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Information Update

Volume 1-23, Number 11

Estimated developmental phase for this month's updated products:

Preclinical

Epibatidine (analgesic; Dept. Health and Human Services, CytoMed)
TOP-53 (antineoplastic; Taiho)

Phase I

NCX-4016 (antithrombotic, cardioprotectant; NicOx)

Phase II

AGM-1470 (angiogenesis inhibitor; Takeda)
Amrubicin hydrochloride (antineoplastic antibiotic; Sumitomo)
D-Cycloserine (cognition enhancer; Searle)
Ecteinascidin 743 (antineoplastic; Univ. Illinois, Pharma Mar)
Lodenosine (anti-HIV, reverse transcriptase inhibitor; Natl. Cancer Inst., U.S. Bioscience)
Renzapride hydrochloride (treatment of IBS, 5-HT_3 antagonist, 5-HT_4 agonist)
Retigabine (antiepileptic; Arzneimittelwerk Dresden, Asta Medica, Wyeth-Ayerst)
Seocalcitol (antineoplastic, vitamin D analog; Leo)

Phase III

Cariporide mesilate (cardioprotectant, Na^+/H^+ exchange inhibitor; Hoechst Marion Roussel)
CI-994 (antineoplastic; Warner-Lambert, Goedecke)
CS-866 (antihypertensive, angiotensin AT_1 antagonist; Sankyo, Recordati)
Darifenacin (treatment of urinary incontinence, muscarinic M_3 antagonist; Pfizer)
Remacemide hydrochloride (antiepileptic, antiparkinsonian, cognition enhancer; AstraZeneca)
SB-265805/LB-20304a (naphthyridine antibacterial; LG Chem, SmithKline Beecham)
TU-199 (gastric antisecretory, H^+/K^+-ATPase inhibitor; Tokyo Tanabe, Hokuriku)

Preregistered

Linezolid (oxazolidinone antibacterial; Pharmacia & Upjohn)
Sivelestat sodium hydrate (neutrophil elastase inhibitor, treatment of acute lung injury; Ono)

Launched/Year

Abacavir sulfate (anti-HIV, reverse transcriptase inhibitor; Glaxo Wellcome)/1999
Amifostine hydrate (radioprotectant; Alza, Schering-Plough, U.S. Bioscience)/1995
Argatroban monohydrate (anticoagulant, thrombin inhibitor; Texas Biotechnology, SmithKline Beecham)/1990
Beraprost sodium (platelet antiaggregatory, treatment of pulmonary hypertension; United Therapeutics, Toray, Yamanouchi)/1992
Fomivirsen sodium (antiviral, treatment of CMV retinitis; Isis, Eisai, Ciba Vision, Abbott)/1998
Lisinopril (antihypertensive, treatment of heart failure, treatment of diabetic complications; Merck & Co.)/1987
Miltefosine (antineoplastic, treatment of protozoal diseases; Asta Medica)/1993
Orlistat (antiobesity; Roche)/1998
Pioglitazone hydrochloride (antidiabetic, Lilly, Takeda, Novo Nordisk)/1999
Reboxetine mesilate (antidepressant, norepinephrine reuptake inhibitor; Pharmacia & Upjohn, Janssen)/1997
Suplatast tosilate (treatment of urinary incontinence; Taiho)/1995
Tacrine (cognition enhancer; Alza, Parke-Davis)/1993

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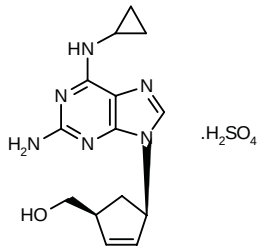
Abacavir Sulfate
1592U89 Sulfate
Ziagen™

Anti-HIV
Reverse Transcriptase Inhibitor

EN: 173602



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

Glaxo Wellcome

The SCID mouse modified model of HIV-1 encephalitis was used to assess the efficacy of abacavir to prevent viral spread in intact brain tissue. Following one round of replication, HIV-1 infected human monocyte-derived macrophages (MDM) were inoculated into the putamen and deep cortical structures of SCID mice, resulting in multinucleated giant cell encephalitis with astrogliosis, microglial nodule formation, neuronal dropout and viral spread among the human MDM. Prior to inoculation and for up to 14 days, mice were administered abacavir, ZDV, 3TC, ddI or d4T. Abacavir reduced viral spread by 85% as assessed by HIV-1 p24 Ag expression on days 7 and 14 after treatment and ZDV and 3TC decreased viral spread by 50% and 95%, respectively. The effects of d4T and ddI were similar to those of ZDV and abacavir, respectively; however, reductions in viral spread were only seen on day 14 (1).

The susceptibility of HIV-1 strains to abacavir was examined using isolates from plasma of 5-HIV-infected patients; the strains carried the Q151M mutation associated with multiple nucleoside revere transcriptase inhibitor resistance. None of the 5 recombinant viruses (1 reverse transcriptase clone in each patient was combined with a reverse transcriptase-deleted laboratory strain) were sensitive to abacavir, with 3 showing a high resistance to the drug. Two of these abacavir-resistant viruses contained the K65R and M184V mutations associated with abacavir resistance in addition to Q151M (2).

Baseline HIV-1 genotypes were assessed in patients receiving abacavir in addition to stable background antiretroviral therapy. After 16 weeks, a similar proportion of 3TC-experienced and 3TC-naive patients had plasma HIV-1 levels < 400 copies/ml (42% and 32%, respectively), with 62% of the patients with initial maximum of 5000 copies/ml achieving < 400 copies/ml as compared to only 16% with > 5000 copies/ml. Ninety-seven percent of baseline isolates from 3TC-experienced patients were 3TC resistant, with 75% sensitive to abacavir; low cross-resistance between abacavir and 3TC was noted in these patients. Due to the low plasma HIV-1 RNA levels after 16 weeks of therapy, only 35 genotypes were obtained, showing that although new ZDV mutations were detected in 13/35 genotypes, no new abacavir mutations developed (3).

Genotypic and phenotypic analyses from isolates of 89 therapy-experienced HIV-infected adults from 4 clinical trials with abacavir added on to background nucleoside reverse transcriptase inhibitor therapy (prior therapy of 3 months to several years) have shown that multiple baseline reverse transcriptase mutations corresponded to phenotypic resistance and poor viral responses. No differences were detected in the efficacy of abacavir when the baseline virus was wild-type or contained 1-2 mutations associated with nucleoside reverse transcriptase inhibitor resistance (4).

Cerebral spinal fluid (CSF) HIV RNA levels were shown to be reduced in a randomized study in which 23 therapy-experienced children received 3TC/ZDV with or without abacavir; CSF samples were obtained at baseline, 8 and 16 weeks. After 16 weeks, CSF HIV RNA was undetectable (< 100 copies/ml) in 67% and 64% receiving abacavir/3TC/ZDV and 3TC/ZDV, respectively. Baseline genotype analysis showed that 3/11 patients had resistance mutations. At weeks 8 and 16, 1/4 (25%) abacavir/3TC/ZDV-treated patients as compared to 3/4 (80%) 3TC/ZDV-treated patients developed new resistance mutations (5).

The efficacy of 3TC/ZDV was compared to lamivudine/zidovudine and to treatment intensification with abacavir for 48 weeks in a randomized, open-label, multicenter study in which 75 therapy-naive HIV-infected patients received either 3TC/ZDV (150 mg b.i.d./300 mg b.i.d.) or lamivudine/zidovudine and after 3 months, offered abacavir add-on therapy. Following abacavir therapy, 75% and 61% of the patients at 16 and 40 weeks, respectively, as compared to 29% at entry had plasma HIV RNA below the detection limits (400 copies/ml) and 6%, 34% and 31% had 20 copies/ml, at entry, 16 and 40 weeks, respectively. $CD4^+$ cell counts were also found to increase to 640 cell/mm^3 at 40 weeks with a mean increase of 79 cells/mm^3. The M184V mutation was found in 77% of the patients prior to abacavir add-on therapy and no patients were phenotypically resistant to abacavir (6).

Abacavir (300 mg b.i.d.) was shown to intensify ZDV/3TC (at least 12 weeks; 300 mg/150 mg b.i.d.) antiretroviral therapy after 16 weeks of treatment. Of 52 HIV-positive patients receiving abacavir, 39 (75%) responded with a decrease in plasma virus to levels below the quantifiable limit and mean $CD4^+$ count increased by 70 cells/mm^3. After analysis of genotypic profiles, 34/44 patients were found to carry the plasma virus with M184V reverse transcriptase mutation, of whom 32/34 responded to abacavir. No pattern in genotype was detected in 16% of patients showing no antiretroviral response, although 5/7 of these individuals had stopped lamivudine/zidovudine or abacavir therapy during this period (7).

Preliminary results from a randomized, placebo-controlled, crossover trial have demonstrated that abacavir effectively enhances multidrug combination antiretroviral

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therapy. In all, 185 patients with stable plasma HIV-1 RNA (400-50,000 copies/ml) on stable background antiretroviral therapy for at least 12 weeks received either abacavir (300 mg b.i.d.) or placebo. After 16 weeks of treatment, significantly more patients treated with abacavir had plasma HIV-1 RNA levels < 400 copies/ml as compared to the placebo group. The treatment regimens were well tolerated (8).

In a randomized trial, 185 HIV-infected patients on stable antiretroviral therapy for more than 12 weeks were administered abacavir (300 mg b.i.d.) or placebo in addition to stable background antiviral therapy for 48 weeks; 3TC-experienced and 3TC-naive patients were included. At week 16, 39% of the patients receiving abacavir had plasma HIV-1 RNA < 400 copies/ml as compared to only 8% in the group receiving the placebo; abacavir was well tolerated with few treatment-limiting side effects (9).

A phase II, open-label, single-arm study has demonstrated the efficacy of abacavir (300 mg b.i.d.), amprenavir (1200 mg b.i.d.) and efavirenz (600 mg q.d.) treatment as a salvage therapy for antiretroviral experienced HIV-infected patients failing their current protease inhibitor regimen. Following baseline genotypic analysis of isolates, 55% were found to be susceptible to amprenavir, 42% to abacavir and 75% to efavirenz. Viral load reductions from baseline up to 1 $\log_{10}$ copies/ml or < 2.6 $\log_{10}$ copies/ml (in isolates sensitive to 2 or 3 study drugs) were observed in 50% and 56% of the patients, respectively; only 18% of the patients had isolates sensitive to one of the drugs (10).

In a randomized trial, 74/82 HIV-infected antiretroviral-naive patients received abacavir (300 mg b.i.d.) in combination with a standard dose of a protease inhibitor (indinavir, nelfinavir, ritonavir, saquinavir or amprenavir). HIV-1 genotypes were obtained from 71 patients at baseline and 15 patients with plasma viral HIV > 400 copies/ml at 16 weeks. Therapy switch was allowed at 16 weeks to include 3TC/ZDV in addition to abacavir and changed protease inhibitors if patients had plasma viral RNA > 400 copies/ml. No abacavir resistant mutations were observed at baseline and 19/71 showed at least 1 PRO mutation or polymorphism associated with resistance to the assigned protease inhibitor. After 16 weeks, HIV-1 isolates from 7/15 patients had previous baseline or developed PRO mutations; abacavir resistant mutations (184V) developed in only 3 patients. No amprenavir PRO mutations were detected (11).

