entecavir 0.1 mg discontinued therapy after 18 weeks due to lethargy and photosensitivity (2).

1. Brown, N.A. et al. (Glaxo Group Ltd.). *Antiviral combinations.* WO 0130329.

2. Lai, C., Rosmawati, M., Lao, J., Van Vlierberghe, H., Anderson, F., Thomas, N., De Hertogh, D. *A phase II study of entecavir vs lamivudine in adults with chronic hepatitis B.* J Hepatol 2001, 34(Suppl. 1): 24.

Original monograph - Drugs Fut 1999, 24: 1173.

Additional References

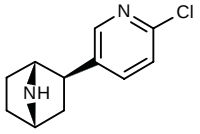
De Man, R.A. et al. *A study of oral entecavir given for 28 days in both treatment-naive and pre-treated subjects with chronic hepatitis B.* Gut 2001, 49(Suppl. 3): Abst 2302.

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

Epibatidine

Analgesic

EN: 202254



$C_{11}H_{13}ClN_2$ **Dept. Health Human Services (US); CytoMed**

Recent experiments examined the sensitivity of ganglionic-type nicotinic receptors expressed in IMR-32 neuroblastoma cells to chronic exposure to various nicotinic receptor ligands. After 3 days of exposure, (–)-nicotine (10 μM) increased [^{3}H]-epibatidine by 280% and [^{125}I]-α-bungarotoxin-labeled nicotinic receptors by 84%. (–)-Nicotine-mediated upregulation was related to an increase in the number of binding sites. (+)-Nicotine was 10-fold less active. [^{3}H]-Epibatidine and [^{125}I]-α-bungarotoxin-labeled nicotinic receptors were also upregulated by the nicotinic agonists (±)-epibatidine, (–)-cytisine, L-lobeline and acetylcholine (1).

It has been found that 2'-pyridine ring substitutions on epibatidine increase neuronal nicotinic acetylcholine receptor subtype selectivity. The -NH_2, -F and -H substitutions markedly increased the difference in affinity between β_2- and β_4-containing receptors. The affinity of each compound for $\alpha_3\beta_2$ and $\alpha_3\beta_4$ differed by 93-fold, 552-fold and 3548-fold for the -NH_2, -F and -H substituted compounds, respectively. The -Br substitution had only modest effects. The α-subunit selectivity of the drug was not enhanced by these substitutions. The -Br, -NH_2 and -F substituted compounds also retained agonist activity (2).

After observing that epibatidine selects by more than 200-fold between the two agonist binding sites in the nicotinic acetylcholine receptor when the receptor is in the desensitized state, researchers used gamma/delta subunit chimeras to identify amino acids that mediate this selectivity. The results indicated that γL104 (equivalent to δY106) is a major determinant of epibatidine selectivity at desensitized nicotinic acetylcholine receptors. At least two other determinants may lie between amino acids 104 and 156 and between 156 and 225 (3).

Researchers have found that epibatidine potentiates the analgesic effects of adrenal medullary (AM) transplants in the spinal subarachnoid space. Rats were implanted with intrathecal catheters and either AM or control striated muscle transplants and tested for nociceptive responses. Nociceptive thresholds to acute

noxious stimuli were elevated at baseline in rats with AM transplants and were further elevated after injection of epibatidine (0.03-0.3 μg). Epibatidine injection also enhanced the suppression of the formalin flinching responses observed in AM transplanted animals (4).

1. Lockhart, B., Stenward, C., Lestage, P. *The effect of chronic exposure with nicotinic receptor ligands on the levels of [^{3}H]-epibatidine and [^{125}I]-α-bungarotoxin-labeled nicotinic receptors in NMR-32 neuroblastoma cells.* Soc Neurosci Abst 2000, 26(Part 1): Abst 138.6.

2. Maddox, F.N., Parker, M.J., Carroll, F.I., Luetje, C.W. *Epibatidine pyridine ring substitutions increase neuronal nicotinic receptor subtype selectivity.* Soc Neurosci Abst 2000, 26(Part 1): Abst 138.17.

3. Prince, R.J., Smith, M., Fisher, S.E., Sine, S.M. *Determinants of epibatidine selectivity at desensitised muscle nicotinic acetylcholine receptors.* Soc Neurosci Abst 2000, 26(Part 1): Abst 138.16.

4. Lee, J.W., Caban, A.J., Hama, A., Hunter, C.W., Castellanos, D.A., Sagen, J. *Nicotinic agonist epibatidine enhances the antinociceptive effects of intrathecal adrenal medullary transplants.* Soc Neurosci Abst 2000, 26(Part 1): Abst 351.10.

Original monograph - Drugs Fut 1997, 22: 1210.

Additional References

Gilbert, S.D. et al. *Antihyperalgesic activity of epibatidine in the formalin model of facial pain.* Pain 2001, 89(2-3): 159.

Javors, M.A. et al. *Extraction and quantification of epibatidine in plasma.* J Chromatogr B - Biomed Sci Appl 2001, 755(1-2): 379.

Khan, I.M. et al. *A-85380 and epibatidine each interact with disparate spinal nicotinic receptor subtypes to achieve analgesia and nociception.* J Pharmacol Exp Ther 2001, 297(1): 230.

Pennington, R.A., Prince, R.J. *Determinants of epibatidine selectivity at muscle nicotinic acetylcholine receptor complexes.* Br J Pharmacol 2000, 131(Suppl.): Abst 193P.

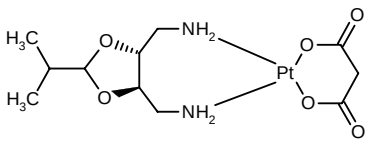
Whiteaker, P. et al. *[^{125}I]epibatidine labels $\alpha_3\beta_4$-like nicotinic acetylcholine receptors in mouse brain.* Soc Neurosci Abst 2000, 26(Part 1): Abst 235.15.

Xiao, Y. et al. *Analysis of agonist concentration-response of the rat $\alpha_3\beta_4$ neuronal nicotinic acetylcholine receptor function: Maximum responses, potencies for activation and potencies for inhibition.* Soc Neurosci Abst 2000, 26(Part 1): Abst 137.8.

Eptaplatin
SKI-2053R
Sunpla®

Oncolytic

EN: 210284



$C_{11}H_{20}N_2O_6Pt$ **SK Chemicals**

A phase I pharmacokinetic study was carried out in 21 patients with advanced refractory malignancies to determine the maximum tolerated dose and the dose-limiting toxicities of SKI-2053R. No significant toxicity was seen with doses up to 360 mg/m^2. The maximum tolerated dose was 480 mg/m^2, and hepatotoxicity, nephrotoxicity and myelosuppression were the major dose-limiting toxicities. Stable disease was achieved by 4 patients, and a starting dose of 360 mg/m^2 once every 4 weeks was recommended for a phase II study (1).

Eptaplatin is the proposed international nonproprietary name for SKI-2053R (2).

1. Kim, N.K., Kim, T.Y., Shin, S.G., Lee, J.A., Park, Y.I., Cho, Y.B., Kim, K.H., Kim, D.K., Heo, D.S., Bang, Y.J. *A phase I study of cis-malonato[(4R,5R)-4,5-bis(aminomethyl)-1,3-dioxolane]platinum(II) in patients with advanced malignancies.* Cancer 2001, 91(8): 1549.

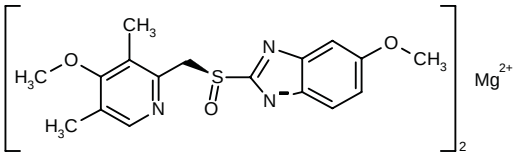
2. *Proposed international nonproprietary names (Prop. INN): List 83.* WHO Drug Inf 2000, 14(2): 114.

Original monograph - Drugs Fut 1995, 20: 1128.

Esomeprazole Magnesium
Nexium®

Antiulcer
Treatment of GERD

EN: 272598



$2C_{17}H_{18}N_3O_3S.Mg$ **AstraZeneca**

A pharmacokinetic study of esomeprazole in the elderly found that dose adjustment is not required for use in this population. Esomeprazole 40 mg was administered once daily for 5 days to 14 healthy elderly volunteers (mean age = 74 years). AUC and C_{max} values increased by 94 and 52%, respectively, between days 1-5. Steady-state AUC and C_{max} values for the elderly volunteers were similar to those for a group of younger GERD patients evaluated in an earlier study, with AUC and C_{max} ratios between the two groups of 1.25 and 1.18, respectively (1).

Two pharmacokinetic studies evaluated esomeprazole 20 and 40 mg given intravenously and orally as single and repeated doses to healthy volunteers. Repeated dosing increased the AUC of the drug, which was considered the result of decreased first-pass elimination and reduced systemic clearance (2).

A randomized, open-label crossover, pharmacokinetic study was performed with 45 healthy male and female volunteers who received single doses of open capsule esomeprazole (mixed with applesauce) or intact capsule

omeprazole (administered with water) on 2 study days separated by a 7-day washout period. The ratio of geometric means for AUC and C_{max} for the open capsule/intact capsule were 0.99 and 0.93, respectively. $T_{1/2}$ (~ 0.9 h) and t_{max} (~ 2.3 h) values were also similar for the open capsule and intact capsule groups. Overall, the two formulations demonstrated bioequivalence and both were well tolerated (3).

A randomized, two-way crossover study compared the effects on intragastric pH of esomeprazole 20 mg and lansoprazole 15 mg. The study drugs were administered to 27 healthy volunteers daily for 5 days with a washout period of a minimum 14 days. Glass electrodes were used to record intragastric pH for 24 h on day 5. The percentage of time with pH ≥ 4 averaged 50.4 and 43.0 in the esomeprazole and lansoprazole groups, respectively. More subjects taking esomeprazole had a pH > 4 for more than 12 h than those taking lansoprazole (50% *vs.* 35%, respectively). Esomeprazole 20 mg, therefore, appeared to be more effective in controlling acid than lansoprazole 15 mg. Neither drug was associated with side effects (4).

Results from an open-label, randomized, 4-way crossover trial in 17 healthy volunteers and another study conducted in 19 healthy subjects showed that esomeprazole (20 or 40 mg once daily) did not affect the pharmacokinetics of amoxicillin (1 g b.i.d.) or clarithromycin (500 mg b.i.d.). Results indicate that esomeprazole has no inhibitory effects on CYP3A4 (5).

Two open, randomized, two-way crossover studies compared the effects on intragastric pH of esomeprazole 40 mg and lansoprazole 30 mg in healthy volunteers. Single oral doses of the study drugs, with a washout period of at least 10 days, were administered to 28 subjects in the first study, and in the second study esomeprazole and lansoprazole were given to 20 subjects once daily for 5 days, with a washout period of 14 days. Glass electrodes were used to record 24-h intragastric pH after drug administration in study one and on day 5 in study two. In study one, esomeprazole-treated subjects had a greater percentage of time with pH > 4 (57.2 *vs.* 51.8 in the esomeprazole and lansoprazole groups, respectively). The percentages of subjects with pH > 4 for more than 12 h were 71 and 61 in the esomeprazole and lansoprazole groups, respectively. In study two, esomeprazole-treated subjects also had a greater percentage of time with pH > 4 (65.4 *vs.* 53.0 in the esomeprazole and lansoprazole groups, respectively). The percentages of subjects with pH > 4 for more than 12 h were 90 and 55 in the esomeprazole and lansoprazole groups, respectively. No side effects were seen with either drug (6).

Esomeprazole 40 mg and rabeprazole 20 mg were compared by their effects on intragastric pH in a randomized, two-way crossover design study. The drugs were administered to 23 healthy volunteers once in the morning for 5 days with a minimum washout period of 14 days. Glass electrodes were used to record intragastric pH for 24 h on day 5 in each period. Subjects in the esomeprazole group had more time with pH > 4 (61.0 and 45.1% of the 24-h period in the esomeprazole and rabeprazole groups, respectively). The percent of subjects with pH > 4 for more than 12 h was 77% in the esomeprazole group and 36% in the rabeprazole group. No side effects were observed in either group (7).

A randomized, double-blind trial conducted in 448 patients with duodenal ulcers and *Helicobacter pylori* infection demonstrated comparable efficacy for 1-week triple therapy including esomeprazole (20 mg b.i.d.) or omeprazole and amoxicillin (1 g b.i.d.) and clarithromycin (500 mg b.i.d.) in eradicating infection. Both treatments were well tolerated. Eradication rates in the intention-to-treat (n = 400) and per protocol (n = 377) populations treated with esomeprazole-based triple therapy were 90 and 91%, respectively, as compared to 88 and 91%, respectively, in patients receiving omeprazole-based triple therapy; no significant differences were seen between treatment groups (8).

Results from 4 randomized, repeated-dose, crossover studies conducted in a total of 67 patients with GERD and 43 healthy subjects showed that esomeprazole (40 mg once daily for 5 days) was significantly more effective in controlling intragastric acid secretion than once-daily treatment with omeprazole (20 mg), pantoprazole (40 mg), lansoprazole (30 mg) or rabeprazole (20 mg) for 5 days (9).

Results from a prospective, multicenter, randomized, double-blind, placebo-controlled study in 440 patients with GERD with or without erosive esophagitis and typical reflux symptoms showed the efficacy of esomeprazole (20 mg b.i.d. or 40 mg once daily for 2 weeks) in relieving heartburn symptoms. Total relief rates by the fourth treatment day for patients treated with 20 and 40 mg esomeprazole were 63-70 and 67-73%, respectively, as compared to 21-32% in placebo. Patients with esophagitis had higher rates of relief (71-80%) as compared to patients without esophagitis (65-73%). The best responses were seen in patients diagnosed using pH monitoring. Since no benefit was observed with twice-daily dosing, once-daily dosing was recommended (10).

A multicenter, randomized, double-blind, parallel-group trial in 4877 patients with erosive esophagitis compared the healing rates following once-daily treatment for up to 8 weeks with esomeprazole (40 mg) or omeprazole (20 mg). Of the 2935 and 3572 patients who experienced resolution by treatment week 4 of heartburn and acid regurgitation, respectively, healing rates were significantly higher in esomeprazole- as compared to omeprazole-treated patients. Absence of symptoms at week 4 of esomeprazole treatment may therefore be an indicator of healing (11).

Results from a retrospective study examining the results of several trials comparing the efficacy of

esomeprazole (40 mg once daily for up to 8 weeks) with that of omeprazole (20 mg once daily for up to 8 weeks) and involving up to 4877 patients with erosive esophagitis, showed that significantly more patients treated with esomeprazole were more likely to be healed as compared to those treated with omeprazole. Healing rates for patients treated with esomeprazole were > 90% regardless of gender, age, body mass index or presence of hiatal hernia. In contrast, males and patients 50 years or younger were less likely to respond to omeprazole treatment as compared to females (83.4 *vs.* 90.8%) and patients over 50 years of age (83.7 *vs.* 90.5%) (12).

A multicenter, randomized, double-blind, parallel-group study conducted in 4877 patients with GERD and erosive esophagitis showed that treatment for up to 8 weeks with esomeprazole (40 mg once daily) was more effective than omeprazole (20 mg once daily) in resolving nocturnal heartburn (88.1 ± 0.421 *vs.* 85.1 ± 0.452%) (13).

The impact on intragastric pH of esomeprazole 40 mg and omeprazole 40 mg were compared in patients with symptomatic gastroesophageal reflux disease. In the open, randomized, two-way crossover study, 130 patients received either drug once in the morning for 5 days with a minimum washout period of 14 days. Intragastric pH was recorded for 24 h on days 1 and 5 in each period. Patients in the esomeprazole group experienced 48.6% of day 1 with pH > 4, while that figure for the omeprazole group was 40.6%. The percentages of patients in the esomeprazole and omeprazole groups with pH > 4 for more than 12 h on day 1 were 50 and 34%, respectively. On day 5, patients in the esomeprazole group spent 68.4% of the day with pH > 4, while this figure in the omeprazole group was 62%. The percentages of patients with pH > 4 for more than 12 h on day 5 were 88 and 77% for the esomeprazole and omeprazole groups, respectively. No side effects were seen with either drug (14).

Data from 4 multicenter, double-blind, randomized trials in a total of 6708 erosive esophagitis patients were pooled and analyzed to compare the effect of baseline disease severity on healing rates with once-daily esomeprazole 40 mg and 20 mg and omeprazole 20 mg. Treatments lasted for up to 8 weeks. Esomeprazole 40 mg was found to have a higher overall healing rate and showed greater consistency of healing rates across all grades of baseline disease than esomeprazole 20 mg and omeprazole 20 mg. Baseline severity of disease significantly impacted healing rates with omeprazole 20 mg. While all treatments effectively healed erosive esophagitis at week 8, the healing rates were greater with both doses of esomeprazole than with omeprazole 20 mg (15).