Potent viral suppression and increases in CD4 cell counts were observed in an ongoing phase II clinical trial involving 27 newly and 12 chronically infected protease inhibitor/3TC-naive HIV patients administered twice-daily abacavir (300 mg), amprenavir (1200 mg) and ZDV/3TC (300/1500 mg) for 17 months. Adverse effects included nausea, vomiting and fatigue and the mean time on study was 9.7 months. Grade II or less rash was observed in 5 newly and 2 chronically infected patients. The change in viral load at week 8 was 156,725 and 54,416 copies/ml for newly and chronically infected patients, respectively. Plasma HIV RNA was undetectable at 12, 24 and 52 weeks in 21/22, 17/17 and 9/9 newly infected patients, respectively, and in 10/12, 9/10 and 10/10 chronically infected subjects, respectively. Sustained plasma RNA levels of < 50 copies/ml were achieved after 1 year in 7/9 and 6/10 newly and chronically infected patients, respectively. After 1 year, the mean change in CD4 was +197 cells/μl in newly infected and +193 cells/μl in chronically infected individuals. Significant changes in naive $CD4^+CD62L^+RA^+$ cells were observed by week 26 with even greater increases in naive CD8 cells (12).

The tolerability and long-term safety of abacavir (in combination with ZDV/3TC) were demonstrated in a randomized, open-label, crossover trial involving 60 antiretroviral-naive patients with plasma HIV-1 RNA of at least 30,000 copies/ml and $CD4^+$ counts of at least 100 cells/mm^3. Patients received three doses of abacavir for 24 weeks. After 72 weeks, 47 patients remained in the study of whom 90% continued with the triple combination therapy. Of the 8 patients who withdrew during the open-label phase, 6 were lost to follow-up and 2 dropped out due to adverse effects. Adverse effects included nausea/vomiting, malaise/fatigue, headache, muscle pain and gastrointestinal discomfort or pain (13).

A pharmacokinetic study reported the effects of coadministration of methadone and abacavir in 19 HIV-positive narcotic drug users given single-dose abacavir (600 mg) on day 1 and methadone (40 mg/day or more) on days 2-4 followed by abacavir (600 mg b.i.d.) + methadone combination treatment on days 15-28. Results showed that although methadone caused a slight delay in the rate, but not extent, of abacavir absorption, the antiviral activity of abacavir should not be affected. Increases in methadone oral clearance with coadministration indicated that a minor dose adjustment of methadone may be necessary (14).

In order to evaluate possible therapeutic options for HIV patients, the resistance profiles of the predominant virus were determined in patients (plasma HIV-1 RNA > 400 cells/ml) on abacavir and other combination therapies. Most patients on combination therapy with abacavir showed sustained suppression of HIV-1 replication. Those patients with detectable viral HIV-1 RNA after 16 weeks of treatment were found to have the M184V mutation. Since this mutation is only associated with resistance to 3TC, the majority of NRTIs, all NNRTIs and all protease inhibitors were concluded to be therapeutic options for these patients (15).

Sixty patients with HIV-1 infection were randomized to 1 of 3 treatment groups of oral abacavir (100, 300 and 600 mg b.i.d.) for 24 weeks. Subjects completing randomized therapy or who met predefined switch criteria began open-label, twice-daily treatment with abacavir (300 mg), zidovudine (300 mg) and lamivudine (150 mg) for an additional 24 weeks. At 24 weeks, a greater reduction in plasma HIV RNA levels was seen with the 600-mg dose of abacavir as compared to the 300- and 100-mg doses. During the open-label phase, a further mean reduction of 1.74 $\log_{10}$ copies/ml in plasma HIV RNA was seen. Abacavir was well tolerated with few clinically

significant adverse events. Overall, combination therapy (abacavir + zidovudine + lamivudine) was a highly effective antiretroviral regimen (16).

Abacavir sulfate (Ziagen™) was recently introduced in the U.K. for combination antiretroviral therapy in the treatment of HIV infection. Abacavir has proven to be additive or synergistic in combination with other NRTIs such as didanosine, zalcitabine, lamivudine, stavudine and zidovudine, and thus offers the possibility of triple nucleoside therapy as an option in the treatment of HIV/AIDS. The product is available as tablets containing the equivalent of 300 mg of abacavir and as a strawberry- and banana-flavored oral solution containing the equivalent of 20 mg/ml of abacavir. The first launch for Ziagen™ was in the U.S. in January and it has been approved in a number of other markets, including Canada, New Zealand and the other E.U. countries (17-23).

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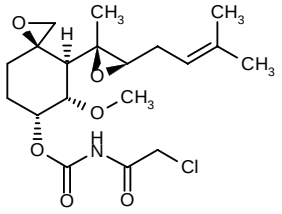
AGM-1470
TNP-470

Angiogenesis Inhibitor

EN: 161076



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

TNP-470 has been examined for its antiproliferative effects against human squamous cell lung cancer *in vitro* and *in vivo*. Concentration-dependent inhibition of the proliferation of H226B and the p53 variant H226Br cell lines was observed at concentrations of 100 ng/ml to 10 mcg/ml. In nude mice bearing H226Br tumors, treatment with doses of 30 or 100 mg/kg s.c. every other day produced inhibition of both tumor growth and neovascularization. The higher dose was, however, also associated with toxicity, *i.e.*, a decrease in body weight. It appears that the mechanism of action of TNP-470 involves both a direct effect and an angiogenesis factor-mediated effect (1).

TNP-470 (50 mg/kg i.p. at time of laser and on day 7) was shown to significantly decrease the incidence of laser photocoagulation-induced retinal choroidal neovascularization (22.7 *vs.* 61.4% in controls). TNP-470-treated rats showed no changes in basic fibroblast growth factor (bFGF) expression, whereas controls displayed an upregulation on days 3 and 7; no differences in vascular endothelial growth factor expression were observed between groups. TNP-470-treated rats had significantly less bFGF mRNA positive cells (retinal pigment epithelial and outer and inner nuclear layer cells) in the

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regenerated retina as compared to control rats on days 3 and 14 (2).

TNP-470 was shown to significantly delay cutaneous wound healing in a murine dorsal excisional wound model. Homozygous/hairless mice with dorsum full-thickness wounds were treated with TNP-470 alone (0.05, 0.5 and 5 mg/kg on days 0, 2 and 4 or 0-6) or a combination of TNP-470 (5 mg/kg on days 0, 2 and 4) and minocycline (4 and 10 mg/kg) or topical bFGF (1 mcg/wound on days 0-2). TNP-450 significantly and dose-dependently decreased wound healing with the highest dose resulting in maintenance of 20.4% of the wound area. Although minocycline did not enhance TNP-470 effects, bFGF abolished the effects of the agent, resulting in wound areas similar to controls (3).

A novel model for studying the effects of antiangiogenic agents on tumor vascularization and the angiogenic mechanisms responsible for hemangioma progression has been described. Four-day old rats showed development of multiple cutaneous, i.m. and cerebral hemangiomas after i.p. injection with murine polyomavirus. Immature lesions were detected 4 days after infection. Lesions were blood filled cysts which were positive for proliferating cell nuclear antigen, urokinase-type plasminogen activator and VEGF; cerebral lesions, expressing von Willebrand factor, resulted in death at 19.2 ± 1.1 days after infection. Survival was significantly increased to 28.2 ± 3.3 days in animals treated with TNP-470 (50 mg/kg twice weekly) starting on day 3 postinfection (4).

TNP-470 and 2-methoxyestradiol were shown to be effective against angiosarcoma in mice, indicating that the agents may be effective in humans with angiosarcoma and hemangioendothelioma. Tumor size was decreased by 84% and 68% with the respective agents (5).

TNP-470 was shown to prevent radiation-induced microvascular damage in U87 human glioblastoma xenografts (s.c.). When tumors reached 7 mm, nude mice were treated with TNP-470 (6.7 mg/kg/day s.c.) and radiation (10 Gy) alone or in combination with TNP-470 given 1 week prior to radiation. Although radiation-treated tumors excised at 8 and 48 h showed irregular vessels with protrusion and swelling of epithelial cells as compared to the control group, these differences were not observed in tumors from mice given TNP-470 alone or in combination with radiation (6).

The effects of TNP-470 on the primate ovulatory cycle were investigated to determine the role of angiogenesis in luteal function and to characterize its effects in a model related to man. Short-term treatment with TNP-470 produced no effect on the corpus luteum. Findings in this study differ from those found in a mouse model due to interspecies variance or differential susceptibility to its antiantagonistic effect. It was determined that clinical doses of TNP-470 would not affect the ovulatory cycle in women (7).

TNP-470 was shown to significantly inhibit allogenic- or mitogenic-induced human $CD4^+$ T cell proliferation *in vitro.* TNP-470 (10 μg/ml) appeared to directly affect cell cycle progression in contrast to inhibiting T cell proliferation, cytokine production or autocrine response to IL-2. TNP-470 did not induce cell death since proliferation was partially restored with recombinant IL-2. Thus, TNP-470 may be a potential drug for use after transplantation (8).

The antitumor effects of TNP-470 (30 mg/kg s.c. twice weekly) were examined in athymic mice bearing tamoxifen-stimulated MCF-7 tumor. No major side effects were noted with TNP-470 treatment and tumor growth was significantly inhibited with no observed reductions in body weight or effects on tamoxifen metabolism in tumor, serum or liver. Treatment also decreased the number of microvessels and VEGF production and significantly induced tumor cell apoptosis (9).

Inhibition of tumor formation with TNP-470 was found to be schedule-dependent and effective only beyond the first 3 days after inoculation. Nude mice bearing human U87 glioblastoma xenografts were treated with the agent (7 mg/kg/day s.c.) before and until day 3, 7, 11 or 15 after inoculation. Tumor growth in the day 3 group was not delayed as compared to controls, while longer treatments resulted in delays in initiation of exponential growth proportional to treatment time. The time to recovery varied from 4-7 days and was independent of treatment duration (10).

TNP-470 administered after stem cell transplant in mice was shown not to adversely affect the engraftment. Irradiated FVB mice infused with littermate bone marrow expressing human IgM heavy and light chain as the transgene were treated with TNP-470 for 30 days. Multilineage engraftment and normal B cell maturation were observed in both treated and control mice (11).