Examination of 693 *Helicobacter pylori*-negative patients with healed erosive esophagitis who were treated once daily for up to 6 months with either esomeprazole (10, 20 or 40 mg) or placebo showed that male gender, a BMI of more than 30 and severe disease (LA grade C and D) at baseline were associated with relapse. The risk for relapse was significantly lower in patients treated with 20 or 40 mg esomeprazole as compared to placebo and the 10 mg esomeprazole group (16).

A randomized, multicenter, double-blind, placebo-controlled trial was carried out to assess the efficacy of esomeprazole in preventing relapse in patients with healed esophagitis. The percentages of patients who remained healed at 6 months were 29.1, 54.2, 78.7 and 87.9% in the placebo and esomeprazole 10, 20 and 40 mg groups, respectively. Esomeprazole also delayed the onset of relapse when it occurred. Mild, infrequent adverse effects were not significantly different between groups (17).

The efficacy of esomeprazole in the maintenance therapy of healed erosive esophagitis was examined in a multicenter, double-blind, randomized, placebo-controlled trial. This study included 318 patients with healed erosive esophagitis from a previous trial comparing esomeprazole 20 or 40 mg and omeprazole 20 mg, and compared once-daily maintenance therapy with esomeprazole 10, 20 or 40 mg or placebo for 6 months. Doses of 20 or 40 mg esomeprazole were highly effective, maintaining healing in 93.2% and 93.6% of patients, respectively, *versus* 57.1% on esomeprazole 10 mg and 29.1% on placebo. Moreover, the time to recurrence of esophagitis in relapsing patients was significantly prolonged on esomeprazole, from 34 days on placebo to 78 days on 10 mg, 115 days on 20 mg and 163 days on 40 mg drug. Esomeprazole was also effective in maintaining symptom control, being associated with less frequent and less severe heartburn than placebo, and over 70% of esomeprazole-treated patients remained symptom-free during the study. No serious drug-related adverse events and no clinically relevant changes in vital signs or physical examination were seen (18).

AstraZeneca has launched esomeprazole magnesium 20 or 40 mg (Nexium®) in the U.S. for the short-term (4- to 8-week) treatment of diagnosed erosive esophagitis. Marketing approvals have previously been granted in several countries, including the U.K., Sweden, Denmark, Germany, Norway and Ireland (19).

1. Hasslegren, G., Hassan-Alin, M., Andersson, T., Claar-Nilsson, C., Nilsson, L.-G., Röhss, K. *Pharmacokinetics of esomeprazole are unaltered in the elderly.* 8th United Eur Gastroenterol Week (Nov 25-30, Brussels) 2000, Abst P.47.

2. Hassan-Alin, M., Andersson, T., Bredberg, E., Röhss, K. *Pharmacokinetics of esomeprazole after oral and intravenous administration of single and repeated doses to healthy subjects.* Eur J Clin Pharmacol 2000, 56(9-10): 665.

3. Andersson, T., Magner, D., Patel, J., Rogers, P., Levine, J. *Esomeprazole open capsule mixed with applesauce is bioequivalent to the intact capsule when administered to healthy volunteers.* 8th United Eur Gastroenterol Week (Nov 25-30, Brussels) 2000, Abst P.48.

4. Wilder-Smith, C., Claar-Nilsson, C., Röhss, K., Rydlholm, H. *Esomeprazole 20 mg provides more effective acid control than lansoprazole 15 mg.* 8th United Eur Gastroenterol Week (Nov 25-30, Brussels) 2000, Abst P.49.

5. Andersson, T., Wayne, P.A., Rohss, K., Hassan-Alin, M. *Drug interaction studies of esomeprazole with amoxicillin and clarithromycin.* Dig Dis Week (May 20-23, Atlanta) 2001, Abst 2954.

6. Thomson, A.B.R., Claar-Nilsson, C., Hasselgren, G., Niazi, M., Röhss, K., Nyman, L. *Esomeprazole 40 mg provides more effective acid control than lansoprazole 30 mg during single and repeated administration.* 8th United Eur Gastroenterol Week (Nov 25-30, Brussels) 2000, Abst P.50.

7. Wilder-Smith, C. et al. *Esomeprazole 40 mg provides more effective acid control than rabeprazole 20 mg.* 8th United Eur Gastroenterol Week (Nov 25-30, Brussels) 2000, Abst P.51.

8. Van Zanten, S.V., Lauritsen, K., Delchier, J. et al. *One-week triple therapy with esomeprazole provides effective eradication of Helicobacter pylori in duodenal ulcer disease.* Aliment Pharmacol Ther 2000, 14(12): 1605.

9. Röhss, K., Wilder-Smith, C.H., Claar-Nilsson, C., Lundin, C., Hasselgren, G. *Esomeprazole 40 mg provides more effective acid control than standard doses of all other proton pump inhibitors.* Dig Dis Week (May 20-23, Atlanta) 2001, Abst 2140.

10. Johnsson, F., Hatlebakk, J.G., Klintenberg, A.-C., Roman, J. *The symptom relieving effect of esomeprazole 40 mg daily in patients with heartburn.* Dig Dis Week (May 20-23, Atlanta) 2001, Abst 2229.

11. Johnson, D.A., Vakil, N.B., Hwang, C., Levine, J.G. *Absence of symptoms in erosive esophagitis (EE) patients treated with esomeprazole is a highly reliable indicator of healing.* Dig Dis Week (May 20-23, Atlanta) 2001, Abst 2237.

12. Vakil, N.B., Hwang, C., Levine, J.G. *Effect of gender, age, hiatus hernia (HH), and body mass index (BMI) on healing of erosive esophagitis (EE).* Dig Dis Week (May 20-23, Atlanta) 2001, Abst 2243.

13. Vakil, N.B., Katz, P.O., Hwang, C., Levine, J.G. *Nocturnal heartburn (HB) is rare in patients with erosive esophagitis (EE) treated with esomeprazole.* Dig Dis Week (May 20-23, Atlanta) 2001, Abst 2250.

14. Röhss, K., Lundin, C., Rydholm, H., Vyman, L. *Esomeprazole 40 mg provides more effective acid control than omeprazole 40 mg.* 8th United Eur Gastroenterol Week (Nov 25-30, Brussels) 2000, Abst P.52.

15. Vakil, N., Richter, J., Hwang, C., Marino, V., Levine, J. *Does baseline severity of erosive esophagitis impact healing with esomeprazole?* 8th United Eur Gastroenterol Week (Nov 25-30, Brussels) 2000, Abst P.53.

16. Vakil, N.B., Johnson, D.A., Hwang, C., Levine, J.G. *Obesity, male gender and initially severe esophagitis are associated with relapse after initial healing of erosive esophagitis (EE).* Dig Dis Week (May 20-23, Atlanta) 2001, Abst 2213.

17. Vakil, N.B., Shaker, R., Johnson, D.A., Kovacs, T., Baerg, R.D., Hwang, C., Damico, D., Hamelin, B. *The new proton pump inhibitor esomeprazole is effective as a maintenance therapy in GERD patients with healed erosive oesophagitis: A 6-month, randomized, double-blind, placebo-controlled study of efficacy and safety.* Aliment Pharmacol Ther 2001, 15(7): 927.

18. Johnson, D.A., Vakil, N.B., Benjamin, S.B., Goldstein, J.L., Lamet, M., Whipple, J., D'Amico, D., Hamelin, B. *Esomeprazole once daily for 6 months is effective therapy for maintaining healed erosive esophagitis and for controlling gastroesophageal reflux disease symptoms: A randomized, double-blind, placebo-controlled study of efficacy and safety.* Am J Gastroenterol 2001, 96(1): 27.

19. *AstraZeneca's Nexium for erosive esophagitis launched in U.S.* DailyDrugNews.com (Daily Essentials) March 23, 2001.

Original monograph - Drugs Fut 1999, 24: 1178.

Additional References

Andersson, T. et al. *Drug interaction studies with esomeprazole, the (S)-isomer of omeprazole.* Clin Pharmacokin 2001, 40(7): 523.

Andersson, T. et al. *Pharmacokinetic studies with esomeprazole, the (S)-isomer of omeprazole.* Clin Pharmacokin 2001, 40(6): 411.

Baxter, G. et al. *Lansoprazole 15 mg provides as effective acid control as esomeprazole 20 mg.* Gut 2001, 49(Suppl. 3): Abst 2430.

Castell, D.O. et al. *Esomeprazole is more effective than lansoprazole for treating daily and nocturnal heartburn in GERD patients with erosive esophagitis (EE).* Am J Gastroenterol 2001, 96(9, Suppl.): Abst 16.

Castell, D.O. et al. *Esomeprazole provides more effective healing than lansoprazole in GERD patients with erosive esophagitis (EE).* Am J Gastroenterol 2001, 96(9, Suppl.): Abst 17.

Eriksson, K. et al. *Speed of onset of intragastric acid control. Lansoprazole and esomeprazole compared.* Gut 2001, 49(Suppl. 3): Abst 2392.

Johanson, J. et al. *Prevalence of erosive esophagitis (EE) in patients with gastroesophageal reflux disease (GERD).* Dig Dis Week (May 20-23, Atlanta) 2001, Abst 1219.

Johnson, D.A. et al. *Impact of esomeprazole on symptom control in patients with healed erosive esophagitis (EE).* Dig Dis Week (May 20-23, Atlanta) 2001, Abst 2247.

Johnsson, F. et al. *One-week esomeprazole treatment: An effective confirmatory test in patients with suspected gastroesophageal reflux disease (GERD).* Gut 2001, 49(Suppl. 3): Abst 2265.

Malfertheiner, P. et al. *Role of H. pylori infection and gastritis phenotype in erosive vs nonerosive gastroesophageal reflux disease (GERD) - Analysis based on the ProGERD study initiative.* Dig Dis Week (May 20-23, Atlanta) 2001, Abst 2177.

Maton, P.N. et al. *Safety and efficacy of long term esomeprazole therapy in patients with healed erosive oesophagitis.* Drug Saf 2001, 24(8): 625.

Maton, P.N. et al. *The impact of baseline severity of erosive esophagitis (EE) on heartburn (HB) resolution in patients treated with esomeprazole or omeprazole.* Dig Dis Week (May 20-23, Atlanta) 2001, Abst 2221.

Richter, J.E. et al. *Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: A randomized controlled trial.* Am J Gastroenterol 2001, 96(3): 656.

Roach, A.C. et al. *Evidence-based analysis of the benefits of esomeprazole in the treatment of erosive esophagitis (EE).* Gut 2001, 49(Suppl. 3): Abst 2755.

Talley, N.J. et al. *Improvement in health-related quality of life following esomeprazole treatment in patients with endoscopy-neg-*

ative gastro-oesophageal reflux disease (GORD). Gut 2001, 49(Suppl. 3): Abst 2365.

Talley, N.J. et al. *On-demand treatment with esomeprazole: Relationship between dosing frequency and antacid use in patients with endoscopy-negative gastro-oesophageal reflux disease (GORD).* Gut 2001, 49(Suppl. 3): Abst 2366.

Talley, N.J. et al. *Why do patients with gastroesophageal reflux disease (GERD) have a poor health-related quality of life (HRQL)?* Dig Dis Week (May 20-23, Atlanta) 2001, Abst 2158.

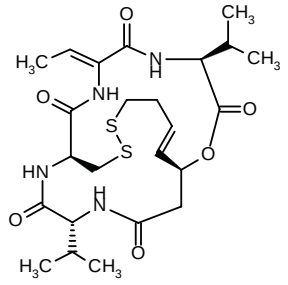
Vakil, N.B. et al. *Demographic characteristics as predictors of responses to treatment in patients with endoscopy-negative GERD.* Dig Dis Week (May 20-23, Atlanta) 2001, Abst 2157.

Vakil, N.B. et al. *Obesity, male gender and initially severe esophagitis are associated with relapse after initial healing of erosive esophagitis (EE).* Gut 2001, 49(Suppl. 3): Abst 2780.

FR-901228
NSC-630176
FK-228

Oncolytic

EN: 158963



$C_{24}H_{36}N_4O_6S_2$ **Fujisawa; Natl. Cancer Inst. (US)**

The molecular effects of various concentrations of FR-901228 were investigated in Ras-transformed and normal counterpart cells. In the Ras-transformed cells, FR-901228 suppressed the mitogenic pathway, activated the stress and apoptotic pathways and induced p33QIK kinase. P21Cip1 expression was unaffected. FR-901228 treatment of normal cells resulted in p33QIK and p21Cip1 induction. The differences in these effects may help explain the selectivity of FR-901228 for Ras-transformed cells (1).

1. Fecteau, K.A., Wang, H.R. *Molecular effect of an anticancer agent FR901228 on signaling pathways in normal and Ras-transformed cells.* Proc Amer Assoc Cancer Res 2001, 42: Abst 1113.

Original monograph - Drugs Fut 1999, 24: 1184.

Additional References

Ding, W. et al. *Gene therapy with wild-type p53 combined with histone deacetylase inhibitors.* Jpn J Cancer Res 2001, 92(Suppl.): Abst 747.

He, L.-Z. et al. *Histone deacetylase inhibitors induce remission in transgenic models of therapy-resistant acute promyelocytic leukemia.* J Clin Invest 2001, 108(9): 1321.

Kitazono, M. et al. *Construction of gene therapy vectors targeting thyroid cells. Enhancement of activity and specificity with histone deacetylase inhibitors and agents modulating the cAMP pathway. Demonstration of activity in folicular and anaplastic thyroid carcinoma cells.* Proc Amer Assoc Cancer Res 2001, 42: Abst 3708.

Kitazono, M. et al. *Low concentrations of the histone deacetylase inhibitor, depsipeptide (FR901228), increase expression of the Na^+/I^- symporter and iodine accumulation in poorly differentiated thyroid carcinoma cells.* J Clin Endocrinol Metab 2001, 86(7): 3430.

Naoe, Y. et al. *Prediction of antitumor effects of FK228 by gene expression.* Jpn J Cancer Res 2001, 92(Suppl.): Abst 636.

Piekarz, R. et al. *Histone deacetylase inhibitor for the treatment of peripheral or cutaneous T-cell lymphoma.* Proc Am Soc Clin Oncol 2001, 20(Part 2): Abst 2680.

Plekarz, R. et al. *Potential value of the histone deacetylase inhibitor depsipeptide (FR901228) in the treatment of peripheral and cutaneous T-cell lymphoma.* AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Oct 29-Nov 2, Miami Beach) 2001, Abst 360.

Schrump, D.S. et al. *5-Aza-2'-deoxycytidine (DAC) and depsipeptide FR901228 (DP) differentially mediate induction of cancer testis antigen and tumor suppressor gene expression in lung cancer cells.* Mol Biol New Ther Strategies: Cancer Res 21st Century (Feb 12-16, Maui) 2001, A-19.

Wei, M. et al. *Modifying effects of histone deacetylase inhibitor FK228 and cisplatin on N-butyl-N-(4-hydroxybutyl) nitrosamine-induced urinary bladder carcinogenesis in p53 (±) mice.* Jpn J Cancer Res 2001, 92(Suppl.): Abst 615.

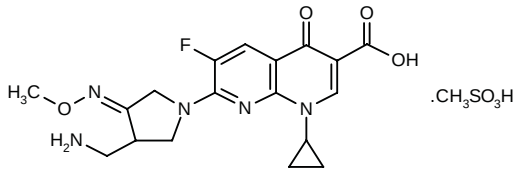
Weiser, T.S. et al. *Sequential 5-aza-2'-deoxycytidine-depsipeptide FR901228 treatment induces apoptosis preferentially in cancer cells and facilitates their recognition by cytolytic T lymphocytes specific for NY-ESO-1.* J Immunother 2001, 24(2): 151.

Yamamoto, S. et al. *Enhancement of suicide cancer gene therapy by a histone deacetylase inhibitor FR901228.* 4th Annu Meet Am Soc Gene Ther (May 30-June 3, Seattle) 2001, Abst 285.

Gemifloxacin Mesilate
Factive®

Naphthyridine Antibacterial

EN: 226496



$C_{18}H_{20}FN_5O_4.CH_4O_3S$ **LG Chem; GlaxoSmithKline**

Among 204 anaerobic isolates, gemifloxacin demonstrated selective activity against most *Peptostreptococcus*, *Porphyromonas* and *Fusobacterium* species and

variable activity against other Gram-negative anaerobes (1).

Scientists applied a new approach to the *in vitro* comparison of the animicrobial effects (AMEs) of gemifloxacin and ciprofloxacin on *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*. They calculated that a daily ciprofloxacin dose which would be as effective as 320 mg gemifloxacin against a hypothetical strain of *S. aureus* (with MICs = MIC_{50}s) would be as high as 2 x 3200 mg (2).