The *in vitro* antiproliferative activity and *in vivo* efficacy in an experimental model of choroidal neovascularization of TNP-470 conjugated with the water-soluble polymer poly(vinyl alcohol) (PVA) have been evaluated. The inhibitory activity of TNP-470-PVA against the growth of human umbilical vein endothelial cells was similar to that of free drug, with an EC_{50} of 0.6 μg/ml. It was less effective in bovine retinal pigment epithelial cells, giving an EC_{50} of 60 μg/ml. In rabbits with experimental choroidal neovascularization induced by subretinal injection of bFGF-containing gelatin microspheres, intravenous treatment with TNP-470-PVA for 3 days significantly inhibited the development of choroidal neovascularization (12).

A phase I study examined the pharmacokinetics of TNP-470 (25-235 mg/m^2 i.v. over 4 h once weekly) in 36 patients with refractory solid tumors or at high risk for recurrence. Results showed short mean plasma $t_{1/2}$ values for TNP-470 and its metabolite AGM-1883 (2 and 6 min, respectively) and no drug was found in plasma 60 min after infusion, indicating that a prolonged i.v. infusion schedule is required. Toxicities were observed with doses of 133, 177 and 235 mg/m^2 and included dizziness, lightheadedness, vertigo, ataxia, reduction in ability to concentrate and short-term memory, confusion, anxiety and depression. Neurological toxicities were dose-related, progressed with treatment and were resolved within 2 weeks of drug discontinuation. Dose-limiting toxicity (cerebellar neurotoxicity) was seen in 2 patients receiving

235 mg/m^2 after 6 weeks of treatment and the maximum tolerated dose was concluded to be 177 mg/m^2 over 4 h once weekly. One patient with malignant melanoma showed stabilization for 2 weeks with treatment. No evidence of disease recurrence was noted after 13 months and > 3 years of treatment in 2 patients, respectively, with colon adenocarcinoma or soft tissue sarcoma who did not have clinically detectable disease at study onset. Progression of disease was observed in all other patients after 1-6 months of treatment (13).

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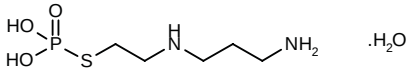
Amifostine Hydrate
Ethyol®

Radioprotectant

EN: 090725



$C_5H_{15}N_2O_3PS.H_2O$

Alza; Schering-Plough; U.S. Bioscience

Amifostine (Ethyol®) has been granted E.U. approval for use in association with standard fractionated radiation therapy to protect against acute and late xerostomia in head and neck cancer. As a result, U.S. Bioscience will receive a milestone payment from Schering-Plough, its marketing partner for Ethyol® in Europe (1).

The FDA has approved Ethyol® for the reduction of moderate to severe xerostomia in patients undergoing postoperative radiation treatment for head and neck cancer in which the radiation port includes a substantial portion of the parotid glands. Ethyol® is the first therapy to be approved by the FDA for the treatment of radiation-induced dry mouth. The approval specifically applies to patients undergoing postoperative radiation therapy. Therefore, Ethyol® should not be administered in patients receiving definitive radiation therapy except in the context of a clinical trial (2, 3).

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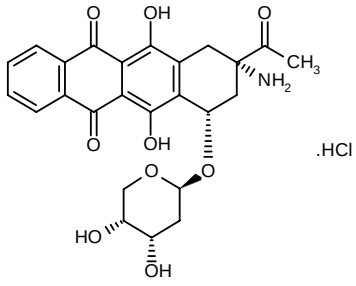
Amrubicin Hydrochloride

Antineoplastic Antibiotic

EN: 142668



$C_{25}H_{25}NO_9.HCl$

Sumitomo

Amrubicin and its metabolite amrubicinol were evaluated against 17 human tumor cell lines. Amrubicinol displayed 5-54 times greater potency than amrubicin and was as potent as doxorubicin in cell growth inhibition following continuous exposure over 3 days. In addition, amrubicinol closely replicated doxorubicin's activities in the tested tumor cell lines (1).

The disposition and metabolism of amrubicin (25 mg/kg i.v.) were examined in mice and compared to doxorubicin (12.5 mg/kg i.v.). In amrubicin-treated animals, the 13-hydroxy metabolite amrubicinol, 10-11 times more cytotoxic than amrubicin, was the major metabolite found in blood and tissues; aglycones of amrubicin were also found. Amrubicin had a smaller distribution volume and shorter half-life than doxorubicin. Although the concentrations of amrubicin and amrubicinol were lower in several tissues as compared to doxorubicin, tumor levels of

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amrubicinol were higher, demonstrating selective distribution of this agent (2).

A study evaluating the chronic cardiotoxic potential of amrubicin and its ability to potentiate doxorubicin cardiotoxicity were evaluated in beagle dogs administered clinically relevant doses of amrubicin (2.5 mg/kg i.v.) or doxorubicin (1.5 mg/kg i.v.) once every 3 weeks for 6 months. Animals given doxorubicin showed ECG changes, reduced blood pressure and high-grade histopathological cardiomyopathy, whereas animals given amrubicin showed no such changes. In dogs in which low-grade cardiomyopathy was induced by 4 courses of doxorubicin, the addition of doxorubicin for 4 more courses enhanced the cardiotoxic changes, but amrubicin did not induce further deterioration. The results from this study further underscore the cardiac safety of amrubicin and suggest its promise both as first-line therapy in cancer patients and in those at risk for anthracycline cardiotoxicity (3).

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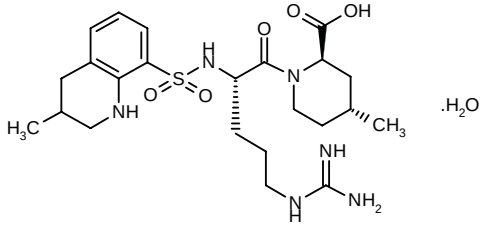
Argatroban Monohydrate
Novastan®
Slonnon®

Anticoagulant
Thrombin Inhibitor

EN: 090744



$C_{23}H_{36}N_6O_5S.H_2O$

Texas Biotechnology; SmithKline Beecham

Argatroban is under regulatory review in Europe for the treatment of heparin-induced thrombocytopenia and thrombosis syndrome and is in phase II testing as an adjuvant to thrombolytics in the treatment of myocardial infarction (1).

Following discussions with the FDA, Texas Biotechnology has corrected the amendment to the argatroban (Novastan®) NDA, which involved correcting the coding of patient endpoint data and dates on which they occurred. Data involving 33 of 304 patients in a pivotal phase III trial, when corrected, improved one of the efficacy analyses for Novastan®. In a second phase III follow-up trial, 6 of 264 patient endpoints were miscoded and, when corrected, had no clinically substantive effects on the efficacy results. Overall, the corrected analyses do not change the positive clinical interpretation of the efficacy endpoints and have no effect on the safety analysis of the drug. Novastan® has been developed by Texas Biotechnology in collaboration with SmithKline Beecham as an anticoagulant for use in patients with heparin-induced thrombocytopenia. A response from the FDA on the amended NDA is expected by February (2, 3).

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Beraprost Sodium
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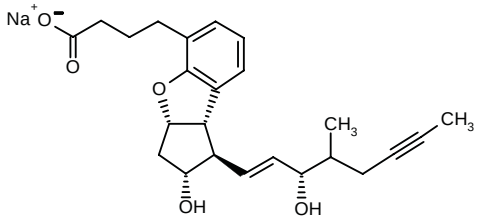
Platelet Antiaggregatory
Treatment of Pulmonary Hypertension

EN: 116067



$C_{24}H_{29}O_5.Na$

United Therapeutics; Toray; Yamanouchi

United Therapeutics and Toray entered into an agreement to cooperatively test beraprost sodium in North America for the treatment of pulmonary vascular disease and peripheral vascular disease. Phase II trials are expected to be completed during 1999 and phase III trials by 2001 (1).

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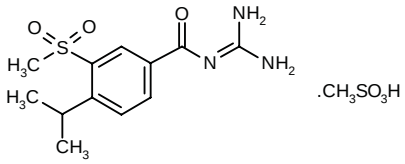
Cariporide Mesilate
Hoe-642

Cardioprotectant
Na^+/H^+ Exchange Inhibitor

EN: 215949



$C_{12}H_{17}N_3O_3S.CH_4O_3S$

Hoechst Marion Roussel

The cardioprotective effects of ischemic preconditioning on cardiac arrhythmias and infarction were found not to be due to Na^+/H^+ exchange activity in an *in vivo* study using cariporide (0.3 mg/kg) in rats. Animals were subjected to 30 min of coronary occlusion and 150 min of reperfusion and preconditioning induced either by a 3-min ischemia and 10-min reperfusion (1PC) or 3 episodes of 3-min ischemia and 5-min reperfusion (3PC). Cariporide given 30 min before coronary ligation reduced the incidence of ventricular fibrillation (from 45% to 0%) and infarct size (from 34 ± 4% to 9 ± 2%) while cariporide given 45 min prior to ligation had no effect. Similarly, 3PC also reduced ventricular fibrillation (to 0%) and infarct size (to 10 ± 2%) while 1PC had no effect. However, a combination of 1PC with cariporide given 45 min prior to ligation decreased the incidence of ventricular fibrillation (to 0%) and infarct size (15 ± 3%), indicating additive activity (1).

Inhibition of the Na-H exchanger with cariporide was found to delay the onset and reduce the degree of regional dysfunction due to repeated ischemia and reperfusion. Pigs were exposed to 25 cycles of ischemia (2 min) and reperfusion (8 min) of the left circumflex artery (LCx). A significant reduction in LCx systolic wall thickening was observed after only 5 cycles of ischemia/reperfusion, with a stable 55% reduction observed after 20 cycles. Cariporide administration significantly reduced systolic wall thickening only after 15 and 25 cycles of ischemia/reperfusion (80 and 72%, respectively) (2).

Cariporide was shown to depress lethal arrhythmias and protect the metabolic status of the heart in a study using reperfused hearts from rats treated with cariporide (0.1 or 1.0 mg/kg i.v.) or vehicle after ligation (5 min) of the left coronary artery and 2 min before reperfusion; hearts were removed 3 min after fibrillation onset. Lethal ventricular fibrillation was decreased in animals treated with the low (27%) and high (7%) doses of cariporide as compared to untreated controls (53%). Cariporide treatment also significantly reduced creatinine phosphate overshoot and glycogenolysis during reperfusion since lower creatinine phosphate and higher ATP and glycogen content were observed in treated animals as compared to untreated controls (3).

Cariporide was shown to protect against acute cardiac allograft rejection from ischemia/reperfusion injury. Both donor and recipient rats were treated orally with the

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agent for 7 days before transplant and recipient rats for 7 days posttransplant (30 mg/kg t.i.d. s.c. and p.o.); cardioplegic solution also contained the agent (10 μM). Cardiac allograft survival was significantly prolonged from 6.0 ± 0.5 to 9.9 ± 1.4 days in the treated group. Grafts from treated animals showed a significant reduction in mononuclear cell infiltration as compared to grafts of untreated animals, which displayed upregulated ICAM-1 after transplantation, increased infiltration of $ED1^+$ macrophages and monocytes and α/β^+ T cells and more cells expressing MHC II (4).