Gemifloxacin MICs were ≤ 0.5 μg/ml against all 2632 *Streptococcus pneumoniae* isolates tested in an international antimicrobial susceptibility study conducted between 1997-1999 (3).

Gemifloxacin was found to be very active against recent isolates of enteropathogenic bacteria, including *Salmonella* spp. (106), *Hafnia alvei* (32), *Yersinia enterocolitica* (22), *Shigella* spp. (21) and *Aeromonas* spp. (16), but not against *Campylobacter jejuni* (91) (4).

Gemifloxacin was found to rapidly penetrate human polymorphonuclear leukocytes, with intracellular concentrations 8 times higher than extracellular concentrations. Intracellular activity against *S. aureus* was seen with therapeutic extracellular gemifloxacin concentrations (5).

The *in vitro* activity of gemifloxacin against 400 isolates of β-haemolytic and viridans group streptococci was compared to that of 5 other quinolones and 6 other antimicrobial agents. The activity of the quinolones from highest to lowest was as follows: gemifloxacin, trovafloxacin, sparfloxacin, grepafloxacin, ciprofloxacin and levofloxacin (6).

In both rats and dogs, the principal metabolites formed after oral administration of gemifloxacin were the (*E*)-isomer and the acyl glucuronide of gemifloxacin (4-6% and 2-6% of dose, respectively). In rats, *N*-acetyl gemifloxacin (2-5% of dose) was formed. Following intravenous administration in dogs, gemifloxacin-related material was eliminated approximately equally by urinary excretion, biliary secretion and gastrointestinal secretion. In rats, urinary excretion accounted for a higher proportion of the dose (46%) than biliary secretion (12%) (7).

Drug concentrations and urine bactericidal titers against *E. coli* ATCC 25922 and *Staphylococcus saprophyticus* ATCC 1970 were determined after administration of gemifloxacin (320 mg) and trovafloxacin (200 mg) to healthy volunteers. Because of the effect of urine on the susceptibility of the *E. coli* strain, significantly lower urine bactericidal titers were found with gemifloxacin than was predicted, although they were significantly higher than those for trovafloxacin against the strains over 72 h (8).

Gemifloxacin (320 mg p.o. for 7 days) was found to reduce the numbers of enterobacteria, enterococci and streptococci in the aerobic intestinal microflora of healthy volunteers. The drug did not affect other aerobic microorganisms. The numbers of anaerobic cocci and lactobacilli were also decreased in the anaerobic microflora during drug administration (9).

Healthy male volunteers were administered oral gemifloxacin (160, 320, 480 and 640 mg once daily for 7 days) in studies to characterize the agent's pharmacokinetics and tolerability. The drug was generally well tolerated and demonstrated linear pharmacokinetics which were independent of dose (10).

A study of the pharmacokinetics and tissue penetration of single-dose gemifloxacin (320 mg) in 10 healthy volunteers found that the drug enters into inflammation sites in concentrations sufficient to inhibit many pathogens. The peak concentration in the inflammatory fluid was 0.74 ± 0.3 mg/l which was reached at a mean time of 3.40 ± 1.7 h; the mean penetration into inflammatory fluid was 61.19 ± 10.4% (11).

In a randomized, crossover, phase I trial in 12 healthy volunteers, both gemifloxacin and trovafloxacin were found to reduce the number of *Enterobacteriaceae* and aerobic Gram-positive organisms, whereas gemifloxacin was more effective than trovafloxacin in reducing *E. coli* and had lower MICs for quinolone-resistant *E. coli* strains (12).

A substudy of the Gemifloxacin Long-term Outcomes in Bronchitis Exacerbations (GLOBE) study examined data corresponding to 364 of the enrolled patients who were smokers or exsmokers. These patients were randomized to either once-daily gemifloxacin (320 mg) for 5 days or twice-daily clarithromycin (500 mg) for 7 days. Over 26 weeks, the St. George's Respiratory Questionnaire Total and Symptoms scores improved by 15 and 26.3 units, respectively, for patients receiving gemifloxacin, while these improvements were 12.4 and 20 units, respectively, for those administered clarithromycin. The results indicated that following acute exacerbation of chronic bronchitis, treatment with gemifloxacin was associated with better health than clarithromycin in this subpopulation (13).

Patients enrolled in the GLOBE study were also assessed for clinical status and the use of healthcare resources. By week 26, 71% of gemifloxacin-treated patients and 58.5% of clarithromycin-treated patients had their initial condition resolved and experienced no recurrences. In addition, fewer patients receiving gemifloxacin (5/214) were hospitalized for RTI-related events than clarithromycin patients (14/224) (14).

Humanistic outcomes were also evaluated as part of the GLOBE study. At 4, 12 and 26 weeks after acute treatment began, greater improvements in the total weighted St. George's Respiratory Questionnaire score were seen with gemifloxacin than with clarithromycin. Gemifloxacin-treated patients also had fewer days off from usual activities during the follow-up period. The percentages of patients experiencing a negative impact on their work performance due to bronchitis were 31.8 and 51.8% for gemifloxacin and clarithromycin, respectively,

at week 26. Those experiencing a negative impact on their usual activities due to bronchitis were 49.1 and 61.3% of gemifloxacin- and clarithromycin-treated patients, respectively, at week 26. Overall, humanistic outcomes were consistent with clinical findings from the study (15).

A double-blind, randomized, controlled trial has compared gemifloxacin 320 mg once daily for 5 days to clarithromycin 500 mg twice daily for 7 days in 709 chronic bronchitis patients with an acute exacerbation. The most common pathogen isolated was *Haemophilus influenzae*, which was eradicated in 7/7 gemifloxacin patients and 3/9 clarithromycin patients with evaluable sputum samples after 1 day of treatment. By day 6, *H. influenzae* was still present in 1 of the clarithromycin-treated patients and none of the gemifloxacin-treated patients. At follow-up, clinical success rates were similar for gemifloxacin and clarithromycin (85.4 *vs.* 84.6%), and bacteriological success rates favored gemifloxacin over clarithromycin (86.7 *vs.* 73.1%). Adverse events included diarrhea (6.6 and 8.4% for gemifloxacin and clarithromycin, respectively), headache (6.3 and 8.7% for gemifloxacin and clarithromycin, respectively) and taste perversion (0 and 5% for gemifloxacin and clarithromycin, respectively) (16).

A randomized, open, multicenter study in patients with community-acquired pneumonia was conducted to compare the efficacy of gemifloxacin (320 mg p.o. once daily for 7-14 days) with ceftriaxone (2 g i.v. 1-7 days) followed by cefuroxime (500 mg p.o. b.i.d. for 1-7 days). Patients in the ceftriaxone/cefuroxime group were also allowed to receive a macrolide. At 21-28 days posttherapy, the clinical success rates in the per protocol population were 92.2 and 93.4% for the gemifloxacin and ceftriaxone/cefuroxime groups, respectively. Respective bacteriological responses in this population were 90.6 and 87.3% for the gemifloxacin and ceftriaxone/cefuroxime groups. The gemifloxacin regimen, therefore, appeared to be as effective as the ceftriaxone/cefuroxime regimen for the treatment of community-acquired pneumonia (17).

Gemifloxacin and trovafloxacin were well tolerated and showed similar efficacy in treating acute exacerbations of chronic bronchitis in a randomized, double-blind study in 617 patients. Clinical and bacterial success rates were 91.5 and 86.8%, respectively, for gemifloxacin and 87.6 and 82.4%, respectively, for trovafloxacin (18).

A randomized, double-blind, multicenter, parallel-group study compared the efficacy and safety of gemifloxacin (320 mg once daily) and trovafloxacin (200 mg once daily) in 571 patients with community-acquired pneumonia. Gemifloxacin was safe and had a significantly superior clinical success rate in the intent-to-treat population compared to trovafloxacin (87.6 *vs.* 81.1%) (19).

The FDA has issued a nonapprovable letter for gemifloxacin mesilate (Factive®) for the treatment of respiratory tract infections. GlaxoSmithKline intends to work with the FDA to address issues raised in the letter (20).

1. Kleinkauf, N., Ackermann, G., Schaumann, R., Rodloff, A.C. *Comparative in vitro activities of gemifloxacin, other quinolones, and nonquinolone antimicrobials against obligately anaerobic bacteria.* Antimicrob Agents Chemother 2001, 45(6): 1896.

2. Firsov, A.A., Zinner, S.H., Lubenko, I.Y., Vostrov, S.N. *Gemifloxacin and ciprofloxacin pharmacodynamics in an in-vitro dynamic model: Prediction of the equivalent AUC/MIC breakpoints and doses.* Int J Antimicrob Agents 2000, 16(4): 407.

3. Hoban, D.J., Bouchillon, S.K., Karlowsky, J.A., Johnson, J.L., Butler, D.L., Miller, L.A., Poupard, J.A. *A comparative in vitro surveillance study of gemifloxacin activities against 2,632 recent Streptococcus pneumoniae isolates from across Europe, North America, and South America.* Antimicrob Agents Chemother 2000, 44(11): 3008.

4. Fernández-Roblas, R., Cabria, F., Esteban, J., López, J.C., Gadea, I., Soriano, F. *In vitro activity of gemifloxacin (SB-265805) compared with 14 other antimicrobials against intestinal pathogens.* J Antimicrob Chemother 2000, 46(6): 1023.

5. García, I., Pascual, A., Ballesta, S., Joyanes, P., Perea, E.J. *Intracellular penetration and activity of gemifloxacin in human polymorphonuclear leukocytes.* Antimicrob Agents Chemother 2000, 44(11): 3193.

6. Kerawala, M., Ambler, J.E., Lee, P.Y.C., Drabu, Y.J. *In vitro activity of gemifloxacin (SB-265805) compared to eleven other antimicrobial agents against streptococcal isolates, excluding Streptococcus pneumoniae.* Eur J Clin Microbiol Infect Dis 2001, 20(4): 271.

7. Ramji, J.V., Austin, N.E., Boyle, G.W. et al. *The disposition of gemifloxacin, a new fluoroquinolone antibiotic, in rats and dogs.* Drug Metab Dispos 2001, 29(4): 435.

8. García-Calvo, G., Parra, A., Aguilar, L., Ponte, C., Giménez, M.J., Carcas, A., Kinsig-Schippers, M., Soriano, F. *Antibacterial properties of gemifloxacin and trovafloxacin in urine ex vivo: Phase I study.* Antimicrob Agents Chemother 2001, 45(6): 1876.

9. Barker, P.J., Sheehan, R., Teillol-Foo, M., Palmgren, A.C., Nord, C.E. *Impact of gemifloxacin on the normal human intestinal microflora.* J Chemother 2001, 13(1): 47.

10. Allen, A., Bygate, E., Yousden, M., Oliver, S., Johnson, M., Ward, C., Cheon, A.-J., Choo, Y.S., Kim, I.-C. *Multiple-dose pharmacokinetics and tolerability of gemifloxacin administered orally to healthy volunteers.* Antimicrob Agents Chemother 2001, 45(2): 540.

11. Gee, T., Andrews, J.M., Ashby, J.P., Wise, R. *Pharmacokinetics and tissue penetration of gemifloxacin following a single oral dose.* J Antimicrob Chemother 2001, 47(4): 431.

12. García-Calvo, G., Molleja, A., Giménez, M.J., Parra, A., Nieto, E., Ponte, C., Aguilar, L., Soriano, F. *Effects of single oral doses of gemifloxacin (320 milligrams) versus trovafloxacin (200 milligrams) on fecal flora in healthy volunteers.* Antimicrob Agents Chemother 2001, 45(2): 608.

13. Jones, P.W. *Greater improvement in health status of smokers and ex-smokers treated for AECB with gemifloxacin versus clarithromycin: The GLOBE study.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P106.

14. Wilson, R., Ball, P., Mandell, L., File, T., Kirsch, J., Chinn, C., Henkel, T. *Gemifloxacin Long-term Outcomes in Bronchitis Exacerbations (GLOBE) study - An assessment of health out-*

come benefits in AECB patients following 5 days' gemifloxacin (GEMI) therapy. J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P108.

15. Kirsch, J.M., Statham, J., Wilson, R. *Humanistic outcome benefit of gemifloxacin versus clarithromycin for the treatment of AECB: The GLOBE study.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P109.

16. Wilson, R., Ball, P., Mandell, L., File, T., Henkel, T., Adelglass, J., Baird, I., Schentag, J. *Efficacy of once-daily gemifloxacin for 5 days compared with twice-daily clarithromycin for 7 days in the treatment of AECB.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P116.

17. Lode, H., File, T., Mandell, L., Ball, P., Pyopstra, R. *Efficacy of oral gemifloxacin (7-14 days) compared with intravenous ceftriaxone followed by oral cefuroxime (each given for 1-7 days, ± a macrolide) in the treatment of CAP.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P117.

18. Ball, P., Wilson, R., Mandell, L., Brown, J., Henkel, T. *Efficacy of gemifloxacin in acute exacerbations of chromic bronchitis: A randomised, double-blind comparison with trovafloxacin.* J Chemother 2001, 13(3): 288.

19. File, T.M. Jr., Sclemmer, B., Garau, J., Cupo, M., Young, C. *Efficacy and safety of gemifloxacin in the treatment of community-acquired pneumonia: A randomized, double-blind comparison with trovafloxacin.* J Antimicrob Chemother 2001, 48(1): 67.

20. *Factive denied approval by FDA.* DailyDrugNews.com (Daily Essentials) Dec 19, 2000.

Original monograph - Drugs Fut 1998, 23: 1199.

Additional References

Antoniadou, A. et al. *Comparative in vitro activity of gemifloxacin against Gram-positive and Gram-negative nosocomial isolates.* Clin Microbiol Infect 2001, 7(Suppl. 1): Abst P829.

Appelbaum, P.C. et al. *In vitro selection of resistance to gemifloxacin, trovafloxacin, ciprofloxacin, gatifloxacin and moxifloxacin in Streptococcus pneumoniae.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P61.

Ball, P. et al. *Efficacy and safety of gemifloxacin 320 mg once-daily for 7 days in the treatment of adult lower respiratory tract infections.* Int J Antimicrob Agents 2001, 18(1): 19.

Baltch, A.L. et al. *Antibacterial effect of gemifloxacin, comparative fluoroquinolones, and erythromycin against intracellular Legionella pneumophila and Legionella micdadei.* 39th Annu Meet Infect Dis Soc Am (Oct 25-28, San Francisco) 2001, Abst 566.

Bébéar, C.M. et al. *In vitro selection of resistance to gemifloxacin in two human mycoplasmas: Mycoplasma pneumoniae and Mycoplasma hominis.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P63.

Blondeau, J. et al. *Comparison of gemifloxacin, gatifloxacin, levofloxacin and moxifloxacin by the mutation prevention concentration (MPC) using a large number of clinical isolates of Streptococcus pneumoniae (SP).* Int J Antimicrob Agents 2001, 17(Suppl. 1): Abst EP3.05.

Blondeau, J.M. et al. *The mutant prevention concentration (MPC) of gemifloxacin against clinical isolates of Streptococcus pneumoniae (SP) that were susceptible (PS), intermediate (PI) or resistant (PR) to penicillin.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P81.

Blondeau, J.M. et al. *The relationship between the mutant prevention concentration (MPC) of fluoroquinolones (FQ) against Streptococcus pneumoniae (SP) and the 24 hour dose response curves.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P71.

Boos, M. et al. *Dissociated development of resistance among six fluoroquinolones in Streptococcus pneumoniae and Streptococcus pyogenes.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P72A.

Bowker, K.E. et al. *Comparative anti-pneumococcal effects of gemifloxacin and moxifloxacin investigated using a pharmacokinetic model of infection.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P88.

Davidson, R.J. et al. *In-vitro selection of fluoroquinolone resistance in Streptococcus pneumoniae.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P69.

Edelstein, P.H. et al. *In vitro activity of gemifloxacin (SB-265805, LB20304a) against Legionella pneumophila and its pharmacokinetics in guinea pigs with L. pneumophila pneumonia.* Antimicrob Agents Chemother 2001, 45(8): 2204.

Felmingham, D. et al. *The Alexander project 2000: European surveillance data.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P33.

Firsov, A. et al. *Different integral endpoints of the total antimicrobial effect at clinically achievable ratios of area under the curve to MIC: The pharmacodynamics of gemifloxacin with Moraxella catarrhalis in an in vitro dynamic model.* Clin Microbiol Infect 2001, 7(Suppl. 1): Abst P828.

Fisher, L.M. et al. *Cleavable complex formation with wild-type and mutant Streptococcus pneumoniae topoisoimerases targets by gemifloxacin, an enhanced-affinity fluoroquinolone.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P30.