Hyper- and normocholesterolemic rabbits were treated acutely (0.3 mg/kg) or chronically (0.1% in chow for 4 weeks) with cariporide mesilate prior to occlusion and reperfusion (30 min plus 2 h) of the LAD. Infarct size in cholesterol-fed rabbits was significantly greater than in animals fed a normal diet (63 ± 3% *vs.* 41 ± 3%), and acute treatment with cariporide reduced infarct size in rabbits with normal and high cholesterol by 61% and 65%, respectively, as compared to untreated controls. Chronic cariporide treatment was associated with similar reductions in infact size (–53% and –49%) in normo-and hypercholesterolemic rabbits, respectively (5).

A preclinical study was conducted with the aim of clarifying the exact mechanism by which cariporide improves mechanical recovery following ischemia. Langendorff rat hearts were subjected to 30 min each of ischemia and reperfusion, with or without study drug (1 μM) added to the perfusate 30 min before ischemia. Pretreatment with cariporide had no effect on baseline mechanical function, Ca^{2+} transients or pH. Mechanical recovery was significantly better in hearts treated with cariporide, as evidenced by measurements of developed pressure and diastolic pressure. Ischemic contracture did not differ significantly between treated and untreated hearts. Intracellular calcium peaked during the first 30 seconds of reperfusion; this effect was attenuated significantly in the cariporide group (2.0 ± 0.3 μM *vs.* 3.2 ± 0.3 μM). Intracellular pH, measured 30 and 60 seconds and at least 7 min postreperfusion, did not differ significantly although acidosis was prolonged from 2 min (untreated controls) to 6 min (cariporide-treated hearts). Thus, it appears that cariporide improves postischemic recovery via two mechanisms: first by reducing calcium overload during ischemia and in the early stages of reperfusion, and later by prolonging acidosis during reperfusion (6).

In a rabbit model of myocardial reperfusion injury (60 min ischemia plus 3 h reperfusion), animals were administered cariporide (1 mg/kg) or vehicle 5 min prior to reperfusion. Myocardial injury in cariporide-treated rabbits was reduced significantly as compared to vehicle-treated controls (13 ± 3.1% *vs.* 22.6 ± 2.5%). Increased plasma creatine kinase activity in response to reperfusion, a marker of myocardial injury, was suppressed significantly in cariporide-treated animals, while myeloperoxidase activity in the necrotic zone, a marker of PMN accumulation, decreased significantly with cariporide as compared to vehicle. Neutrophil accumulation was reduced significantly in the reperfused myocardium of rabbits treated with the active drug (7).

Preliminary results from a double-blind, randomized, placebo-controlled, parallel-group phase II/III trial assessing the efficacy and safety of cariporide have been reported. Over 11,500 patients were enrolled in this multinational study and received treatment with cariporide 20, 80 or 120 mg i.v. every 8 h, or placebo, in addition to standard therapies. The patient population studied included three subgroups: patients with unstable angina pectoris or non-Q wave myocardial infarction, patients undergoing percutaneous transluminal coronary angiopasty (PTCA) and coronary artery bypass graft (CABG) patients. The results showed a safety profile comparable to placebo for cariporide. Although statistical significance was not reached for the primary endpoint of a reduction in the incidence of death or myocardial infarction 36 days after randomization, subgroup analysis indicated a reduction in events in the CABG patient group on the highest dose of cariporide. The death/MI rate in placebo-treated patients was 13.4%, compared to 13.5, 14.1 and 12.2%, respectively, on cariporide 20, 80 and 120 mg. CABG patients on placebo showed an incidence of death/MI of 16.7%, compared to an incidence of only 12.8% on cariporide 120 mg (8, 9).

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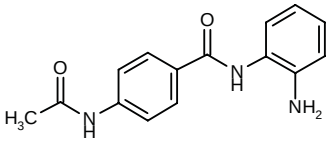
CI-994 *Antineoplastic*
Acetyldinaline
Goe-5549
PD-123654

EN: 137584



$C_{15}H_{15}N_3O_2$ **Warner-Lambert; Goedecke**

CI-994 was shown to increase histone acetylation *in vitro* in HCT-8 cells by a mechanism other than inhibition of histone deacetylase. Levels of acetylated histone H3 were increased even at 30 min after CI-994 (10 μM) addition and continued to increase up to 24 h (IC_{50} = > 100 μM); similar increases were observed with addition of the histone deacetylase inhibitor, trichostatin (IC_{50} = < 6 nM). Both CI-994 and trichostatin increased gelsolin expression, suggesting a more differentiated phenotype (1).

The *in vivo* antitumor activity of CI-994 in combination with gemcitabine was greater than with each agent alone against LC12 squamous cell lung carcinoma implanted s.c. Animals were treated on day 10 posttumor implant with each agent alone (60 and 80 mg/kg, respectively) or with CI-944 (30 and 45 mg/kg p.o. every day times 5 for 3 weeks) simultaneously with or following gemcitabine (80 mg/kg i.p every 3 days times 4). Tumor growth delays of 16.6 and 16.0 days were observed in animals treated with CI-994 and gemcitabine alone, respectively, while combination simultaneous and sequential treatment resulted in greater delays of 36.0 and 30.7 days, respectively (2).

The pharmacokinetics and cerebral spinal fluid (CSF) penetration of CI-994 were examined in 4 nonhuman primates given 4 doses (80 or 100 mg/m^2 i.v. over 20 min). Plasma elimination was shown to be triexponential in 4/5 and biexponential in 1/5 cases. Plasma $t_{1/2}$, volume distribution and clearance were 7.4 ± 2.5 h, 15.4 ± 1.7 l/m^2 and 39 ± 6 ml/min/m^2, respectively; the AUC for 80 mg/m^2 was 125 ± 17 μM·h. CI-994 was detected in CSF after completion of the first infusion with peak levels of 3.41 ± 0.3 μM. CSF elimination was nonexponential (2/4) or biexponential (2/4) with $t_{1/}2$ and AUC values of 12.9 ± 2.5 h and 55 ± 18 μM·h, respectively. The AUC_{CSF}:AUC_{plasma} ratio was 44 ± 10% (3).

Results of a phase II trial of CI-994 (8 mg/m^2 p.o.) in 32 patients with advanced nonsmall cell lung cancer showed that treatment was well tolerated although the response rate was low. Of the 29 patients evaluable for response, 2 had partial response and median time to disease progression and median survival were 8 and 30 weeks, respectively. Three patients showed improved disease-related symptoms or performance status. During the first month, platelet counts decreased but rebounded with treatment; grade 3 and 4 platelet nadirs were observed in 1 and 2 patients, respectively. Other grade 1 or 2 adverse effects observed were fatigue, anorexia, nausea, vomiting and paresthesia. It was concluded that the low response rate may be due to the cytostatic mechanism of action of CI-994 (4).

Results of a phase II trial of CI-994 (8 mg/m^2 p.o.) in 48 patients with metastatic renal cell carcinoma showed that treatment was well tolerated although response rate was low. Of the 45 patients evaluable for response, the best response was stable disease in 26 patients for 8 weeks or more with a median duration of 23 weeks. Median time to disease progression and median survival were 15 and 48 weeks, respectively. Two patients showed improved disease-related symptoms or performance status and minor responses were observed. During the first month, platelet counts decreased but rebounded with treatment; grade 3 and 4 platelet nadirs were observed in 6 and 1 patients, respectively. Other grade 1 or 2 adverse effects included fatigue, anorexia, nausea, vomiting and paresthesia. The low response rate was suggested to be due to the cytostatic mechanism of action of CI-994 (5).

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Original monograph - Drugs Fut 1997, 22: 1201.

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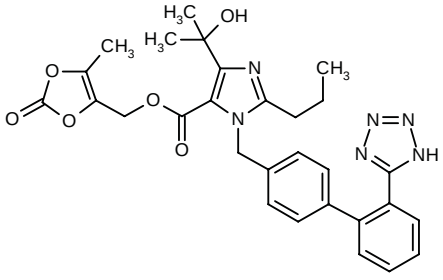
CS-866
Olmesartan

Antihypertensive
Angiotensin AT_1 Antagonist

EN: 217950



$C_{29}H_{30}N_6O_6$

Sankyo; Recordati

CS-866 was shown to be effective as a treatment for diabetic nephropathy in the Zucker diabetic fatty rat. At 12 weeks of age, when microalbuminuria was detected, rats were treated for 10 weeks with CS-866 in the diet (0.001 and 0.01%). The lower dose of CS-866 significantly reduced blood pressure and urinary protein excretion. The low plasma albumin and high plasma lipids levels seen in Zucker rats were normalized by treatment and also glomerular and tubular injury in the kidney were decreased. Body weight, urinary volume, plasma and urinary glucose and plasma insulin were unaffected by treatment (1).

Concomitant administration of an antacid with the optimum dose of CS-866 (20 mg p.o. once daily on days 4-8) in healthy male subjects did not significantly affect the bioavailability of CS-866 or its active metabolite RNH-6270. The bioavailability of the metabolite decreased slightly following coadministration of CS-866 with the antacid, but the difference was not considered to be clinically significant. Rate of absorption and elimination half-life of RNH-6270 did not vary significantly (2).

A randomized, double-blind, placebo-controlled, 2-way crossover study in 24 healthy male subjects showed that combination administration of warfarin (titrated doses) and CS-866 (40 mg once daily) for 7 days was well tolerated and had little effect on warfarin pharmacokinetics. The AUC_{0-24} and C_{max} values for (*R*)- and (*S*)-enantiomers of warfarin were not altered by CS-866 administration and coadministration had little effect on Quick and PTT coagulation factors (3).

The dose-response relationship of CS-866 has been established in healthy male volunteers in a double-blind, randomized, 4-way crossover, dose-escalating study. Subjects in this study were administered 4 single doses of CS-866 (2.5, 5, 10, 20 or 40 mg p.o.), enalapril (20 mg) and/or placebo in a random fashion, with each drug dose preceded and followed by administration of a standard i.v. bolus dose of angiotensin I (10-40 ng/kg as needed to raise systolic blood pressure by 25-30 mmHg), and effects on blood pressure were compared. Treatments were separated by a 2-week washout period. The angiotensin I-induced increase in systolic blood pressure was inhibited more effectively by CS-866 at all dose levels than by placebo. At the 3 highest dose levels, CS-866 produced more than 50% inhibition for up to 24 h after dosing. The maximum blocking effect was obtained at doses of 10-20 mg and was comparable to that obtained with 20 mg enalapril; higher doses did not provide a significant increase in inhibition. At the 20-mg dose, pharmacodynamic effects of CS-866 were significantly different from those of enalapril. Peak effect of the study drug at all dose levels was observed 4-6 h postdosing. CS-866 was well tolerated, with no relevant side effects (4).

Olmesartan is the new proposed international nonproprietary name for CS-866 (5).

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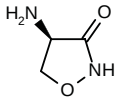
D-Cycloserine

Cognition Enhancer

EN: 166169



$C_3H_6N_2O_2$ **Searle**

The effects of D-cycloserine (5 mg/kg) alone or in combination with ST-587 (100 μg/kg) were examined on nondelayed and delayed foraging behavior of rats using the radial arm maze. Both agents administered alone decreased working memory errors, *i.e.*, reentries into previously entered arms. However, combination treatment did not result in an enhanced effect (1).

Results from a placebo-controlled, double-blind, parallel study in 26 patients with chronic schizophrenia showed that D-cycloserine (100 mg) combined with typical antipsychotics and anticholinergics worsened psychotic symptoms and general psychopathology as compared to placebo and did not alter negative symptoms; no effects on extrapyramidal symptoms were observed. The antagonistic effects of the compound at the glycine recognition site of the NMDA receptor suggest that the NMDA system may be involved in the pathogenesis of schizophrenia (2).

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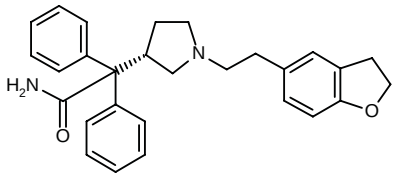
Darifenacin

Treatment of Urinary Incontinence
Muscarinic M_3 Antagonist

EN: 168032



$C_{28}H_{30}N_2O_2$ **Pfizer**

Darifenacin is in advanced-stage clinical trials for urinary urge incontinence (1).

1. *Pfizer: Q4 1998 highlights.* DailyDrugNews.com (Daily Essentials) Feb 19, 1999.

Original monograph - Drugs Fut 1996, 21: 1105.

Additional Reference

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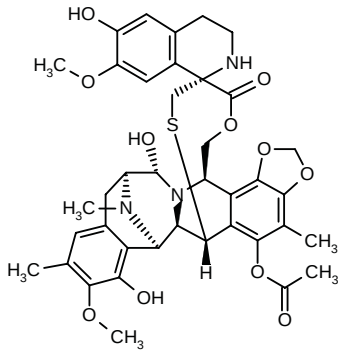
Ecteinascidin 743
ET-743

Antineoplastic

EN: 139221



$C_{39}H_{43}N_3O_{11}S$ **Univ. of Illinois; Pharma Mar**

ET-743 was shown to induce topoisomerase I-mediated protein-linked DNA breaks with topoisomerase I positively identified as the target for the agent. Topoisomerase I was purified using an oligonucleotide with high affinity binding sites for ET-743 and nuclear extracts. The purified topoisomerase I in the presence of ET-743 produced cleavage complexes in SV40 DNA; the distribution of drug-induced topoisomerase I sites varied for ET-743 and camptothecin (1, 2).

A study using gel shift assays showed that the anticancer mechanism of action of ET-743 may involve interference with the binding of DNA binding proteins to DNA.

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ET-743 had no affect on Sp1, Maf, MYB and MYC DNA binding but inhibited binding of TATA binding protein, E2F and SRF at concentrations of 0-300 μM; NF-Y binding was inhibited with concentrations of 10-30 μM and was independent of prior ET-743 DNA binding. ET-743 at concentrations of 3-10 μM was also shown to reduce and completely suppress the nucleosomal band at 100 nm (3).

The cytotoxicity of ET-743 was examined using 18 different tumor cells including cells derived from pediatric tumors and 2 nonmalignant cells exposed to the agent (0.0001-0.1 μg/ml) for 1, 3, 6, 8 and 24 h. Immediate and delayed effects were found to have different pharmacodynamics. Immediate effects were higher with increasing exposure time while the greatest sensitivity of the delayed effect was achieved at 3 and 8 h (4).

A study has shown that the cytotoxicity of ET-743 may be due to targeting of telomeric sequences directly or through cross-linking DNA with telomeric proteins. Results showed that 10.5 and 24 h incubation of sea urchin embryos (containing telomeric repeats identical to humans) with 1 μM ET-743 caused an arrest in growth and formation of stringy chromosomes and incubation with 100 nM ET-743 resulted in some nuclear disintegration and chromosomal end-to-end fusions (5).

The action of ET-743 in combination with doxorubicin, docetaxel, cisplatin, navelbine or DTIC was investigated against several human tumor cell lines with results demonstrating additive drug interactions between these agents in most cell lines. A greater than additive interaction was observed with ET-743 and docetaxel against lung (2/3) and breast tumor (1/3) cell lines with one possible antagonistic effect observed against a breast cancer cell line. Results show that ET-743 can be effectively combined with several cytotoxic agents against several tumor types (6).

Studies on the mechanism of action of ET-743 have shown that EE-743, in contrast to all other known minor groove DNA-alkylating agents, bends DNA into the major groove. Furthermore, the unique wedge-shaped structure of the compound imparts a novel minor groove occupancy not seen with other DNA-reactive drugs. This novel mechanism of action is expected to contribute to the outstanding potency of the compound as well as its lack of myelosuppression, a common side effect with this class of drugs (7, 8).

The effects of ET-743 on a human hepatocellular carcinoma cell line (HA22T) were examined *in vitro* and *in vivo* with results showing time-dependent inhibition of clonogenic survival (IC_{50} = 0.6 nM at 24 h and 25 nM at 1 h), apoptotic cell death and mitotic arrest in the G_2/M phase. ET-743 (33 and 17 μg/kg every 4 days for 3 doses) inhibited tumor growth in mice bearing HA22T tumors (s.c.) with the median doubling increasing to 36 days compared to 18 days in controls. Results indicate that ET-473 may be a potential treatment for hepatoma (9).

ET-743 was assessed for its *in vitro* effects against 93 tumor specimens taken from patients. Specimens were exposed to the compound for 1 h and/or 14-day continuous exposure at concentrations from 0.1 nM to 1 μM. The duration of exposure was an important factor and long-term exposure may be preferable in future trials. A plasma concentration of 100 nM should be considered the target in clinical development of this compound. In addition, continuous/protracted exposure of ET-743 in future trials needs to be considered (10).

A phase I pharmacokinetic study of ET-743 (72 h continuous i.v.) in cancer patients demonstrated the advantage of prolonged exposure to the agent. In 3 patients, C_{max} values of 220 ± 51 pg/ml and 324 ± 181 pg/ml for 200 and 300 mg/m^2/day, respectively, were obtained and $t_{1/2}$ following exponential delay of 13.6 ± 5.3 min and 46 ± 22 h for initial and terminal disposition phases, respectively, were observed. A 2-fold decrease in plasma ET-743 was observed about 1 h from the end of treatment to the beginning of the terminal phase and therefore plasma levels could be measured > 96 h postinfusion. Mean residence was 32 ± 18 h showing that the slow terminal phase influenced ET-743 disposition (11).

The pharmacokinetics of ET-743 at the recommended doses (1500 μg/m^2 24- or 3-h infusion and 325 μg/m^2 30-min infusion) were examined in a phase I trial in 113 cancer patients. Clearance, distribution volume and $t_{1/2}$ values for the doses were 30-60 l/h/m^2, 1000-2000 l/m^2 and 20-40 h, respectively. AUC values were similar for the 3 dosing schedules and were comparable to those values obtained in mice. Dose linear kinetics were obtained even though interpatient variability was high; no schedule dependency was observed. Modeling of results indicated that transaminitis and dose-limiting neutropenia observed with ET-473 were related to AUC (12).

The pharmacokinetics of ET-743 (50-1800 μg/m^2 24-h continuous infusion for 57 cycles) were determined in a phase I study in 40 cancer patients of whom 5 had significant liver involvement. Grade 3-4 toxicities (at 1800 and 1500 μg/m^2) included neutropenia (94% in 15/16 cycles and 40% in 7/57 cycles, respectively), thrombopenia (25% in 4/16 cycles and 12% in 7/57 cycles) and transaminitis (37.5% in 6/16 cycles and 40% in 23/57 cycles) peaking at 3-7 days and reversible by day 14. AUC values of 60 μg·h/l or more correlated with grade 3-4 transaminitis and grade 3-4 neutropenia lasting 5 days or more. The duration of transaminitis was dose-dependent. Dose-limiting toxicities (neutropenia and transaminitis) were observed with 1800 μg/m^2 in 3/4 patients and with 1500 μg/m^2 in 7/22 patients. It was concluded that 1800 μg/m^2 and 1500 μg/m^2 are the maximum tolerated (MTD) and recommended doses, respectively, with the latter dose considered the MTD for poor risk patients (13).

A phase I trial examined the tolerability of ET-743 (50-1800 μg/m^2 24-h infusion every 3 weeks) in 49 patients with advanced solid tumors including colorectal, sarcoma, breast, ovary, renal, bladder, gastric, larynx and melanoma. Acute grade 2 nausea/vomiting occurred with a dose of 600 μg/m^2 or more, with emesis easily controlled. Transaminase elevations were observed with the 4 highest doses, peaking at 3-7 days and rever-sible by day 14. The maximum tolerated dose was concluded

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to be 1800 μg/m^2 with neutropenia and thrombopenia the dose-limiting toxicities. Partial responses were seen in 1 patient with metastatic breast cancer refractory to anthracyclines and docetaxel and 1 heavily pretreated patient with metastatic osteosarcoma. Several minor and biological responses were seen in patients with breast, sarcoma and colon cancers receiving 1200 μg/m^2 or more of the agent (14).

Preliminary results from a phase I study in 11 treatment-refractory advanced sarcoma patients showed the efficacy of ET-743 (1500 or 1800 μg/m^2). Two partial responses, 2 MRs and 3 stable diseases were seen. Grade 3/4 toxicities included reversible transaminitis on days 3-5 (52%), neutropenia (39.5%) and thrombocytopenia (10.5%); febrile neutropenia (5%) was observed in 2 out of the 38 cycles. A phase II study is ongoing (15).

A phase I and pharmacokinetic study examined the efficacy and tolerability of escalated ET-743 (600, 900 and 1200 μg/m^2 as 72-h i.v. infusion every 21 days) in 15 patients with metastatic solid tumors. No grade 3 transaminitis, the dose-limiting toxicity, was observed in the 6 patients given the first two doses while 2 patients receiving 900 μg/m^2 showed this toxicity. Two and 5 patients had grade 4 and 3 transaminitis, respectively, of the 9 patients at 1200 μg/m^2 completing 15 cycles. One patient at 1200 μg/m^2 had grade 4 rhabdomyolysis, grade 4 neutropenia, grade 3 thrombocytopenia and acute renal failure in cycle 2; another patient at 1200 μg/m^2 had grade 3 neutropenia. The ET-743 plasma profiles were biphasic with a mean half-life of 59.9 ± 33.4 h. C_{max} values for the 3 doses were 283, 581 and 908 pg/ml, respectively, with AUC values of 12, 24.7 and 42.7 ng·h/ml, respectively. Evidence of activity as assessed by PET and CT scans was observed in 2 patients at 1200 μg/m^2 and another patient with mesothelioma showed almost a partial response. One patient with choroidal melanoma had reduced fluoride-oxyglucose uptake seen in PET scan after 1 cycle (16).