Gee, T. et al. *Comparative in vitro activity of gemifloxacin against clinical isolates.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P22.

Goldstein, E.J.C. et al. *Comparative in vitro activity of gemifloxacin against aerobic and anaerobic pathogens isolated from antral sinus punctures from patients with sinusitis.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P23.

Halpern, M.T. et al. *Cost-effectiveness of gemifloxacin versus clarithromycin in the treatment of AECB: The GLOBE study.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P107.

Hansen, H. et al. *Effect of gemifloxacin on in vitro selected mutants and field isolates of Salmonella spp. with mutations in gyra, gyrb, parc and marr.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P80.

Hoban, D.J. et al. *Molecular characterization of fluoroquinolone resistant Streptococcus pneumoniae clinical isolates obtained from across Canada.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P62.

Hong, C.Y. et al. *Discovery of gemifloxacin (Factive, LB20304a): A quinolone of a new generation.* Farmaco 2001, 56(1-2): 41.

Kang, M.W. et al. *In vitro activity of gemifloxacin against recent clinical isolates of bacteria in Korea.* Int J Antimicrob Agents 2001, 17(Suppl. 1): Abst P19.042.

Kutlin, A. et al. *Effect of gemifloxacin on viability of Chlamydia pneumoniae in an in vitro continuous infection model.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P21.

Le, T.P., Xiong, Y.-Q. *Gemifloxacin.* Drugs Today 2001, 37(6): 401.

Lewis, R.J. et al. *The real-time effect of gemifloxacin on self-bioluminescent clinical isolates of bacteria.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P54.

Lopez, H. et al. *Comparative in vitro activity of gemifloxacin against Gram-positive and Gram-negative clinical isolates in Argentina.* Diagn Microbiol Infect Dis 2001, 40(4): 187.

Lubenko, I. et al. *Gemifloxacin and ciprofloxacin pharmacodynamics against Haemophilus influenzae and Moraxella catarrhalis.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P96.

Lubenko, I. et al. *Gemifloxacin versus ciprofloxacin against Moraxella catarrhalis in an in vitro dynamic model.* Int J Antimicrob Agents 2001, 17(Suppl. 1): Abst P9.022.

Martínez-Martínez, L. et al. *Activities of gemifloxacin and five other antimicrobial agents against Listeria monocytogenes and coryneform bacteria isolated from clinical samples.* Antimicrob Agents Chemother 2001, 45(8): 2390.

Minehart, H.W., Chalker, A.F. *In vitro activity of gemifloxacin against Helicobacter pylori.* J Antimicrob Chemother 2001, 47(3): 360.

Morrissey, I. et al. *The bactericidal activity of fluoroquinolones (FQS) against S. pneumoniae (SP) at peak lung tissue concentrations.* Int J Antimicrob Agents 2001, 17(Suppl. 1): Abst P19.018.

Puthisigamani, M. et al. *Gemifloxacin (Gemi) pharmacokinetic (PK) and pharmacodynamic (PD) studies using isogenic Streptococcus pneumoniae (Spn): Wild type (WT) ± efflux pumps (EP) ± a ParC mutation in a murine thigh infection model (MTIM).* 39th Annu Meet Infect Dis Soc Am (Oct 25-28, San Francisco) 2001, Abst 471.

Saravolatz, L. et al. *In vitro activity and pharmacodynamics of nine quinolones tested against S. pneumoniae.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P100.

Souli, M. et al. *In vitro activity of newer versus older quinolones against 723 recent nosocomial isolates collected in Greece.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P59.

Vostrov, S. et al. *Interspecies prediction of the antimicrobial effects of gemifloxacin and ciprofloxacin on Haemophilus influenzae based on the comparative pharmacodynamic studies in an in vitro model.* Clin Microbiol Infect 2001, 7(Suppl. 1): Abst P827.

Wedermann, B. et al. *In vitro pharmacology of modern quinolones against respiratory tract pathogens.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P99.

Woodnutt, G. et al. *Efficacy of gemifloxacin against experimental respiratory tract infections in rats caused by Streptococcus pneumoniae.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P86.

Wootton, M. et al. *In-vitro activity of four fluoroquinolones (FQ) against hetero-vancomycin intermediate Staphylococcus aureus (H-VISA) and VISA.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P49.

Zhanel, G.G. et al. *Pharmacodynamic activity of respiratory fluoroquinolones (FQ) versus ciprofloxacin-resistant Streptococcus pneumoniae (CIP-R SPN) using an in vitro model.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P94.

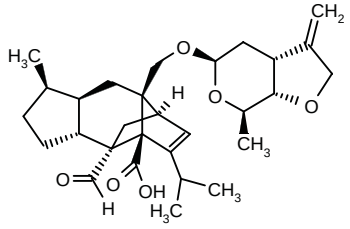
Zinner, S. et al. *Strain-independent anti-pneumococcal effects of gemifloxacin in an in vitro dynamic model.* J Antimicrob Chemother 2001, 47(Suppl. 1): Abst P97.

Zinner, S.H. et al. *Comparative anti-staphylococcal effects of gemifloxacin and trovafloxacin in an in vitro dynamic model in terms of AUC/MIC and dose relationships.* Diagn Microbiol Infect Dis 2001, 40(4): 167.

GM-237354

Antifungal

EN: 250638



$C_{29}H_{40}O_6$ **GlaxoSmithKline**

GM-237354 demonstrated efficacy in an experimental oral *Candida albicans* infection model in immunosuppressed rats. Treatment with 15 or 30 mg/kg/day for 1 week and 30 mg/kg/day for 4 days completely eliminated *C. albicans* as measured in oral swabs from infected rats (1).

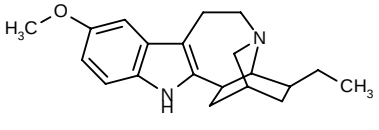
1. Martinez, A., Regadera, J., Jimenez, E., Santos, I.N., Gargallo-Viola, D. *Antifungal efficacy of GM237354, a sordarin derivative, in experimental oral candidiasis in immunosuppressed rats.* Antimicrob Agents Chemother 2001, 45(4): 1008.

Original monograph - Drugs Fut 1997, 22: 1221.

Ibogaine
Endabuse®

Narcotics Antagonist

EN: 119975



$C_{20}H_{26}N_2O$ **NDA Int.; OmniChem**

When administered to rats, dose-related increases in tremors were seen with ibogaine but not with its metabolite noribogaine. Ibogaine also stimulated corticosterone secretion more potently than noribogaine, although significant elevations in plasma corticosterone and prolactin were seen with both drugs. Noribogaine was more potent than ibogaine in increasing extracellular serotonin levels, but neither drug affected extracellular dopamine levels. Results indicated that the metabolite might be safer than the parent drug for development as a medication (1).

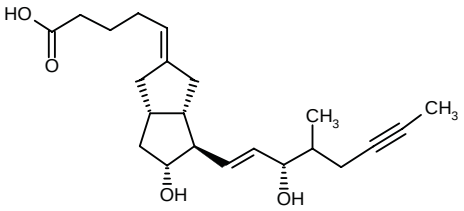
  CCC: 0377-8282/2001

1. Baumann, M.H., Rothman, R.B., Pablo, J.P., Mash, D.C. *In vivo neurobiological effects of ibogaine and its O-desmethyl metabolite, 12-hydroxyibogamine (noribogamine), in rats.* J Pharmacol Exp Ther 2001, 297(2): 531.

Original monograph - Drugs Fut 1996, 21: 1109.

Iloprost *Treatment of Peripheral Vascular Disease*
Ilomedin® *Treatment of Pulmonary Hypertension*
Ilomédine®

EN: 117952



$C_{22}H_{32}O_4$ **Berlex; Schering AG; Eisai**

Investigators have examined the effects of aerosolized iloprost, sildenafil citrate given orally and combination of the two treatments in 8 patients with pulmonary hypertension. Iloprost was more effective in reducing mean pulmonary arterial pressure than sildenafil, but combination of the two drugs was significantly more effective than iloprost alone. None of the treatments produced significant alterations in heart rate or systemic arterial pressure (1).

1. Wilkens, H., Groechil-Guth, A., Koening, J., Forestier, N., Boehm, M., Sybrecht, G.W. *Inhaled iloprost plus oral sildenafil in patients with pulmonary hypertension.* Eur Respir J 2001, 18(Suppl. 33): Abst 2162.

Original monograph - Drugs Fut 1981, 6: 676.

Additional References

Allcock, R.J. et al. *Nebulised iloprost for pulmonary arterial hypertension associated with congenital heart disease: One centre's experience.* Eur Respir J 2001, 18(Suppl. 33): Abst 2166.

Baumgartner, R. et al. *Acute effects, 1-year, and 2-year follow up of iloprost-aerosol therapy in severe primary pulmonary hypertension.* Eur Respir J 2001, 18(Suppl. 33): Abst 2161.

Behr, J. et al. *Acute effects and 1-year follow-up of iloprost-aerosol therapy in severe primary and secondary pulmonary hypertension.* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A540.

Behr, J. et al. *Consistency of the acute hemodynamic response to inhaled iloprost in pulmonary hypertension patients treated long-term with iloprost aerosol.* Eur Respir J 2001, 18(Suppl. 33): Abst 2160.

Blumberg, F.C. et al. *Effects of aerosolized iloprost in pulmonary hypertension at rest and during exercise.* Eur Respir J 2001, 18(Suppl. 33): Abst 2165.

Caneva, J.O. et al. *Acute hemodynamic effects of nebulized iloprost in severe pulmonary hypertension.* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A114.

Ewert, R. et al. *Iloprost as inhalative or intravenous long-term treatment of patients with primary pulmonary hypertension. Register of the Berlin Study Group for Pulmonary Hypertension.* Z Kardiol 2000, 89(11): 987.

Fruhwald, F. et al. *Monitoring the effect of inhaled iloprost in pulmonary hypertension using an implantable haemodynamic monitor (Chronicle).* Eur Heart J 2001, 22(Suppl.): Abst P1726.

Gessler, T. et al. *Co-application of oxygen improves iloprost inhalation in pulmonary hypertension patients with long-term oxygen therapy.* Eur Respir J 2001, 18(Suppl. 33): Abst 2163.

Higenbottam, T., Siddons, T. *Trials of inhaled iloprost and other new vasodilating prostaglandins.* Eur Respir J 2001, 17(1): 6.

Machherndl, S. et al. *Long-term treatment of pulmonary hypertension with aerosolized iloprost.* Eur Respir J 2001, 17(1): 8.

Nikkho, S. et al. *One-year observation of iloprost inhalation therapy in patients with pulmonary hypertension.* Eur Respir J 2001, 18(Suppl. 33): Abst 2164.

Phillips, P.G. et al. *The effect of iloprost and phosphodiesterase inhibitors on chronic hypoxia-induced pulmonary hypertension.* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A114.

Schaar, J. et al. *A new treatment of pulmonary hypertension: Simultaneous pursatile inhalation of nitric oxide and iloprost.* J Am Coll Cardiol 2001, 37(2, Suppl. A): 243A.

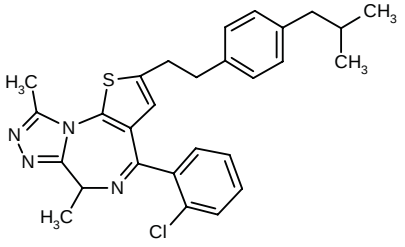
Schermuly, R.T. et al. *Combined inhalation of iloprost and phosphodiesterase (PDE) inhibitors in a model of acute pulmonary hypertension.* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A115.

Schermuly, R.T. et al. *Combined inhalation of iloprost and the dual selective phosphodiesterase (PDE) inhibitor tolafentrine in a model of acute pulmonary hypertension.* Eur Respir J 2001, 18(Suppl. 33): Abst P1398.

Wiedemann, R. et al. *Atrial natriuretic peptide in severe primary and secondary pulmonary hypertension — response to iloprost inhalation.* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A396.

Israpafant *Antiallergy/Antiasthmatic*
Pafnol®

EN: 144822



$C_{28}H_{29}ClN_4S$ **Welfide**

Pretreatment of rats with Y-24180 (0.3 and 3 mg/kg i.v.) had a protective effect against ciclosporin-induced acute renal failure, suggesting that platelet-activating factor is involved in renal vasoconstriction induced by ciclosporin. Study results provide further evidence for the

contribution of endothelin-1 to ciclosporin-induced nephrotoxicity (1).

Y-24180 was investigated in allergic cutaneous reactions in actively sensitized mice. Both oral Y-24180 (twice daily) and topical hydrocortisone (once daily) inhibited increases in ear thickness at 1 h (immediate phase reaction) and at 24 h (late phase reaction); Y-24180 enhanced the effect of hydrocortisone when administered in combination (2).

1. Kawaguchi, A., Sugimoto, K., Fujimura, A. *Preventive effect of platelet-activating factor antagonist, Y-24180, against cyclosporine-induced acute nephrotoxicity.* Life Sci 2001, 68(10): 1181.

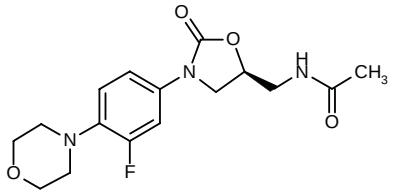
2. Yamaguchi, S., Tomomatsu, N., Komatsu, H. *Effect of Y-24180, a receptor antagonist to platelet-activating factor (PAF), on allergic cutaneous reactions in actively sensitized mice.* Inflamm Res 2000, 49(11): 584.

Original monograph - Drugs Fut 1993, 18: 1016.

Linezolid
Zyvox®
Zyvoxam®
Zyvoxid®

Oxazolidinone Antibacterial

EN: 224298



$C_{16}H_{20}FN_3O_4$ **Pharmacia**

Topical ophthalmic compositions containing an oxazolidinone antibiotic are claimed to be useful for the treatment or prevention of ocular infections. Particularly preferred is an aqueous polymeric suspension containing 0.1-2% of the antibiotic linezolid and 0.1-10% of a water-swellable, water-insoluble crosslinked carboxy-vinyl polymer (1).

What appears to be the first case of a patient infected with a strain of *Staphylococcus aureus* resistant to linezolid has been reported. The patient, an 85-year-old man being treated for dialysis-associated peritonitis, was also resistant to methicillin. Minimum inhibitory concentrations (MICs) of linezolid recovered from the patient's peritoneal dialysis fluid over a 3-week period were 32 mg/l for linezolid-resistant isolates. Treatment with other antimicrobials was successful. Representatives from the manufacturer noted that no other cases of linezolid-resistant *S. aureus* have been found, despite the fact that more than 80,000 patients have been treated with the drug. They also note that the patient in question met many of the criteria defining risk for the development of resistance and that until more cases are reported, the significance of the discovery will be difficult to judge (2).

Due to reports from the spontaneous reporting system of myelosuppression in patients receiving Zyvox®, new safety information has been added to the prescribing information for linezolid injection, tablets and oral suspension. The drug is indicated for the treatment of adult patients with infections caused by susceptible strains of vancomycin-resistant *Enterococcus faecium*, nosocomial pneumonia, complicated and uncomplicated skin and skin structure infections and community-acquired pneumonia, including cases with concurrent bacteremia (3).

Since April 2001, linezolid has been approved in Japan (Zyvox®), Canada (Zyvoxam®) and the E.U. (Zyvoxid®) (4-6).

1. Bowman, L.M. et al. (InSite Vision Inc.). *Topical treatment for prevention of ocular infections.* WO 0119366.

2. Tsiodras, S., Gold, H.S., Sakoulas, G., Eliopoulos, G.M., Venkataraman, C., Moellering, R.C. Jr., Ferraro, M.J. *Linezolid resistance in a clinical isolate of Staphylococcus aureus.* Lancet 2001, 358(9277): 207.

3. *New safety data added to Zyvox prescribing information.* DailyDrugNews.com (Daily Essentials) March 5, 2001.

4. *Japanese approval of Zyvox marks achievement of regulatory milestone.* DailyDrugNews.com (Daily Essentials) April 9, 2001.

5. *Pharmacia's Zyvoxam approved in Canada for Gram-positive bacterial infections.* DailyDrugNews.com (Daily Essentials) May 10, 2001.

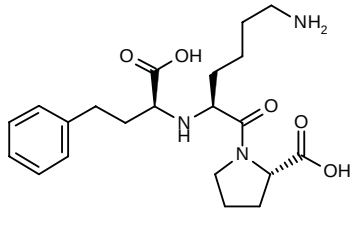
6. *Q2 2001 at Pharmacia marked by three E.U. approvals, making way for upcoming market launches.* DailyDrugNews.com (Daily Essentials) Aug 2, 2001.

Original monograph - Drugs Fut 1996, 21: 1116.

Lisinopril
Zestril®

Antihypertensive
Treatment of Heart Failure

EN: 090853



$C_{21}H_{31}N_3O_5$ **Merck & Co.; AstraZeneca**

A *post-hoc* analysis of the ATLAS (Assessment of Treatment with Lisinopril And Survival) trial comprising over 3000 patients with chronic heart failure who were treated with low (2.5-5.0 mg/day) or high doses (32.5-

  CCC: 0377-8282/2001

35.0 mg/day) of lisinopril was reported. This study served to elucidate the sequence of events in heart failure progression. Over half of the patients (61.1%) had a least one cardiovascular hospitalization during the study and just under half (42.5%) of all patients died, mainly cardiovascular deaths. The results indicated that vascular events (arrhythmias and myocardial infarction/unstable angina) and possibly also ventricular remodeling, were the major mechanisms underlying the progression of heart failure and sudden death. Compared with low-dose lisinopril, high doses of the drug were associated with a reduced risk of death or hospitalization for any reason, and of death or hospitalization for worsening heart failure. Time to all-cause mortality and hospitalization for chronic heart failure were also delayed on high-dose lisinopril, suggesting vascular protective effects for the ACE inhibitor (1).

A recent study demonstrated that prophylactic therapy with lisinopril was effective in the prevention of migraine. This randomized, double-blind, placebo-controlled, crossover study assessed the effects of lisinopril in 60 subjects aged 19-59 years who experienced 2-6 migraine attacks per month. Half of the participants received 10 mg lisinopril once daily for the first week, followed by 20 mg lisinopril once daily for 11 weeks, and the other half received placebo. Following a 2-week washout period, participants were crossed over to the alternative sequence of treatment. Lisinopril at 20 mg/day significantly reduced hours with headache by 20%, days with headache by 17% and days with migraine by 21% as compared to placebo. In addition, the headache severity index scores showed a 20% reduction in patients receiving lisinopril as compared to those receiving placebo. Overall, prophylactic therapy with lisinopril improved primary efficacy parameters by about 20% as compared to placebo and by about 30% as compared to baseline. During treatment with lisinopril, mean blood pressure was 121/78 mmHg and mean heart rate was 69 beats/min, as compared to 128/83 mmHg and 71 beats/min during treatment with placebo. Treatment was generally well tolerated, with dizziness, dry cough, fatigue and a tendency to faint being the most frequently reported adverse events. The researchers suggested that the prophylactic efficacy of lisinopril may be related to the recent finding that migraine without aura appears to be more common in individuals with the ACE DD gene. Lisinopril is currently indicated for the treatment of hypertension, as adjunctive therapy in the management of heart failure in patients not responding adequately to diuretics and digitalis, and for the treatment of hemodynamically stable patients within 24 h of acute myocardial infarction to improve survival (2).

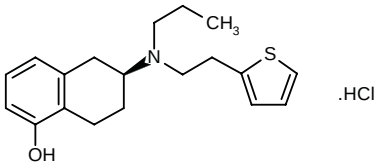
1. Cleland, J.G.F., Thygesen, K., Uretsky, B.F. et al. *Cardiovascular critical events pathways for the progression of heart failure.* Eur Heart J 2001, 22(17): 1601.

2. Schrader, H., Sand, T., Sand, T., Helde, G., Bovim, G. *Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): Randomised, placebo controlled, crossover study.* Br Med J 2001, 322(7277): 19.

Original monograph - Drugs Fut 1983, 8: 925.

N-0923 *Antiparkinsonian*
Rotigotine Hydrochloride

EN: 171120



.HCl

$C_{19}H_{25}NOS.HCl$ **Discovery Therapeutics; Schwarz**

In a randomized study, 242 patients with early PD received placebo or rotigotine at doses of 4.5, 9.0, 13.5 or 18.0 mg daily. The study protocol included a 4-week dose-titration period, a 7-week dose maintenance period, a 1-week dose deescalation period and a 2-week safety follow-up period. At week 11, patients randomized to the 13.5 and 18 mg doses showed significant improvements in the Activities of Daily Living and Motor components of the Unified Parkinson's Disease Rating Scale (UPDRS II/III), the primary study endpoint. The changes in UPDRS II/III scores between baseline and week 11 as compared to placebo were 1.4 units (4.5 mg dose), 2.6 units (9.0 mg dose), 5.1 units (13.5 mg dose) and 5.2 units (18.0 mg dose). Rotigotine was generally well tolerated, with nausea, vomiting, fatigue and somnolence being the main adverse effects. Application site skin reactions were also more common in the higher dosage groups (1).

The efficacy and safety of rotigotine as an adjunctive therapy to levodopa were assessed in patients with advanced Parkinson's disease and levodopa-induced motor fluctuations. In a multicenter, double-blind, placebo-controlled trial, 324 patients were randomized to placebo or rotigotine at a dose of 9, 18 or 27 mg daily. Following a 5-week dose-titration period, patients were maintained at target doses for 7 weeks, then followed for safety for 2 additional weeks. No significant differences in the change from baseline to end of treatment in absolute time spent "off," the primary efficacy endpoint, were observed between the placebo and rotigotine groups, possibly due to a large placebo effect. However, the magnitude of decrease in time spent "off" was greatest in the 27 mg rotigotine group (2.44 h), as compared to 1.72, 2.12 and 1.81 h for the 18 mg and 9 mg rotigotine groups and placebo, respectively. In the subgroup of patients with Hoehn and Yahr stage 4 and 5 disease and no major

protocol violations, the reduction in "off" time was even greater: 2.88 h (27 mg dose), 2.74 h (18 mg dose), 2.49 h (9 mg dose) and 1.96 h (placebo). The rotigotine transdermal delivery system was well tolerated and most patients rated patch handling as good or excellent (2).

A double-blind, randomized, placebo-controlled phase II trial examined the efficacy of N-0923 TDS for replacing levodopa in 85 Parkinson's disease patients. The patients were randomized to placebo or N-0923 at doses of 8.4, 16.8, 33.5 or 67 mg over 21 days. The primary efficacy endpoint was achieved on the two higher doses. Doses of 33.5 and 67 mg N-0923 produced significant reductions in levodopa use of 26 and 28%, respectively, compared to 7% on placebo. The transdermal therapy was well tolerated, with mostly mild adverse events typical of dopaminergic agonists or transdermal patches (3).

The Parkinson patch concept and design of the clinical phase III trials for rotigotine TDS were presented to regulatory agencies in the U.S. and Europe. Both authorities have approved the proposed study, and the phase III program was scheduled begin in the fall 2001 (4).

Rotigotine hydrochloride is the proposed international nonproprietary name for N-0923 (5).

1. Fahn, S. *Rotigotine transdermal system (SPM-962) is safe and effective as monotherapy in early Parkinson's disease (PD).* Parkinsonism Relat Disord 2001, 7(Suppl. 1): Abst P-TU-181.

2. Quinn, N. *Rotigotine transdermal delivery system (TDS) (SPM 962) - A multicenter, double-blind, randomized, placebo-controlled trial to assess the safety and efficacy of rotigotine TDS in patients with advanced Parkinson's disease.* Parkinsonism Relat Disord 2001, 7(Suppl. 1): Abst P-TU-223.

3. Hutton, J.T., Metman, L.V., Chase, T.N. et al. *Transdermal dopaminergic D_2 receptor agonist therapy in Parkinson's disease with N-0923 TDS: A double-blind, placebo-controlled study.* Mov Disord 2001, 16(3): 459.

4. *Schwarz updates clinical trial programs.* DailyDrugNews.com (Daily Essentials) Aug 23, 2001.

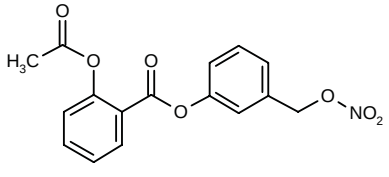
5. *Proposed international nonproprietary names (Prop. INN): List 83.* WHO Drug Inf 2000, 14(2): 129.

Original monograph - Drugs Fut 1993, 18: 1005.

NCX-4016

Nitric Oxide Donor

EN: 252036



$C_{16}H_{13}NO_7$ **NicOx**

Rats administered aspirin and celecoxib were found to have gastric mucosal damage, possibly due to inhibition of gastric cyclooxygenase-2. In contrast, rats administered NCX-4016 and celecoxib had mucosal damage only with the highest dose (30 mg) of celecoxib, indicating that NCX-4016 does not potentiate the detrimental effects of celecoxib on gastric mucosa (1).

The results of a study on the neuroprotective effects of NCX-4016 in rats with permanent focal cerebral ischemia indicated that nitric oxide release associated with aspirin provides neuroprotection against ischemic injury. Analysis of rat brains 24 h after treatment revealed that NCX-4016 significantly reduced total infarct volume compared to treatment with acetylsalicylic acid (–20%), tacrolimus (–18%) and vehicle (–20%) (2).

The gastric toxic effects of aspirin (100 mg/kg) and NCX-4016 (190 mg/kg) were compared in normal, cirrhotic and arthritic rats. Arthritic and cirrhotic rats were found to be more susceptible to gastric mucosal damage induced by aspirin due in part to acid hypersecretion. The animals experienced less gastric toxicity with NCX-4016 due to increased gastric mucosal blood flow mediated by nitric oxide released by the drug (3).

The cardioprotective effects of NCX-4016 were evaluated in anesthetized rats subjected to myocardial ischemia (30 min) and reperfusion (120 min) and compared to those of aspirin. Both drugs were administered orally for 5 days, NCX-4016 at doses of 10, 30 or 100 mg/kg and aspirin at a dose of 54 mg/kg. NCX-4016 produced marked and dose-dependent cardioprotection, evidenced by increased survival and reductions in the number of ventricular premature beats, the incidence of ventricular tachycardia and fibrillation and infarct size, whereas aspirin was significantly less effective. For example, the highest dose of NCX-4016 completely prevented mortality, reduced the incidence of ventricular tachycardia and ventricular fibrillation from 100% and 59%, respectively, during ischemia in vehicle-treated animals to 36% and 14%, respectively, reduced the number of ventricular premature beats by 72% and reduced infarct size from 60.1% of area at risk to 22.7%. Plasma creatine phosphokinase and cardiac myeloperoxidase activities were also significantly reduced on NCX-4016 compared to both vehicle and aspirin. The addition of NCX-4016 (100 mg/kg p.o.) was associated with a marked attenuation of the aggravation of myocardial damage induced by L-NAME, confirming that the beneficial effects of the nitroderivative are due mainly to the nitric oxide moiety (4).

A study in LDL cholesterol receptor-deficient mice investigated the preventive and therapeutic effects of NCX-4016 on restenosis after balloon angioplasty. NCX-4016 significantly reduced vascular smooth muscle cell (VSMC) proliferation and macrophage deposition at the site of injury. By comparison, aspirin produced a more modest reduction in VSMC proliferation and did not significantly inhibit macrophage deposition. Both NCX-4016 and aspirin significantly reduced the neointimal global area as compared to controls, but mice treated with

  CCC: 0377-8282/2001

NCX-4016 showed lower neointimal hyperplasia and cell density as compared to those receiving aspirin. When administered 7 days prior to and 21 days after balloon injury, NCX-4016 showed greater beneficial effects than when administered only after injury. Overall, NCX-4016 at the lowest dose tested (10 mg/kg) reduced all parameters related to restenosis as compared to both controls and aspirin at the highest dose tested (54 mg/kg). NCX-4016 may therefore have potential for reducing restenosis in individuals with concomitant hypercholesterolemia and/or gastrointestinal damage (5).

Preclinical data showed that the daily administration of NCX-4016 prevented neointimal thickening in pig vein grafts 1 month after implantation. Following vein grafting of the saphenous vein-carotid artery performed in pigs, NCX-4016 (60 mg/kg) or placebo was administered orally once daily for 1 month. Grafts were then removed, pressure-fixed and their surface studied using planimetry. Data indicated that there was a highly significant reduction in neointimal thickness in animals treated with NCX-4016 compared to placebo. These study results, together with published antithrombotic effects, could make NCX-4016 a valuable drug for treating both early and late vein graft failure, and clinical trials for this indication are expected to begin next year (6).

1. Fiorucci, S., Mencarelli, A., Palazzetti, B. *COX-2 selective inhibitors cause gastric damage in aspirin treated rats. Protective effect of nitroaspirin (NCX-4016).* Dig Dis Week (May 20-23, Atlanta) 2001, Abst 3023.

2. Fredduzzi, S., Mariucci, G., Tantucci, M., Del Soldato, P., Ambrosini, M.V. *Nitro-aspirin (NCX 4016) reduces brain damage induced by focal cerebral ischemia in the rat.* Neurosci Lett 2001, 302(2-3): 121.

3. Kato, S. et al. *Low gastric toxicity of nitric oxide-releasing aspirin, NCX-4016, in rats with cirrhosis and arthritis.* Dig Dis Week (May 20-23, Atlanta) 2001, Abst 782.

4. Rossoni, G., Manfredi, B., Colonna, V.D.G., Bernareggi, M., Berti, F. *The nitroderivative of aspirin, NCX 4016, reduces infarct size caused by myocardial ischemia-reperfusion in the anesthetized rat.* J Pharmacol Exp Ther 2001, 297(1): 380.

5. Napoli, C., Del Soldato, P., Cirino, G., Sorrentino, R., Sica, V., Condorelli, M., Pinyo, A., Ignarro, L.J. *Effects of nitric oxide-releasing aspirin versus aspirin on restenosis in hypercholesterolemic mice.* Proc Natl Acad Sci USA 2001, 98(5): 2860.

6. *Preclinical data show NO-aspirin efficacy in preventing vein graft failure.* DailyDrugNews.com (Daily Essentials) Nov 27, 2000.

Original monograph - Drugs Fut 1997, 22: 1231.

Additional References

Minuz, P. et al. *NCX 4016 (NO-aspirin) inhibits tissue factor expression and cytokine release in stimulated human monocytes.* Thromb Haemost 2001, (Suppl.): Abst P1620.

Riffaud, J.P. et al. *Antiproliferative potential of new NO-NSAIDs on human bladder and prostate cell lines.* Inflamm Res 2001, 50(Suppl. 3): Abst 071.

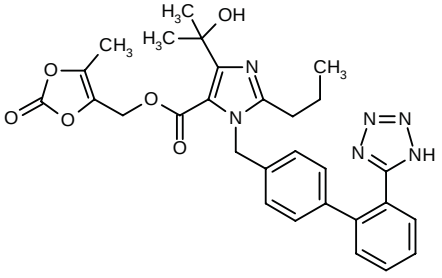
Takemura, S. et al. *Effect of NO-aspirin on metastatic colon cancer in rats.* Jpn J Cancer Res 2001, 92(Suppl.): Abst 449.

Wainwright, C.L. et al. *NO-aspirin, but not naive aspirin, reduces myocardial infarct size in anaesthetised pigs subjected to ischaemia/reperfusion.* Br J Pharmacol 2000, 131(Suppl.): Abst 164P.

Olmesartan Medoxomil Benevas®

Antihypertensive

EN: 217950



$C_{29}H_{30}N_6O_6$ **Sankyo; Recordati; Menarini**

Olmesartan exhibited selectivity for the angiotensin II AT_1 receptor binding site in *in vitro* pharmacological models and potent, long-lasting and dose-dependent antihypertensive activity in a variety of rat and dog models of hypertension (1).

The potential of CS-866 as a treatment for diabetic nephropathy and atherosclerosis was revealed in animal models of these conditions. In the Zucker diabetic fatty rat, CS-866 in the diet brought about dose-dependent reductions in urinary protein excretion. In monkeys fed a high-fat diet, CS-866-treated animals had a reduction in plaque area in the aorta of 64% as compared to controls. In a rabbit model of atherosclerosis, CS-866 treatment reduced the lesion area by 40% and by 50% when given in combination with pravastatin as compared to controls (2).

The authors of an open, phase I study comparing olmesartan 10 mg/day in 26 patients with varying degrees of renal impairment to the same treatment in 8 healthy volunteers concluded that dose adjustments were unnecessary in patients with mild to moderate renal dysfunction. The drug was well tolerated in all groups (3).

Though increased plasma concentrations of olmesartan were found in elderly and very elderly patients as well as in those with mild and moderate renal and hepatic impairment, dose adjustment for these patients is not considered necessary. Dose adjustments are recommended, however, for patients with severe renal impairment (4).

The use of single-dose clinical pharmacological studies of drugs affecting the renin-angiotensin system in healthy volunteers and in salt-depleted subjects was validated by comparison of two such studies of olmesartan to results from a conventional dose-finding study of the drug in patients with mild to moderate hypertension. All of

the studies gave similar indications as to the effective dose range of olmesartan (5).