Results from a phase I and pharmacokinetic study of ET-743 (6-380 μg/m^2/day as 1-h infusion x 5 every 3 weeks) in 36 patients with advanced solid tumors showed that myelosuppression was the main dose-limiting toxicity (DLT). Out of 7 patients receiving 325 μg/m^2, none had DLT. Transient transaminase elevations lasting < 7 days were common (grade 3 in 51% for 94% of the course) in patients receiving 216 μg/m^2 or more although severity did not increase with dose. Other mild to moderate toxicities were emesis, asthenia, phlebitis and transient renal dysfunction. No major response were observed. Linear pharmacokinetics were obtained on days 1 and 5 from 26 patients, with drug accumulation observed on day 5. Clearance, steady-state volume of distribution, $t_{1/2}$ and $AUC_{(0-\infty)}$ values for 325 μg/m^2/day were 68.47 ± 23.64 l/h/m^2, 1738.5 ± 1198 l/m^2, 16.96 ± 7.9 h and 6.42 ± 2.06 μg·h/l, respectively. The recommended dose for phase II evaluation was 325 μg/m^2/day for 5 days every 3 weeks (17).

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Epibatidine *Analgesic*
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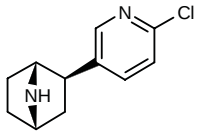


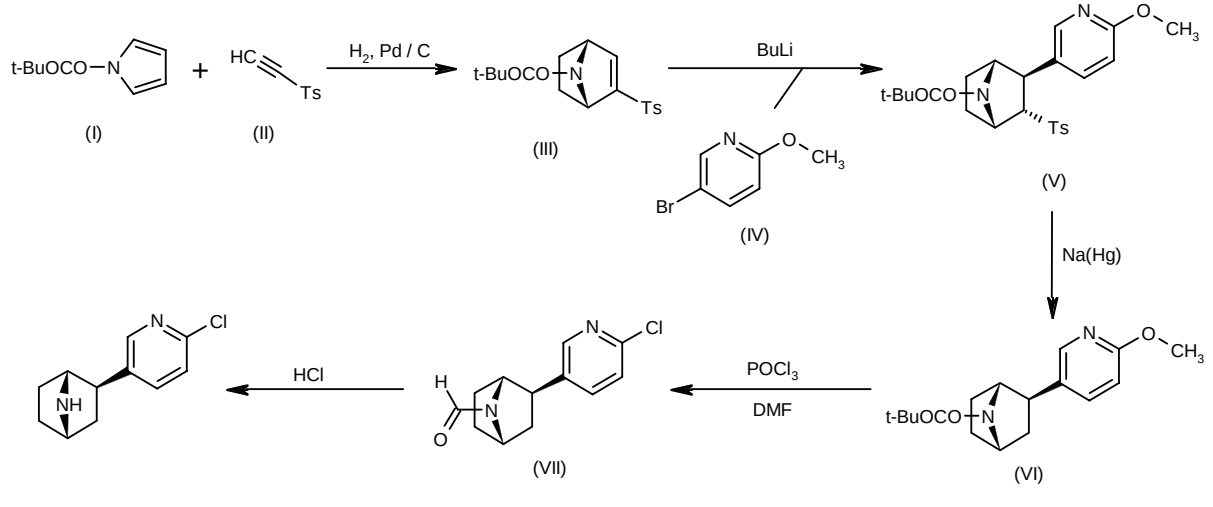
$C_{11}H_{13}ClN_2$ **Dept. of Health & Human Services; CytoMed**

A total synthesis of epibatidine has been reported: The cyclization of 1-(*tert*-butoxycarbonyl)pyrrole (I) with tosylacetylene (II) by means of H_2 over Pd/C in acetonitrile gives the bicyclic compound (III), which is condensed with 5-bromo-2-methoxypyridine (IV) by means of BuLi in THF, yielding the 2*exo*-(6-methoxy-3-pyridyl) derivative (V). The detosylation of (V) by means of Na(Hg) in methanol/THF affords the intermediate (VI), which is treated with $POCl_3$ in DMF to effect the conversion of the methoxypyridine into the desired chloropyridine derivative (VII), with simultaneous elimination of the *tert*-butoxycarbonyl protecting group and *N*-formylation. Finally, this formyl group is eliminated with HCl in hot THF (1). Scheme 1.

A new synthesis of epibatidine has been reported: The reaction of 2-tosyl-7-azabicyclo[2.2.1]hept-2-ene-7-carboxylic acid *tert*-butyl ester (I) with tributyltin hydride (II) by means of azobis(isobutyronitrile) (AIBN) in benzene gives the tin derivative (III), which by treatment with tetrabutylammonium fluoride in THF provides 7-azabicyclo[2.2.1]hept-2-ene-7-carboxylic acid *tert*-butyl ester (IV). The condensation of (IV) with 5-iodopyridine-2-amine (V) by means of palladium acetate/tetrabutylammonium chloride/potassium formate in hot DMF yields *exo*-2-(6-amino-3-pyridyl)-7-azabicyclo[2.2.1]heptane-7-carboxylic acid tert-butyl ester (VI), which is finally submitted to diazotization with $NaNO_2$/HCl and treated with CuCl (2). Scheme 2.

Epibatidine was shown to be highly potent with a broad spectrum of activity on neuronal and neuromuscular nicotinic receptors *in vitro* as compared to nicotine and suxamethonium. Agonistic effects of epibatidine included contraction of guinea pig ileum, increases in blood pressure in pithed atropinized rats and activation of nicotinic receptors at the peripheral terminals of afferent C-fibers in rabbit ear and in rat brain (shown via antidiuretic effects); effects were followed by long duration receptor desensiti-

Scheme 1: Synthesis of Epibatidine



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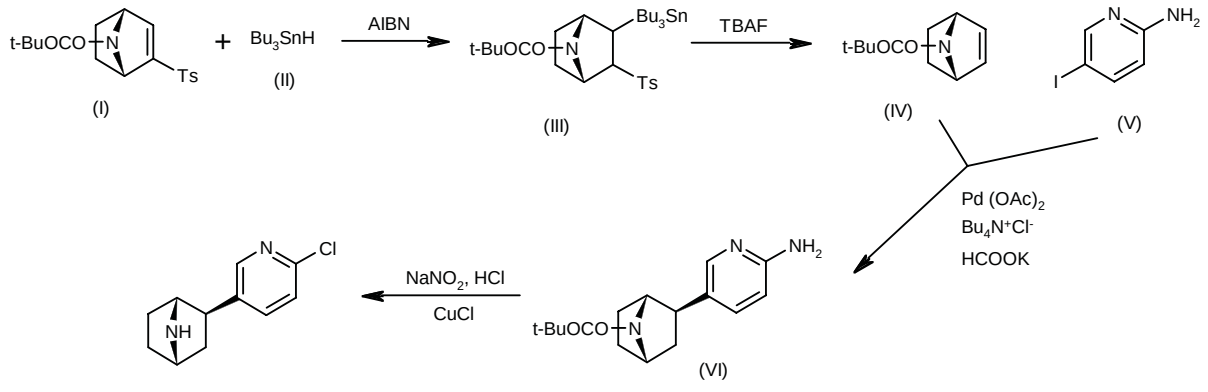
Scheme 2: Synthesis of Epibatidine



zation. Equipotent neuromuscular inhibition was observed on muscle and end plate nicotinic receptors in the rat diaphragm with epibatidine and suxamethonium. Epibatidine at a 100-fold lower dose than suxamethonium caused contraction in depolarized extraocular rabbit muscle *in vitro* and results from the Straub tail reaction in mice indicated that the effects of epibatidine were via sustained stimulation of motor end plate receptors of "slow contracting" muscle fibers (3).

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Fomivirsen Sodium Vitravene™

Antiviral
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Isis; Eisai; Ciba Vision; Abbott

The safety and efficacy of fomivirsen in two dose schedules were demonstrated in a study involving patients with previously uncontrolled cytomegalovirus (CMV) retinitis. In regimen A, 228 eyes were treated for up to 972 days with weekly intravitreal injections of fomivirsen (330 μg) for 3 weeks followed by every other week. In regimen B, 42 eyes were treated every other week for 2 doses followed by dosing every fourth week for up to 463 days. No systemic adverse effects or laboratory test abnormalities were reported. Transient and clinically manageable ocular adverse effects in regimen A *vs.* B included anterior chamber inflammation (20% *vs.* 10%), viritis (12% *vs.* 10%) and increased intraocular pressure (20% *vs.* 12%). Discontinuation due to treatment was uncommon (1).

The pharmacokinetics of fomivirsen (164 or 330 μg intravitreal injection) were examined in 16 patients with CMV retinitis; implant surgery was performed 1 h or 3, 7 or 14 days postinjection. Vitreal concentrations of intact fomivirsen were 551 ± 4.87, 1.49, 0.055-0.110, 0.037 μM and undetectable at 1 h, 3, 7, 12 and 17 days, respectively, after injection of 165 μg and 6.18-32.7 μM at 1 h and 0.293-0.395 at 7 and 8 days after injection of 330 μg. Vitreal intact fomivirsen decreased from 96% at 1 h postinjection to 41% (165 μg) and 44% (330 μg) at day 7. Fomivirsen or its metabolites were not detected in plasma (2).

Vitravene™ (fomivirsen sodium injectable) has been launched in the U.S. and has been approved in the

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European Union and in Brazil. Developed by Isis Pharmaceuticals and marketed by Ciba Vision, the eye-care unit of Novartis, Vitravene™ is indicated for the local treatment of newly diagnosed or advanced CMV retinitis in AIDS patients for whom other treatments are deemed unsuitable or ineffective (3-6).

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Linezolid
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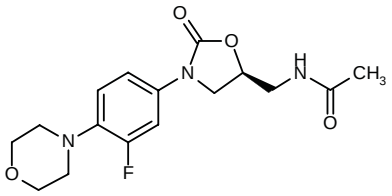

$C_{16}H_{20}FN_3O_4$ **Pharmacia & Upjohn**

A study has shown that linezolid treatment (10, 40 and 125 mg/kg/day for 90 days) *in vivo* in rats did not induce hepatic microsomal cytochrome P450 enzymes. In addition, linezolid did not inhibit cloned human cytochrome P450s *in vitro*. Metabolism studies using human liver microsomes showed that the agent undergoes slow nonenzymatic oxidation mediated by reactive oxygen species; oxidation was not affected by cytochrome P450 inhibitors. It was concluded that drug interactions mediated via induction or inhibition of cytochrome P450 by linezolid are unlikely (1).

An *in vitro* study has shown that linezolid combined with other antibacterial agents including amoxicillin, ampicillin, oxacillin, penicillin, cefotaxime, cefpodoxime, clindamycin, rifampin, aztreonam and chloramphenicol resulted in mainly additive or indifferent interactions against staphylococci, penicillin-sensitive, -intermediate and -resistant pneumococci, vancomycin-sensitive and -resistant enterococci and enteric bacteria strains. Of the 381 organism-drug combinations examined, 97.1% resulted in additive/indifferent responses and only 1.6% and 1.3% were synergistic and antagonistic, respectively (2).