In an open, randomized phase I trial, 12 healthy volunteers received aluminium magnesium hydroxide (800 mg q.i.d.) for 8 days in combination with olmesartan (20 mg o.d.) on days 4-8. After 1-2 weeks of washout, olmesartan (20 mg o.d.) was given alone for 5 days. The treatment sequence was reversed in another group of 12 volunteers. Although coadministration of the drugs lowered the bioavailability of olmesartan, the reduction was slight and no dose adjustments were believed to be necessary for concomitant olmesartan plus aluminium magnesium hydroxide use (6).

A randomized, double-blind, placebo-controlled phase I study examined the influence of olmesartan on the pharmacodynamics, pharmacokinetics and safety of warfarin in 24 healthy volunteers. Warfarin was first given alone for 13 days, followed by the addition of olmesartan 2 x 20 mg or placebo for 7 days. Subjects then crossed over to the other treatment for 7 days. Coadminstration of the active agents had no effect on coagulation factors or the pharmacokinetic behavior of the (*R*)- and (*S*)-enantiomers of warfarin (7).

A double-blind, placebo-controlled phase I trial examined the effect of olmesartan on the pharmacokinetics of digoxin in 24 healthy volunteers. Subjects received 3 x 0.375 mg digoxin on day 1 followed by 0.375 mg digoxin once daily for 10 days, after which they were randomized to placebo or olmesartan 20 mg in addition to digoxin for 7 days. This was followed by 7 days of digoxin alone after which subjects crossed over to olmesartan or placebo for a final 7 days of treatment. The effects of olmesartan on the pharmacokinetics, safety and tolerability of digoxin were minor (8).

In a phase I, double-blind, randomized, placebo-controlled study, placebo or olmesartan 80 mg once daily was administered to two groups of 18 elderly and 18 young hypertensive patients for 10 days. Also, an open-label phase I trial evaluated olmesartan 10 mg once daily for 14 days in 17 very elderly and 16 young hypertensive patients. The combined results of the trials indicate that the increases in olmesartan bioavailability with age are modest, the drug is still well tolerated and dose adjustments in the elderly will probably not be necessary (9).

Patients with mild to moderate hypertension were randomized to olmesartan 10 mg once daily (n = 165) or atenolol 50 mg once daily (n = 161) in a double-blind study. Doses could be doubled after 4 weeks if diastolic blood pressure was ≥ 90 mmHg and/or if it had decreased by < 10 mmHg. After 12 weeks, the treatments were found to be equally effective in lowering diastolic blood pressure, although olmesartan was better than atenolol in reducing systolic blood pressure (10).

During a 12-week, randomized, double-blind trial, 328 patients with moderate to severe hypertension received once-daily olmesartan (10 mg) or atenolol (50 mg) after a run-in period of once-daily hydrochlorothiazide (25 mg). Treatment could be doubled at 4 weeks if blood pressure was not controlled. The treatments were similarly effective in reducing blood pressure and olmesartan was well tolerated in this population (11).

Olmesartan 5 mg once daily and captopril 12.5 mg twice daily were administered to 291 mild to moderate hypertensive patients in a multicenter, randomized, double-blind phase III study. The doses could be doubled at 4 and 8 weeks if diastolic blood pressure was not controlled. After 12 weeks, olmesartan was found to have a greater diastolic blood pressure lowering effect at trough than captopril (12).

Patients with mild to moderate hypertension (n = 316) in a randomized, multicenter, double-blind, phase III trial received olmesartan 10 mg or losartan 50 mg, both once daily, for as long as 12 weeks. Doses could be doubled if diastolic blood pressure was not controlled and hydrochlorothiazide could be added to the regimen at 12 weeks. Although both agents lowered diastolic blood pressure, the effect of olmesartan was superior (13).

The efficacy and safety of olmesartan were analyzed with data from several clinical trials. Efficacy was evaluated with data from 3055 patients with mild to moderate hypertension from 7 randomized, placebo-controlled trials of olmesartan 2.5-80 mg once daily. Safety was examined with data from 4444 hypertensive patients who took part in 14 clinical trials for up to 52 weeks. The antihypertensive activity of the drug was found to be long lasting and dose-dependent. Olmesartan was very well tolerated and had a side effect profile similar to placebo (14).

Sankyo Pharma, the European subsidiary of Sankyo, has announced plans to launch olmesartan medoxomil in collaboration with Menarini throughout Europe. Olmesartan medoxomil has been filed for approval with the German regulatory authorities and is scheduled to be launched in Germany at the end of the year, with further launches to follow in all the major European markets in 2002. Also, approval by the FDA is expected later this year (15).

1. Koike, H., Sada, T., Mizuno, M. *In vitro and in vivo pharmacology of olmesartan medoxomil, an angiotensin II type AT_1 receptor antagonist.* J Hypertens 2001, 19(Suppl. 1): S3.

2. Koike, H. *New pharmacologic aspects of CS-866, the newest angiotensin II receptor antagonist.* Am J Cardiol 2001, 87(8A): 33C.

3. Laeis, P., Püchler, K., von Bergmann, K. *A comparative pharmacokinetic, safety and tolerability trial of the oral angiotensin II-antagonist olmesartan medoxomil in subjects with varying degrees of renal impairment and in healthy volunteers.* J Hypertens 2001, 19(Suppl. 2): Abst P2.147.

4. von Bergmann, K., Laeis, P., Püchler, K., Sudhop, T., Schwocho, L.R., Gonzalez, L. *Olmesartan medoxomil: Influence of age, renal and hepatic function on the pharmacokinetics of olmesartan medoxomil.* J Hypertens 2001, 19(Suppl. 1): S33.

  CCC: 0377-8282/2001

5. Brunner, H.R., Nussberger, J. *Relevance of clinical pharmacological models for the evaluation of therapeutic dose range of an AT_1-receptor antagonist.* J Hypertens 2001, 19(Suppl. 1): S15.

6. Laeis, P., Püchler, K., von Bergmann, K. *The effect of aluminium magnesium hydroxide on the pharmacokinetics of the oral angiotensin II-antagonist olmesartan medoxomil in healthy male volunteers.* J Hypertens 2001, 19(Suppl. 2): Abst P2.177.

7. Püchler, K., Laeis, P., Kirch, W. *The effect of the oral angiotensin II antagonist olmesartan medoxomil on the pharmacodynamics, pharmacokinetics and safety of warfarin in healthy, male subjects.* J Hypertens 2001, 19(Suppl. 2): Abst P2.178.

8. Laeis, P., Püchler, K., Kirch, W. *The effect of the oral angiotensin II-antagonist olmesartan medoxomil on the safety, tolerability and pharmacokinetics of digoxin in healthy, male subjects.* J Hypertens 2001, 19(Suppl. 2): Abst P2.179.

9. Püchler, K., Nussberger, J., Witte, P.U., Laeis, P., Brunner, H.R. *Pharmacokinetic, safety and tolerability studies of the oral angiotensin II-antagonist olmesartan medoxomil in young, elderly and very elderly patients with hypertension.* J Hypertens 2001, 19(Suppl. 2): Abst P2.180.

10. Van Mieghem, W. *A multi-centre, double-blind, efficacy, tolerability and safety study of the oral angiotensin II-antagonist olmesartan medoxomil versus atenolol in patients with mild to moderate essential hypertension.* J Hypertens 2001, 19(Suppl. 2): Abst P2.174.

11. Püchler, K., Laeis, P., Stumpe, K.O. *A comparison of the efficacy and safety of the oral angiotensin II-antagonist olmesartan medoxomil with those of atenolol in patients with moderate to severe hypertension under continuous treatment with hydrochlorothiazide.* J Hypertens 2001, 19(Suppl. 2): Abst P2.175.

12. Williams, P.A. *A multi-centre, double-blind, efficacy, tolerability and safety study of the oral angiotensin II-antagonist olmesartan medoxomil versus captopril in patients with mild to moderate essential hypertension.* J Hypertens 2001, 19(Suppl. 2): Abst 207.

13. Ball, K. *A multi-centre, double-blind, efficacy, tolerability and safety study of the oral angiotensin II-antagonist olmesartan medoxomil versus losartan in patients with mild to moderate essential hypertension.* J Hypertens 2001, 19(Suppl. 2): Abst P2.176.

14. Püchler, K., Laeis, P., Stumpe, K.O. *Dose related differences in blood pressure response are not related to adverse event incidence.* J Hypertens 2001, 19(Suppl. 2): Abst P1.191.

15. *Sankyo and Menarini to market olmesartan medoxomil for treatment of hypertension in Europe.* DailyDrugNews.com (Daily Essentials) March 27, 2001.

Original monograph - Drugs Fut 1997, 22: 1205.

Additional References

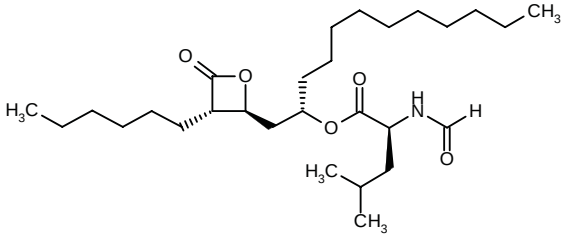
Fliser, D., Haller, H. *Angiotensin II subtype 1-receptor antagonists in the treatment of diabetic nephropathy.* J Hypertens 2001, 19(Suppl. 1): S57.

McInnes, G.T. *Clinical potential: Angiotensin converting enzyme inhibitor or angiotensin II antagonist?* J Hypertens 2001, 19(Suppl. 1): S61.

Sanada, S. et al. *Difference in the subcellular actions of ACE inhibitors and AT_1 blockers on attenuating cardiac hypertrophy induced by chronic inhibition of nitric oxide synthesis in vivo.* Circulation 2001, 104(17, Suppl. 2): Abst 910.

Orlistat *Antiobesity*
Xenical® *Antidiabetic*

EN: 110823



$C_{28}H_{51}NO_5$ **Roche**

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 t.i.d. Pharmaceutical compositions incorporating both compounds are also described (1).

A clinical trial to evaluate the safety and efficacy of orlistat in conjunction with a reduced-calorie diet in the treatment of overweight adolescents aged 12-16 years has been initiated. The trial, involving approximately 450 patients, will take place at 6 centers in Canada and 29 sites in the U.S. All participants will receive nutritional and behavioral modification counseling throughout the study (2).

The FDA has accepted for review Roche's sNDA seeking approval for a new indication of orlistat (Xenical®), *i.e.*, for the improvement of glycemic control in overweight or obese patients with type 2 diabetes when used in combination with other antidiabetic treatments. The sNDA is supported by results from several multicenter, randomized, placebo-controlled clinical trials involving 2600 overweight or obese patients with type 2 diabetes. Clinical data showed that patients treated with orlistat plus a mildly reduced calorie diet lost more weight than those patients treated with placebo plus diet and also had significantly greater and sustained decreases in glycosylated hemoglobin (HbA1c) and fasting plasma glucose (FPG). Decreases in FPG were observed as early as after 2 weeks of treatment, before significant weight loss occurred. In addition, patients with type 2 diabetes treated with orlistat were able to reduce or even discontinue their daily doses of other antidiabetic medications, such as sulfonylureas, insulin and metformin. Notably, overweight and obese patients with type 2 diabetes taking orlistat lost up to 3 times more weight than those on diet

alone. In addition, orlistat improved certain risk factors for cardiovascular disease, such as total cholesterol levels and blood pressure, in diabetic patients (3).

A major European study has confirmed that orlistat is an effective weight loss treatment. The study included a total of 15,549 patients (11,131 women and 4418 men). Orlistat was used in conjunction with a reduced-fat diet in 73% of the patients and physical activity in 53%. The study results showed that average weight loss with orlistat after 7 months of treatment was approximately 11% of total body weight. In addition to weight loss, there were significant improvements in blood sugar control, cholesterol levels and blood pressure in patients who lost weight. For one-third of those with type 2 diabetes and almost half of those with high cholesterol, the weight loss resulted in reductions in the medications needed to control these medical conditions (4).

According to Roche, orlistat is currently the only drug that will be used in Look AHEAD (Action for Health in Diabetes), the first long-term study to examine the effects of weight loss in people with type 2 diabetes. The multicenter, randomized clinical trial, launched in June 2001, will examine the effects of a lifestyle intervention program in approximately 5000 volunteers. Funded by the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK) of the NIH, it is the largest study on the effects of weight loss interventions ever funded by the NIH (5).

1. Heal, D.J. (Knoll AG). *Pharmaceutical compsns. containing sibutramine and orlistat.* WO 0100205.

2. *North American trial to evaluate Xenical in overweight adolescents.* DailyDrugNews.com (Daily Essentials) Feb 8, 2001.

3. *FDA accepts for review Roche's sNDA for new Xenical indication.* DailyDrugNews.com (Daily Essentials) May 23, 2001.

4. *Large European study confirms efficacy of Xenical as weight loss treatment.* DailyDrugNews.com (Daily Essentials) June 11, 2001.

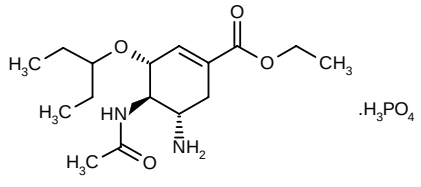
5. *Xenical to be used in NIH-funded study on weight loss and diabetes.* DailyDrugNews.com (Daily Essentials) June 29, 2001.

Original monograph - Drugs Fut 1994, 19: 1003.

Oseltamivir Phosphate Tamiflu®

Antiinfluenza Virus

EN: 241104



$C_{16}H_{28}N_2O_4.H_3O_4P$ **Roche; Gilead; Shionogi**

A new synthesis of oseltamivir phosphate has been described: The opening of the oxirane ring of the already reported oseltamivir intermediate (I) by reaction with allylamine (II) in *t*-BuOMe/MeCN 9:1 provides the allylamino derivative (III), which is deallylated with Pd/C and ethanolamine to give the primary amine (IV). The direct conversion of the amino alcohol (IV) into the vicinal diamine (VIII) is achieved, without isolation of the intermediates, by reaction of compound (IV) with benzaldehyde to give the benzaldehyde imine (V), mesylation of (V) with MsCl and TEA to the mesylate (VI) and treatment of (VI) with allylamine (II) to yield the aziridine intermediate (VII) that opens to the vicinal diamine (VIII). Acylation of the primary amino group of (VIII) with acetic anhydride in acetic acid provides the acetamide (IX), which is finally deallylated with Pd/C and ethanolamine as before and treated with H_3PO_4 (1). Scheme 5.

Roche has entered into a copromotion agreement in Japan for oseltamivir phosphate with Shionogi (2).

Roche has submitted a regulatory application to the European authorities seeking approval to market oseltamivir phosphate (Tamiflu®) for both the treatment of influenza A and B in adults and children and for the prevention of influenza A and B in adolescents and adults. Studies with oseltamivir in adults have shown a significant reduction in both the duration and severity of symptoms, including fever and cough. In children, oseltamivir also reduced the duration of influenza, severity of symptoms and incidence of otitis media. The drug is currently available for the treatment of influenza in a number of countries worldwide, including the U.S., Canada, Japan, Switzerland and many Latin American countries. It is also approved in the U.S. for the prevention of influenza in adolescents and adults and for the treatment of influenza in children aged 1 year and over (3).

1. Karpf, M., Trussardi, R. *New, azide-free transformation of epoxides into 1,2-diamino compounds: Synthesis of the anti-influenza neuraminidase inhibitor oseltamivir phosphate (Tamiflu).* J Org Chem 2001, 66(6): 2044.

2. *Roche highlights recent achievements in Japan.* DailyDrugNews.com (Daily Essentials) Jan 24, 2001.

3. *Gilead seeks Tamiflu approval in E.U.* DailyDrugNews.com (Daily Essentials) Feb 27, 2001.

Original monograph - Drugs Fut 1999, 24: 1189.