Linezolid was shown to have excellent *in vitro* activity against 400 multiresistant Gram-positive clinical isolates including *Staphylococcus aureus*, coagulase-negative staphylococci (including teicoplanin-resistant isolates), *Enterococcus faecalis* and *Enterococcus faecium* (including VanA and VanB isolates). All isolates were inhibited with 4 μg/ml and the MIC_{90} value for all strains was 2 μg/ml (3).

Linezolid showed excellent *in vitro* activity against severe susceptible and multiresistant Gram-positive staphylococci, streptococci and enterococci. The study used 7599 recent clinical isolates from hospitals in North and South America. All susceptible isolates were inhibited by ≤ 4 μg/ml. Quinupristin/dalfopristin, vancomycin and several penicillins and fluoroquinolones were used for comparison, with results showing that quinupristin/dalfopristin was 2- to 4-fold more active by weight than linezolid but had no activity against *E. faecalis* (4).

The activity of linezolid was compared with other antibacterial agents against 3945 clinical Gram-positive isolates. Linezolid showed activity similar to vancomycin

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against all vancomycin-susceptible enterococci, staphylococci and streptococci and the agent was shown to be the most active against oxacillin-resistant staphylococci and vancomycin-resistant enterococci (5).

An *in vitro* study has shown that resistance to linezolid was not observed in Gram-positive isolates (including staphylococci, enterococci and streptococci) containing genes conferring resistance against agents (chloramphenicol, fusidic acid, lincosamides, macrolides, streptogramins and tetracyclines) targeting the 50S ribosomal subunit. Resistance mechanisms involving modification of lincosamides, which affect only structurally related molecules, did not alter the efficacy of linezolid (6).

An *in vitro* study has shown that linezolid had similar activity against methicillin-susceptible and -resistant *S. aureus* (MIC_{90} = 1 mg/l). Similar activity was observed against streptococci and enterococci with no cross-resistance with other agents. Activity of linezolid was determined to be bacteriostatic with slow bactericidal activity against streptococci only observed at high concentrations. Increasing inoculum had little or no effect on MICs and bactericidal activity. A tentative breakpoint of 2 mg/ml was concluded after analysis of distribution susceptibilities (7).

The *in vitro* activity of linezolid with or without aminoglycosides was observed against vancomycin-resistant enterococci with genotype determined using primers specific for VanA, VanB, VanC1 and VanC2/3. The MIC_{90} of the agent against 37 strains including VanA *E. faecium*, VanB *E. faecalis*, VanC1 *E. gallinarum* and Van2/3 *Casseliflavus* was 4 mg/l with all MBCs equal to 8 mg/l. All isolates examined were inhibited after 24 h by linezolid (< 4 mg/l). No synergistic or antagonistic bactericidal actions were observed with 1, 2, 4, 8 or 16 mg/l of the agent with gentamicin (5 mg/l) or streptomycin (20 mg/l) (8).

A study in rabbits has shown that linezolid may not be the most effective treatment for penicillin-sensitive and -resistant pneumococcal meningitis. Results showed that linezolid was less active than ceftriaxone against penicillin-sensitive strains. Similar killing rates were obtained for linezolid for both penicillin-sensitive and -resistant strains (9).

An open-label, noncomparative study of 273 hospitalized patients assessed the efficacy of linezolid against Gram-positive complicated and uncomplicated skin and soft tissue infections. Organisms isolated included *S. aureus* (the most common), *S. epidermidis*, *S. pyogenes* and enterococci. Patients were administered either low-dose (250 mg t.i.d. or 375 mg b.i.d.) or high-dose (375 mg t.i.d. or 625 mg b.i.d.) intravenous linezolid for a minimum of 3 days. After this time, both the low-dose (120 patients) and the high-dose (151 patients) groups were given oral linezolid for the remainder of the treatment. Evaluations made at days 1-14 and days 15-28 posttherapy demonstrated a clinical success rate of 93.2%. Another phase II study, this time in suspected *S. pneumoniae* community-acquired pneumonia, examined the efficacy of linezolid for 5-14 (actual 3-19) days using the same low- and high-dose regimens as the previous study. A clinical success rate of 94.8% was obtained. In the two studies, clinical success rate was based on the combined cured/improved rates for both dose levels excluding indeterminate and not reported. Linezolid was generally well tolerated, with side effects including headache, nausea and diarrhea. The drug's 100% bioavailable oral formulation permits the transition from intravenous to oral administration without dose adjustment, potentially reducing hospital stay (10).

As part of the ongoing clinical evaluation of linezolid, the pharmacokinetics were compared in 7 patients with mild to moderate liver disease and 8 healthy volunteers. Subjects were administered a single oral dose of 600 mg as tablets and pharmacokinetic parameters were assessed. Good tolerance was observed in both groups. In addition, pharmacokinetics were not significantly different in the liver patients, suggesting that dose adjustment will not be necessary in these patients (11).

A single-dose pharmacokinetic study on linezolid (600 mg p.o.) in 29 young and elderly male and female healthy volunteers showed that age did not significantly alter linezolid pharmacokinetics, although renal clearance of the agent did correlate with creatinine clearance. It was concluded that dose adjustments for gender are unwarranted; clearance of the agent was 20% less in females but elimination half-lives were similar. Treatment was well tolerated in all subjects (12).

The hypothesis that the pharmacokinetics of linezolid are a function of measured creatinine was tested using samples from 24 subjects with varying degrees of renal failure given 600 mg and analyzing population pharmacokinetics using the NONMEM program. The covariates assessed were creatinine clearance, body weight, gender and whether a subject was on dialysis. Data were fit to a one-compartment model and the clearance of linezolid, unaltered by renal function, was 6.54 l/h. The interpatient variability was 20% for clearance. Results suggest that dose adjustments of linezolid are unnecessary in patients with renal failure (13).

Two of 169 patients infected with *E. faecium* and treated with linezolid developed resistance to the agent (600 mg i.v. b.i.d. for > 4 weeks). Initial *in vitro* MIC values for isolates from the 2 patients were both 2 μg/ml, while final MICs were 16 and 32 μg/ml. The strains were also resistant to all other antimicrobials tested. The linezolid-resistant isolates were found to have a 23S rRNA mutation on nucleotide 2576 where a guanine was replaced by uracil. *E. faecium* was shown to contain 5 copies of the 23S rRNA gene and linezolid susceptibility was shown to correlate with the ratio of wild type:mutant rRNA (14).

Results from an ongoing compassionate use multicenter trial in 386 patients with significant resistant Gram-positive infections showed the safety and tolerability of intravenous and oral linezolid in adults (600 mg/kg) and children (10 mg/kg). A total of 397 infections have been treated to date, including bacteremia, endocarditis, skin/soft tissue, gastrointestinal abscesses, peritonitis and osteomyelitis. Only 265 patients completed long-term follow-up; nonevaluablility was due to death from under-

lying illness or negative cultures at study onset. The overall rate of adverse events was 32.9% with serious events observed in 5.7%; discontinuation due to adverse effects occurred in 9.3%. Thrombocytopenia and dermatological reactions were the most common adverse events (15).

Two doses of linezolid (i.v. and p.o.) were shown to be safe and well tolerated in 2 open-label, phase II studies in 517 patients with infections. Adverse events were reported in 75.6% of patients, although only 32.7% were considered to be drug-related; no dose dependency was observed in incidence of adverse events. Sixteen patients discontinued due to drug-related adverse events. The most common adverse events were nausea (5.4%), diarrhea (5.2%), tongue discoloration (2.5%) and oral monilia (2.3%) (16).

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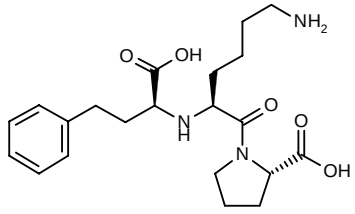

$C_{21}H_{31}N_3O_5$ **Merck & Co.**

Lisinopril (Zestril®) has been approved in several more countries for controlling the risk of progression of diabetic nephropathy. Following the U.K. launch for this use and previous approvals in Finland, Belgium, Portugal, Luxembourg, Ireland, New Zealand and Spain, Zeneca has received regulatory approval in Sweden, the Netherlands, Austria and Denmark. Lisinopril is the only ACE inhibitor licensed for the once-daily treatment of all indications of hypertension, congestive heart failure, acute myocardial infarction and diabetic complications (1).

Zeneca plans to pursue a 6-month extension of U.S. marketing exclusivity for lisinopril after receiving a written request for pediatric studies of the compound from the FDA. Lisinopril is marketed in the U.S. as Prinivil® by Merck & Co., Inc., which will pursue the pediatric studies in cooperation with Zeneca. The requested trials are expected to take approximately 2 years to complete (2).

Zeneca has filed a supplemental NDA with the FDA requesting approval for the use of lisinopril at high doses (up to 35 mg once daily) in the management of heart failure. The rationale for the label change is based on the results of the Assessment of Treatment with Lisinopril and Survival study. The 5-year, randomized, double-blind trial evaluated the effect of low (2.5 mg-5 mg) *versus* high (32.5 mg-35 mg) doses of lisinopril on mortality and morbidity in patients with congestive heart failure. The study results indicated a 12% risk reduction in the combined endpoint of all-cause mortality and all-cause hospitalizations when patients were treated with higher doses of the drug. Adverse events were generally mild and transient, with the most frequent being dizziness, headache, fatigue, diarrhea, upper respiratory symptoms and cough (3).