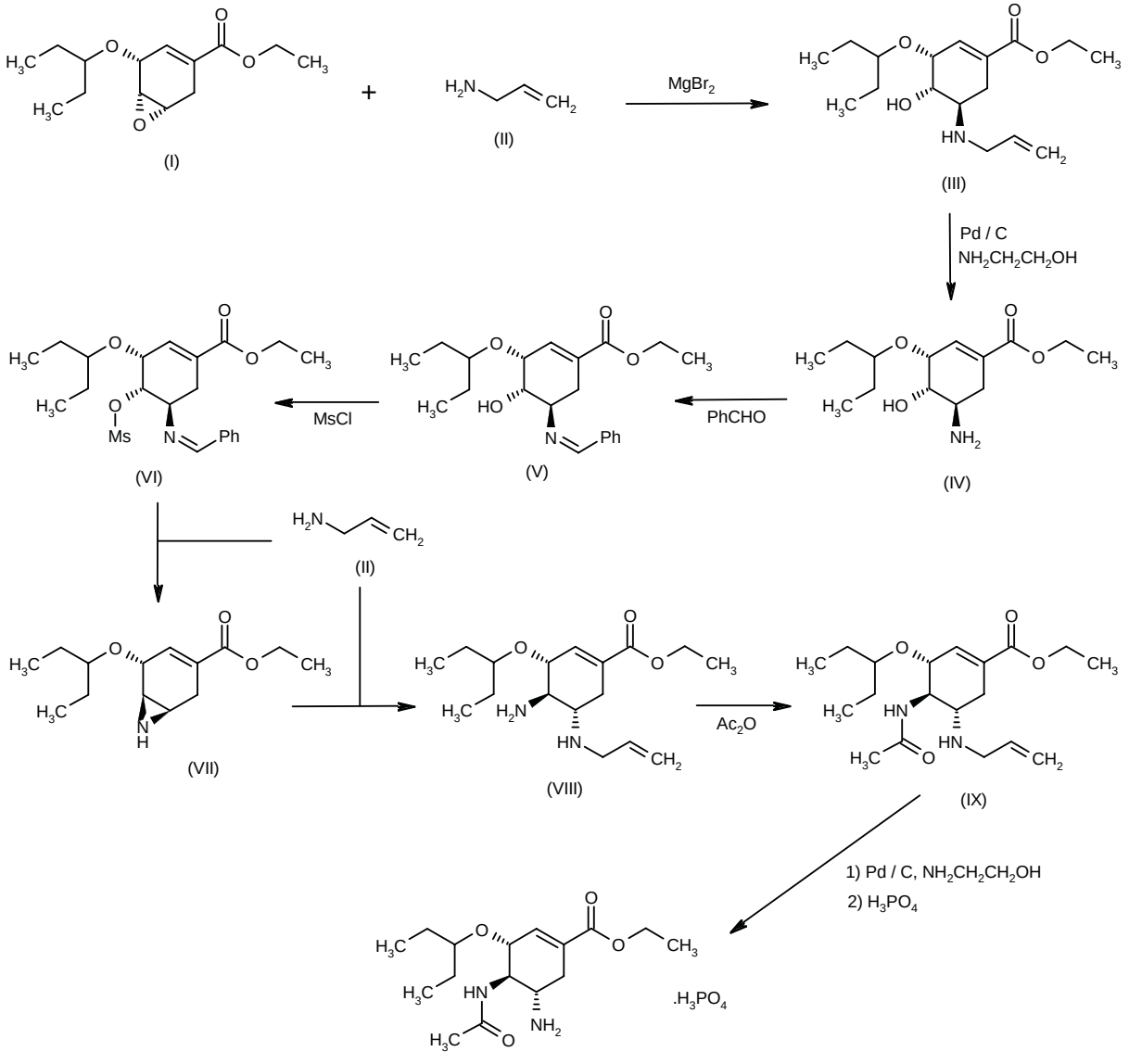
Additional References

Bantia, S. et al. *Comparison of the anti-influenza virus activity of RWJ-270201 with those of oseltamivir and zanamivir.* Antimicrob Agents Chemother 2001, 45(4): 1162.

Kaiser, L. et al. *Oral oseltamivir reduces complications and hospitalizations resulting from influenza infection: A meta-analysis.* Int J Antimicrob Agents 2001, 17(Suppl. 1): Abst P24.002.

McNicholl, I.R., McNicholl, J.J. *Neuraminidase inhibitors: Zanamivir and oseltamivir.* Ann Pharmacother 2001, 35(1): 57.

Scheme 5: Synthesis of Oseltamivir Phosphate



Peters, P.H. et al. *Long-term use of oseltamivir for the prophylaxis of influenza in a vaccinated frail older population.* J Am Geriatr Soc 2001, 49(8): 1025.

Roberts, N. et al. *The detection of influenza virus resistant to oseltamivir carboxylate requires serial sampling of nasal swabs.* Antivir Res 2001, 50(1): Abst 161.

Roberts, N.A. et al. *The lack of resistance to neuraminidase inhibitors: A class phenomenon?* Int J Antimicrob Agents 2001, 17(Suppl. 1): Abst P24.001.

Schmidt, A.C. et al. *Current research on respiratory viral infections: Third International Symposium.* Antivir Res 2001, 50(3): 157.

Watanabe, A., Kobayashi, M. *Socioeconomic analysis of oseltamivir for influenza patients.* Jpn J Chemother 2001, 49(2): 95.

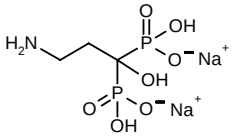
Welliver, R. et al. *Effectiveness of oseltamivir in preventing influenza in household contacts. A randomized controlled trial.* J Am Med Assoc 2001, 285(6): 748.

Whitley, R.J. et al. *Oral oseltamivir treatment of influenza in children.* Pediatr Infect Dis J 2001, 20(2): 127.

Pamidronate Sodium

Aminomux® *Treatment of Paget's Disease*
Aredia® *Treatment of Hypercalcemia*

EN: 090842



$C_3H_9NNa_2O_7P_2$ **Gador; Henkel; Novartis**

A placebo-controlled, crossover study conducted in 24 volunteers examined the gastrointestinal effects of alendronate (10 mg) and enteric coated pamidronate (150 mg/day) or olpadronate (50 mg/day) following twice-daily oral dosing for 5 days. Pamidronate and olpadronate but not alendronate increased the intestinal permeability expressed as the lactulose to manitol ratio. This ratio was 23% greater for pamidronate when compared with olpadronate. Gastroduodenal permeability expressed as sucrose excretion did not significantly change with any of the agents (1).

Researchers have found that giving intravenous pamidronate disodium to men receiving gonadotropin-releasing hormone (GnRH) agonists for prostate cancer helps to prevent bone loss from the hip and lumbar spine. Men with prostate cancer were recruited to this open-label, randomized study if they had locally advanced disease but no bone metastases. Participants received either the GnRH agonist leuprolide depot alone or leuprolide depot and intravenous pamidronate every 12 weeks over a period of 48 weeks. All men also received bicalutamide for the initial 4 weeks and a daily multivitamin containing vitamin D. A total of 43 men from the 47 initially randomized completed baseline assessments, and 41 completed the study, of whom 3 discontinued leuprolide early. Baseline measures were similar in both groups of men. Nadir levels of serum testosterone within the range of castrated men were achieved in all subjects. There was significantly more bone loss in the men receiving leuprolide alone than in those receiving leuprolide and pamidronate. Intention-to-treat analysis showed that whereas those receiving the GnRH agonist alone had significant reductions in bone mineral density (BMD) in the lumbar spine, trochanter and total hip, there were no significant losses at any skeletal site in those receiving GnRH agonist plus bisphosphonate. Serious adverse events were recorded in 3 men taking leuprolide alone and in 5 taking pamidronate and leuprolide. The study authors concluded that pamidronate given intravenously to men with prostate cancer on GnRH agonists prevents bone loss in the hip and lumbar spine. However, the authors also noted that the lack of blinding could have influenced the results and the crucial question of whether an improved BMD translates into a reduction in fractures requires further larger studies (2).

1. Twiss, I.M., van den Berk, A.H.M., de Kam, M.L., Vermeij, P., Burggraaf J. *Differences in gastrointestinal (GI) effects of nitrogen containing bisphosphonates.* Clin Pharmacol Ther 2001, 69(2): Abst PII-39.

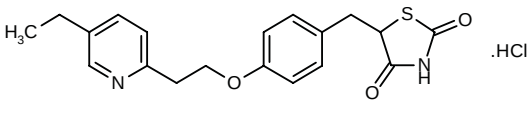
2. Smith, M.R., McGovern, F.J., Zietman, A.L., Fallon, M.A., Hayden, D.L., Schoenfeld, D.A., Kantoff, P.W., Finkelstein, J.S. *Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer.* New Engl J Med 2001, 345(13): 948.

Original monograph - Drugs Fut 1979, 4: 781.

Pioglitazone Hydrochloride *Antidiabetic*

Actos®
Zactos®
Glustin®

EN: 164965



$C_{19}H_{20}N_2O_3S.HCl$ **Takeda; Lilly; Abbott; Novo Nordisk**

SmithKline Beecham has claimed the use of PPARγ agonists for delaying or preventing the development of type 1 diabetes by reducing insulin resistance. This method is particularly indicated in prepubescent persons with elevated levels of antibodies to glutamate decarboxylase (GAD), an indication of predisposition to develop type 1 diabetes. Suitable PPARγ agonists included in the invention are thiazolidinediones, preferably rosiglitazone or its salts as well as pioglitazone, troglitazone or ciglitazone (1).

A series of experiments examined the involvement of PPARγ in the differentiation of macrophages using both wild-type and PPARγ-deficient embryonic stem cells and macrophages from PPARγ-chimeric mice. The results indicated that PPARγ is not essential for macrophage differentiation, nor for macrophage functions. However, PPARγ was shown to play a critical role in the regulation of the oxidized LDL scavenger receptor CD36, but not the SR-A receptor. PPARγ ligands increased CD36 expression in wild-type macrophages, but not PPARγ-deficient macrophages, whereas they reduced the expression of SR-A in wild-type macrophages, resulting in no net effect on cellular cholesterol uptake or accumulation. Overall,

these and previous findings suggest that thiazolidinediones may not exacerbate foam cell formulation and may exert beneficial arterial wall cellular effects, in addition to their favorable influence on systemic risk factors for atherosclerosis (2).

A major clinical trial designed to investigate the impact of reducing insulin resistance on cardiovascular morbidity and mortality in type 2 diabetes has been jointly launched by Takeda and Lilly. The PROspective Actos® Clinical Trial In macroVascular Events (PROactive) will enroll 5000 patients in 10 European countries over 4 years to investigate whether pioglitazone hydrochloride can prevent the progression of macrovascular disease, which is associated with cardiovascular events such as myocardial infarction, in type 2 diabetics. Previous clinical trials have demonstrated that controlling blood glucose levels, reducing high blood pressure and treatment with conventional therapy (*i.e.*, sulfonylureas and insulin) can reduce the risk of microvascular events such as damage to the kidneys, eyes and nerves in the hands and feet. However, such treatment does not appear to produce similar significant reductions in macrovascular events such as heart attack, stroke and amputation. Based on the hypothesis that insulin resistance, found in the majority of patients with type 2 diabetes, is the cause of these macrovascular events, the PROactive trial has been designed to compare the effects of conventional oral therapy and therapy supplemented with pioglitazone on progression to the combined endpoint of heart attack, stroke, amputation, revascularization or cardiovascular death (3).

Pioglitazone hydrochloride (Actos®) is now available from Takeda in the U.K. for use in combination with metformin in obese patients, or with a sulfonylurea in patients with intolerance or contraindication to metformin, in the treatment of type 2 diabetes inadequately controlled by maximum tolerated doses of metformin or sulfonylurea. The product is presented in the form of tablets containing 15 mg and 30 mg of active ingredient (4).

1. Nathwani, A. (SmithKline Beecham plc). *Novel treatment.* WO 0076488.

2. Moore, K.J. et al. *The role of PPAR-γ in macrophage differentiation and cholesterol uptake.* Nat Med 2001, 7(1): 41.

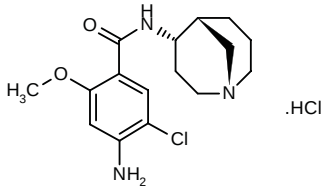
3. *Four-year PROactive study examines effects of Actos on cardiovascular risk.* DailyDrugNews.com (Daily Essentials) Jan 9, 2001.

4. *Actos may now be prescribed in U.K. for the management of type 2 diabetes.* DailyDrugNews.com (Daily Essentials) Jan 26, 2001.

Original monograph - Drugs Fut 1990, 15: 1080.

Renzapride Hydrochloride *Treatment of IBS*

EN: 125657



$C_{16}H_{22}ClN_3O_2.HCl$ **Alizyme**

Alizyme has received regulatory approval from the Medicines Control Agency (MCA) to begin a 500-patient phase IIb trial comparing 3 doses of renzapride and placebo in constipation-predominant irritable bowel syndrome (IBS) patients. The trial will include both men and women and will follow a double-blind, randomized, parallel-group design (1).

The recent approval by the MCA for a 500-patient phase IIb clinical trial of renzapride in constipation-predominant IBS is a significant step forward in the progress towards phase III clinical trials and commercialization of this product. Enrollment for the trial was scheduled to commence last month, with preliminary results expected to be available towards the end of 2002. This trial is intended to provide key information for the design of pivotal phase III studies scheduled to begin in 2003. With the commencement of the phase IIb constipation-predominant trial, Alizyme is now preparing for a clinical study of the drug in mixed-symptom IBS patients. This study will be designed to test the hypothesis that the dual mechanism of action of renzapride (5-HT_4 agonism/5-HT_3 antagonism) can provide benefit for this patient group. Successful results would provide the basis for expanded phase III studies to include mixed-symptom IBS patients (2).

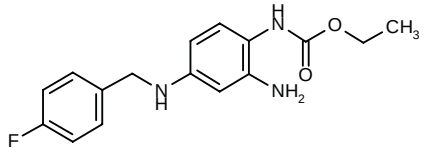
1. *Phase IIb clinical trial of ATL-1251 to begin in U.K. in IBS patients.* DailyDrugNews.com (Daily Essentials) Sept 18, 2001.

2. *Alizyme highlights product development efforts.* DailyDrugNews.com (Daily Essentials) Oct 18, 2001.

Original monograph - Drugs Fut 1987, 12: 1009.

Retigabine *Antiepileptic*

EN: 227505



$C_{16}H_{18}FN_3O_2$ **Arzneimittelwerk Dresden; Asta Medica; Wyeth-Ayerst**

Retigabine (0.1-10 μM) was shown to enhance current through KCNQ2/Q3 potassium channels expressed in Chinese hamster ovary cells, suggesting that these channels play a role in the anticonvulsant activity of retigabine and are a molecular target for the drug (1).

A study of the mechanism of action of retigabine found that the drug concentration-dependently potentiated GABA-induced currents in rat cortical neurons. Retigabine also inhibited voltage-activated Na^+ and Ca^{2+} channels as well as kainate-induced currents at the highest concentration tested (100 μmol/l). The drug had no interaction with NMDA-induced currents (2).

Single doses of retigabine were found to significantly reduce glutamate and glutamine concentrations in the brains of mice, while 5-day treatment significantly reduced the activity of γ-aminobutyric acid (GABA)-transaminase. This indicates that retigabine may function in part by blocking GABA metabolism and lowering concentrations of excitatory neurotransmitters in the brain (3).

Women taking ethinyl estradiol/norgestrel were found to be exposed to efficacious concentrations of the contraceptive when taking retigabine concomitantly. In the study, 18 women were given ethinyl estradiol 0.03 mg/norgestrel 0.3 mg for 2 menstrual cycles and retigabine 150 mg was administered 3 times daily on days 10-13 of the second cycle. Coadministration of retigabine did not significantly alter the pharmacokinetics of either ethinyl estradiol or norgestrel. No clinically important alterations in laboratory values, vital signs or ECGs were seen and adverse events were mild (headache, nausea, sleepiness and vaginitis). Retigabine was well tolerated and no serious adverse events were reported (4).

Results from a study conducted in 15 healthy male volunteers showed tolerability and no pharmacokinetic interaction between phenobarbital and retigabine. Following a single oral dose of retigabine (200 mg), the mean AUC and $t_{1/2}$ values were 4050 ng·h/ml and 6.5 h, respectively. When increasing doses of retigabine (100-200 mg every 8 h for 6 days) were administered with phenobarbital (90 mg p.o. every 8 h for 28 days) there were no changes in the AUC and $t_{1/2}$ values of retigabine. The exposure to phenobarbital was also unchanged after given alone and in combination with retigabine (303 *vs.* 299 mg.h/ml) (5).

1. Wickenden, A.D., Yu, W., Zou, A., Jegla, T., Wagoner, P.K. *Retigabine, a novel anti-convulsant, enhances activation of KCNQ2/Q3 potassium channels.* Mol Pharmacol 2000, 58(3): 591.

2. Rundfeldt, C., Netzer, R. *Investigations into the mechanism of action of the new anticonvulsant retigabine.* Arzneim-Forsch Drug Res 2000, 50(12): 1063.

3. Sills, G.J., Rundfeldt, C., Buthler, E., Forrest, G., Thompson, G.G., Brodie, M.J. *A neurochemical study of the novel antepileptic drug retigabine in mouse brain.* Pharmacol Res 2000, 42(6): 553.

4. Paul, J., Ferron, G.M., Richards, L., Getsy, J., Troy, S.M. *Retigabine does not alter the pharmacokinetics of a low-dose oral contraceptive in women.* Neurology 2001, 56(8, Suppl. 3): Abst P05.052.

5. Ferron, G.M., Patat, A., Parks, V., Rolan, P., Troy, S. *Lack of pharmacokinetic interaction between retigabine and phenobarbital at steady-state in healthy subjects.* Clin Pharmacol Ther 2001, 69(2): Abst PII-64.

Original monograph - Drugs Fut 1995, 20: 1112.

Additional References

De Sarro, G. et al. *Influence of retigabine on the anticonvulsant activity of some antiepileptic drugs against audiogenic seizures in DBA/2 mice.* Naunyn-Schmied Arch Pharmacol 2001, 363(3): 330.

Ferron, G.M. et al. *Pharmacokinetic interaction between valproic acid, topiramate, phenytoin or carbamazepine and retigabine in epileptic patients.* Clin Pharmacol Ther 2001, 69(2): Abst PI-70.

Rundfeldt, C. et al. *Retigabine stabilizes neuronal cell activity in epileptic patients by activating KCNQ2/3 channels and its mutation.* Soc Neurosci Abst 2000, 26(Part 2): Abst 662.12.

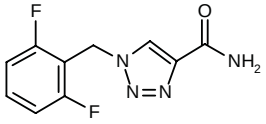
Sachdeo, R.C. et al. *An early determination of drug-drug interaction between valproic acid, phenytoin, carbamazepine or topiramate, and retigabine in epileptic patients.* Neurology 2001, 56(8, Suppl. 3): Abst P05.041.

Schroder, R.L. et al. *KCNQ4 channel activation by BMS-204352 and retigabine.* Neuropharmacology 2001, 40(7): 888.

Rufinamide
RUF-331
CGP-33101
Xilep®

Antiepileptic
Treatment of Neurogenic Pain

EN: 132089



$C_{10}H_8F_2N_4O$ **Novartis**

The results from a study examining the efficacy and safety of adjunctive therapy with rufinamide in epileptic patients were published recently. The trial was a multicenter, double-blind, randomized, placebo-controlled, parallel-group study enrolling 50 patients with partial or primary generalized tonic-clonic seizures who received rufinamide at escalating doses from 400-1600 mg/day or placebo over 28 days. In evaluable patients (23 on rufinamide, 21 on placebo), a reduction in seizure frequency of 41% was recorded in those receiving rufinamide, compared to an increase in seizure frequency of 52% in patients given placebo. Moreover, a reduction in seizure frequency of at least 50% compared to baseline was seen in 39% of rufinamide-treated patients but only 16% of

placebo-treated patients. Adverse events consisted mainly of neurological signs and symptoms and were mostly mild or moderate in severity. Adverse events occurring more frequently on rufinamide than on placebo were tiredness, fatigue and lethargy and tremor. Pharmacokinetic analysis was performed after single doses of rufinamide (800 mg) before and after the double-blind phase. The results demonstrated a steady-state t_{max} of 3.4 h and a mean $t_{1/2}$ of 7.3 h. No accumulation or autoinduction of rufinamide metabolism was seen. Plasma rufinamide AUC and $t_{1/2}$ values were significantly lower in patients also receiving carbamazepine or phenytoin compared to patients receiving concomitant valproate, but this interaction was not expected to be clinically relevant. Furthermore, the lack of effect of rufinamide on the pharmacokinetics of carbamazepine, phenytoin or valproate provided further indication that no dose adjustment will be necessary when rufinamide is given concomitantly with other AEDs (1).

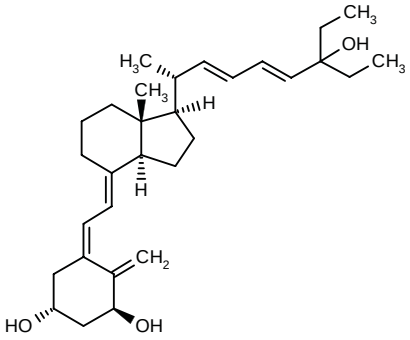
1. Palhagen, S., Canger, R., Henriksen, O., van Parys, J.A., Riviere, M.E., Karolchyk, M.A. *Rufinamide: A double-blind, placebo-controlled proof of principle trial in patients with epilepsy.* Epilepsy Res 2001, 43(2): 115.

Original monograph - Drugs Fut 2000, 25: 1145.

Seocalcitol

Oncolytic

EN: 174617



$C_{30}H_{46}O_3$ **Leo**

Two different breast cancer cell lines resistant to antiestrogens showed greater sensitivity to EB-1089 than the parent MCF-7 cell line, suggesting that the drug may be useful for patients who become refractory to antiestrogen therapy. The antiapoptotic protein Bcl-2 appeared to be a predictive marker for response to EB-1089 (1).

The interaction of EB-1089 with fractionated radiation (5 x 2 Gy over 5 days) was investigated in breast tumor cells. In MCF-7 cells the number of viable cells was reduced by 75, 84 and 95% by fractionated radiation alone, EB-1089 alone and the combination of preexposure to EB-1089 for 2 days and fractionated radiation, respectively. The combination also reduced clonogenic survival by 82%, as compared to 30 and 34% with EB-1089 alone and fractionated radiation alone, respectively. The drug enhanced fractionated radiation-induced apoptosis through changes in cell morphology and the induction of DNA fragmentation. The response to fractionated radiation in the p53 mutant MDA-MB231 breast tumor cell line was not enhanced by EB-1089 (2).

Researchers implanted LNCaP prostate cancer cells in mice to test the effect of EB-1089 treatment. Treatment began immediately following cell implant with no time allowed for tumor development. EB-1089 effectively prevented the development of large tumors from these cells. Most of the treated animals had small tumors at the end of the study, although preliminary analysis indicated that the mitotic index in these tumors was significantly reduced. Treatment with EB-1089 appeared to retard tumor development, as most of the small tumors resembled early-stage control tumors. Treated tumors showed little LNCaP cell growth and severely compromised host stromal recruitment, while control tumors were vascular and recruited an extensive stromal support meshwork. Neither hypercalcemia nor weight loss was seen in the mice during the study (3).

Seocalcitol was investigated in a mouse model in which over half of the animals develop spontaneous hepatocellular carcinomas. Mice were divided into groups to receive the vehicle or seocalcitol at a dose of 0.5 g/ml/kg i.p. every other day for 2, 4 or 6 months starting at 4 months of age. A highly significant beneficial effect was established for seocalcitol on the incidence of hepatocellular carcinomas, with an overall incidence of 3.9% *versus* 36.4% in vehicle-treated controls; no animals treated with seocalcitol for at least 4 months developed hepatocellular carcinomas and only 11.1% of those treated for just 2 months developed these cancers (4).

1. Larsen, S.S., Heiberg, I., Lykkesfeldt, A.E. *Anti-oestrogen resistant human breast cancer cell lines are more sensitive towards treatment with the vitamin D analogue EB1089 than parent MCF-7 cells.* Br J Cancer 2001, 84(5): 686.

2. Gerwitz, D.A., Gupta, M.S. *Enhancement of breast tumor cell sensitivity to fractionated radiation and susceptibility to apoptosis by the vitamin D_3 analog EB 1089.* Proc Amer Assoc Cancer Res 2001, 42: Abst 502.

3. Murthy, S., Polek, T.C., Ayala, G., Weigel, N.L. *EB1089 arrests LNCaP tumors at an early stage of development and inhibits stromal recruitment in a nude mouse model.* Proc Amer Assoc Cancer Res 2001, 42: Abst 2153.

4. Sahpazidou, D., Toliou, T., Stravoravdi, P., Geromichalos, G., Natsis, K., Nenopoulou, H., Boukovinas, J., Papakotoulas, P., Gigis, P. *Significant experimental decrease of the hepatocarcinoma (HPC) incidence in C3H/SY mice after administration of EB1089, a vitamin D analogue.* Eur J Cancer 2001, 37(Suppl. 6): Abst 277.

Original monograph - Drugs Fut 1993, 18: 1057.

Additional References

Akutsu, N. et al. *Regulation of gene expression by 1α,25-dihydroxyvitamin D_3 and its analog EB1089 under growth-inhibitory conditions in squamous carcinoma cells.* Mol Endocrinol 2001, 15(7): 1127.

Bernardi, R.J. et al. *Anti-proliferative effects of 1α,25-dihydroxyvitamin D_3 and vitamin D analogs on murine endothelial cells.* Proc Amer Assoc Cancer Res 2001, 42: Abst 1121.

Blaehr, L.K.A. et al. *Polyclonal antibodies to EB1089 (seocalcitol), an analog of 1α,25-dihydroxyvitamin D_3.* Steroids 2001, 66(7): 539.

Lin, R. et al. *Large-scale profiling of 1,25-dihydroxyvitamin D_3 and EB1089 target genes in cancer cells using cDNA and oligonucleotide arrays.* 83rd Annu Meet Endocr Soc (June 20-23, Denver) 2001, Abst P3-422.

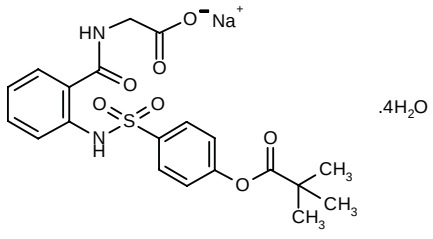
Maenpaa, P.H. et al. *Vitamin D_3 analogs (MC 1288, KH 1060, EB 1089, GS 1558, and CB 1093): Studies on their mechanism of action.* Steroids 2001, 66(3-5): 223.

White, J. et al. *Low calcemic vitamin D_3 analog EB1089 induces the growth arrest and DNA damage gene GADD45 and inhibits growth of head and neck squamous tumors.* 83rd Annu Meet Endocr Soc (June 20-23, Denver) 2001, Abst P1-222.

Sivelestat Sodium Hydrate
Elaspol®

Treatment of ARDS

EN: 157441



$C_{20}H_{21}N_2O_7S.Na.4H_2O$ **Ono; Lilly**

Sivelestat sodium hydrate has been shown to inhibit the liver metastasis of human pancreatic cancer S2-013 in SCID mice when given prior to tumor cell inoculation (1).

Sivelestat had beneficial effects in a rat model of lower limb ischemia/reperfusion injury. The compound was administered at a dose of 10 or 30 mg/kg i.v. following ischemia and before reperfusion, and significant and dose-dependent reductions in elevated creatine phosphokinase levels were seen at 3 and 6 h after reperfusion. Sivelestat is currently undergoing regulatory review in Japan as a treatment for acute lung injury and acute respiratory distress syndrome (ARDS) (2).

1. Inoue, K., Hirota, M., Nozawa, F., Shibata, M., Kuwata, K., Kimura, Y., Ohmuraya, M., Iwamura, T., Ogawa, M. *ONO-5046 Na, a neutrophil elastase inhibitor, inhibits hepatic metastasis of pancreatic cancer cells.* J Jpn Pancreas Soc 2001, 16(3): Abst O-34.

2. Goto, M. et al. *Inhibitory effects of a neutrophil elastase inhibitor (ONO-5046 Na) on ischemia-reperfusion injury in a rat model of lower limb ischemia/reperfusion injury.* J Jpn Coll Angiol 2000, 40(9): Abst A2-12.

Original monograph - Drugs Fut 1994, 19: 1000.

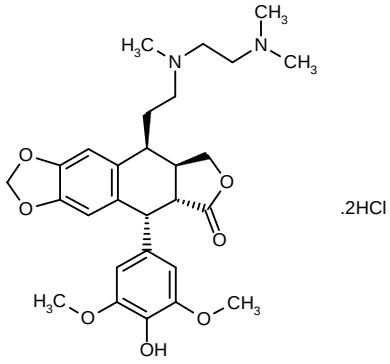
Additional Reference

Ueno, M. et al. *Effect of a neutrophil elastase inhibitor (ONO-5046 Na) on ischemia/reperfusion injury using the left-sided heterotopic canine heart transplantation model.* J Heart Lung Transplant 2001, 20(8): 889.

TOP-53

Oncolytic

EN: 188095



$C_{28}H_{36}N_2O_7.2HCl$ **Taiho**

Investigations of the mechanism of action of TOP-53 found topoisomerase II to be the primary cytotoxic target. TOP-53 showed greater activity in increasing topoisomerase II-mediated DNA cleavage than its parent compound, etoposide, and was highly active against human topoisomerase IIalpha and libeta *in vitro*. Both etoposide and TOP-53 demonstrated similar DNA cleavage site specificity and both drugs increased the level of enzyme-mediated DNA breaks, mostly by inhibiting the DNA religation activity of the enzyme. The enhanced cytotoxicity of TOP-53 appeared to be due to its enhanced activity against topoisomerase II (1).

The mechanism of TOP-53 distribution to the lung and lung-localized tumor was investigated in a study comparing its interaction with phospholipids *in vitro* to that of etoposide. Tissue phosphatidyl serine content and binding affinity were concluded to be the determining factors for the distribution of TOP-53. Specific accumulation of TOP-53 in the lung resulted in greater antitumor activity against cancer metastasizing to the lung as compared to etoposide, with increases of life span of 171 and 78%, respectively (2).

  CCC: 0377-8282/2001

1. Byl, J.A., Cline, S.D., Utsigi, T., Kobunai, T., Yamada, Y., Osheroff, N. *DNA topoisomerase II as the target for the anti-cancer drug TOP-53: Mechanistic basis for drug action.* Proc Amer Assoc Cancer Res 2001, 42: Abst 566.

2. Yoshida, M., Kobunai, T., Aoyagi, K., Saito, H., Utsugi, T., Wierzba, K., Yamada, Y. *Specific distribution of TOP-53 to the lung and lung-localized tumor is determined by its interaction with phospholipids.* Clin Cancer Res 2000, 6(11): 4396.

Original monograph - Drugs Fut 1996, 21: 1136.

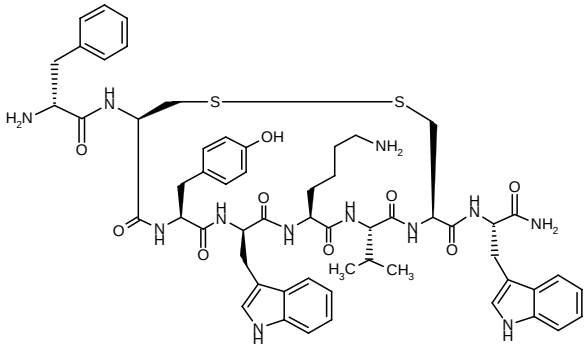
Additional Reference

Tawa, R. et al. *Anticancer activity of a novel podophyllotoxin derivative based on the complex formation with the intracellular metals.* Proc Amer Assoc Cancer Res 2001, 42: Abst 1760.

Vapreotide Octastatin®

Oncolytic

EN: 135014



$C_{57}H_{70}N_{12}O_9S_2$ **Tulane Univ. (US); Debiopharm**

The somatostatin analog RC-160 was labeled with the short-lived radionuclide technetium-99m using the 3+1 mixed ligand approach. This complex was found to bind specifically to HTB-121 breast cancer cells. In mice with breast cancer xenografts, approximately 1.3% of the injected dose of the complex was localized in the tumor after 2 h. The complex is therefore a promising radiopharmaceutical for use in imaging to detect breast cancer (1).

The effects of vapreotide were investigated in 227 patients with cirrhosis who were hospitalized with variceal bleeding. Patients were randomized to receive placebo or vapreotide (50 μg i.v. bolus followed by 50 μg/h i.v. infusion for 5 days) prior to endoscopic treatment. A total of 98 patients per treatment group were available for evaluation. The primary objective of the study was survival and control of bleeding, which was achieved in 66% and 50% of patients in the vapreotide and placebo treatment groups, respectively. Although vapreotide patients required significantly fewer transfusions, the overall survival rates at 42 days were similar (2).

1. Amartey, J.K. *Technetium-99m-labeleted somatostatin analog (RC-160): A potential radiopharmaceutical for cancer detection.* Proc Amer Assoc Cancer Res 2001, 42: Abst 509.

2. Calès, P, Masliah, C., Bernard, B. et al. *Early administration of vapreotide for variceal bleeding in patients with cirrhosis.* New Engl J Med 2001, 344(1): 23.

Original monograph - Drugs Fut 1989, 14: 1052.

Additional Reference

Chatzistamou, I. et al. *Antagonists of growth hormone-releasing hormone and somatostatin analog RC-160 inhibit the growth of the OV-1063 human epithelial ovarian cancer cell line xenografted into nude mice.* J Clin Endocrinol Metab 2001, 86(5): 2144.