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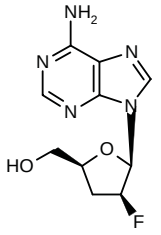


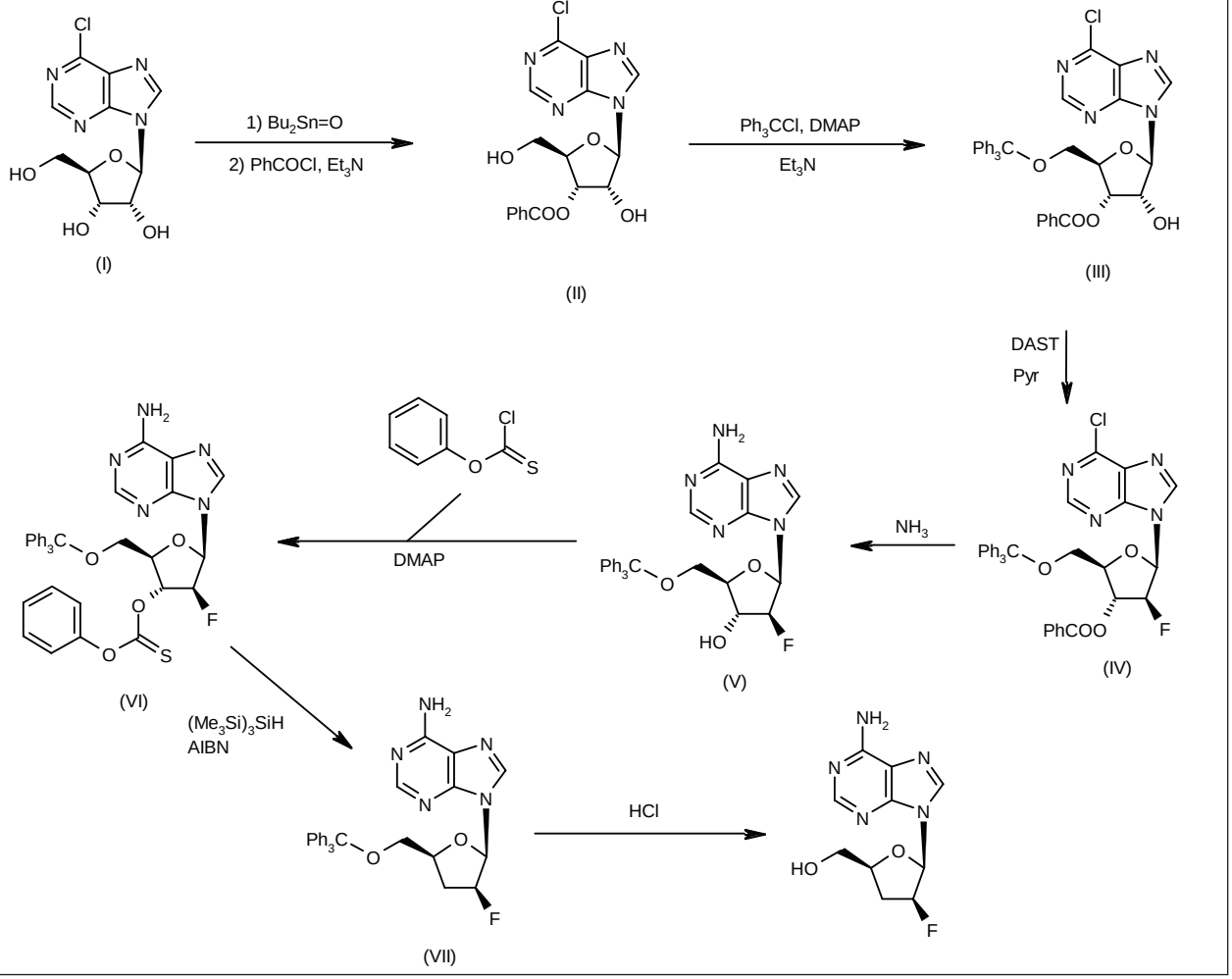
$C_{10}H_{12}FN_5O_2$

Natl. Cancer Inst. (US);
U.S. Bioscience

A new synthesis of lodenosine has been described: The selective benzoylation of the 6-chloropurine riboside (I) with benzoyl chloride and triethylamine through the formation of a complex with dibutyl tin oxide gives the 3'-*O*-benzoyl derivative (II), which is purified by crystallization (minor impurities, about 3%, of the 2'-*O* derivative are present). The protection of the primary OH group of (II) by reaction with trityl chloride, DMAP and Et_3N in DMF yields the 5'-*O*-trityl derivative (III), which is treated with DAST and pyridine to afford the fluorinated arabinofuranoside (IV). The reaction of (IV) with ammonia in methanol displaces the 6-Cl atom and hydrolyzes the 3'-*O*-benzoyl group to give the fluorinated arabinofuranosyladenine (V). The reaction of (V) with phenyl chlorothionoformate and DMAP in acetonitrile yields the thiocarbonate (VI), which is treated with tris(trimethylsilyl)silane and AIBN in hot toluene to afford the 3'-deoxy compound (VII). Finally, this compound is deprotected by reaction with HCl in methanol/water (1). Scheme 3.

The antiviral activity of lodenosine in combination with other inhibitors of HIV-1 replication was examined *in vitro*.

Scheme 3: Synthesis of Lodenosine



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Lodenosine displayed synergistic antiviral interactions with several other nucleoside and nonnucleoside reverse transcriptase and protease inhibitors. Synergistic interactions were greatest with nevirapine, costatolide, AZT, ddC, 3TC, ritonavir and nelfinavir. No increase in toxicity was observed with any combination (2).

Results of a phase I dose escalating study showed that monotherapy with lodenosine was well tolerated and active even in heavily pretreated adult (0.2-3.2 mg/kg b.i.d. for 12 weeks) and 13 pediatric (25-100 mg/m^2 daily for 4 weeks) HIV-infected patients; stavudine and nelfinavor were added to regimens for 52 weeks. All doses were well tolerated. Oral bioavailability in the 26 adults was about 66% fasting and 63% nonfasting and a median decrease in HIV RNA of –0.42 $\log_{10}$ copies/ml was observed at week 6 in 9 adults receiving 1.6 and 3.2 mg/kg lodenosine. At 4 weeks, 6 patients on 3.2 mg/kg had a median decrease of –0.32 $\log_{10}$ copies/ml. Of 7 adults studied, no new resistance mutations were observed at 12 weeks and 2/4 heavily pretreated adults had < 200 HIV RNA copies/ml at this time. A median decrease in viral load of 0.5 and 1.18 $\log_{10}$ was observed in 2 heavily pretreated children at week 4 (3).

Interim results from a 48-week, phase II clinical trial of lodenosine in combination with other antiretrovirals indicated comparable activity to lamivudine in combination with stavudine and indinavir. This multicenter, randomized trial has now enrolled 209 antiretroviral-naive patients and is comparing lodenosine (100, 200 or 300 mg b.i.d.) or lamivudine (150 mg b.i.d.) in combination with stavudine (30-40 mg b.i.d.) and indinavir (800 mg every 8 h). Interim results at 12 weeks for 66 patients demonstrated no significant difference in antiviral efficacy between lodenosine and lamivudine: a 2.6 $\log_{10}$ decrease in plasma HIV RNA levels was detected in patients treated with lodenosine compared to a 2.3 $\log_{10}$ decrease in those treated with lamivudine. Virus levels were below the limits of detection (50 copies/ml) in 59, 55, 50 and 50%, respectively, of patients on lodenosine 100, 200 and 300 mg and lamivudine. Of 13 serious adverse events, none could be attributed to lodenosine. Up to September 10, 1999, 23 patients have discontinued: 7.1, 10 and 13.3%, respectively, on lodenosine 100, 200 and 300 mg compared to 21.1% on lamivudine. The 24-week results are expected to be available next year (4).

U.S. Bioscience has suspended clinical testing of lodenosine and its IND has been put on clinical hold pending review of additional scientific information regarding serious adverse events observed during a phase II clinical trial, including the recent death of a patient. The phase II trial was designed to evaluate the efficacy and safety of three different doses of lodenosine in combination with two other antiretrovirals for the treatment of HIV-infected adults. The trial enrolled approximately 176 patients on lodenosine, all of whom have been discontinued and are being closely monitored. The company is working closely with the FDA to review and assess the data (5).

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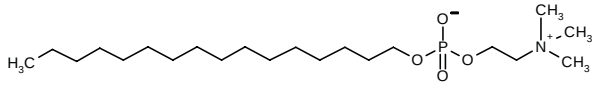

$C_{21}H_{46}NO_4P$

Asta Medica

The efficacy and safety of miltefosine for the treatment of visceral leishmaniasis was tested in a phase I/II trial in 30 Indian men who were divided into groups to receive 28 days of oral treatment with miltefosine 50 mg every 2 days, 100 mg every 2 days, 100 mg/day, 150 mg/day or 250 mg/day. Apparent cure on day 14 was obtained in 21/30 patients and all 29 living patients were apparently cured on day 28; 1 patient on the highest dose died following the development of renal insufficiency and severe diarrhea. Transient vomiting and diarrhea were frequent during the first 2 weeks and 4 patients on 200 or 250 mg/day were withdrawn from miltefosine treatment after 7-10 days due to vomiting. Although 7/10 patients on 50 or 100 mg every 2 days had relapsed by 8 months, 18/19 patients in the other treatment groups appeared to be cured. Included in the 21 definitive cures were 4 patients who received miltefosine for 10 days or less, as well as 12 who had previously failed therapy with

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pentavalent antimony. These preliminary results suggest that miltefosine at doses of 100-150 mg/day for a month is an effective and safe oral treatment for visceral leishmaniasis and that further testing is warranted (1).

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NCX-4016

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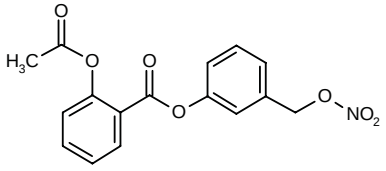

$C_{16}H_{13}NO_7$ **NicOx**

The *in vitro* inhibitory activity of NCX-4016 on human platelet function was shown to be similar to aspirin and SNP. Although NCX-4016 and aspirin dose-dependently inhibited low-dose collagen-induced aggregation in a similar manner (IC_{50} = 76 and 36 μM, respectively), only NCX-4016 was effective in inhibiting U-46619-induced aggregation (IC_{50} = 380 μM). In washed platelets, both NCX-4016 and SNP inhibited U-46619-induced aggregation. Collagen-induced aggregation in whole blood was inhibited by both NCX-4016 and aspirin, although addition of mouse aorta to whole blood samples increased the activity of NCX-4016 more than aspirin. Both NCX-4016 and SNP inhibited platelet adhesion to collagen and increased intraplatelet cGMP while aspirin had no effect (1).

Preclinical data on the cardioprotective effects of NCX-4016 has been reported. In one study NCX-4016 was compared to aspirin in perfused rabbit hearts subjected to ischemia and reperfusion. Compounds were perfused starting 20 min before ischemia and continuing for 60 min. Although, as expected, aspirin was associated with marked aggravation of the ischemic insult to the hearts (increase in left ventricular end-diastolic pressure, decrease in left ventricular developed pressure), NCX-4016 protected the hearts in a concentration-dependent manner, with a significant reduction in LVEDP and a marked recovery of LVDP at a concentration of 100 μM. Also in contrast to aspirin, NCX-4016 concentration-dependently inhibited creatine kinase release. Although its mechanism of action has not been clearly established, it is suggested that its cardioprotective effects may be related to its ability to act as a cytoprotective NO donor (2, 3).

NCX-4016 (60 mg/kg i.p.) given 30 min before collagen + epinephrine injection was shown to inhibit pulmonary thromboembolism in mice in a manner similar to nitric oxide donors. Mortality was reduced in animals treated with NCX-4016 and ISMN (10 mg/kg i.v. 2 min before challenge) by 42.1 and 50%, respectively, as compared to animals given aspirin (83.3% with 30 mg/kg) and controls (90%). Plasma TxB_2 levels were reduced by 57.7 and 91% in animals receiving NCX-4016 and aspirin, respectively. Both ISMN and NCX-4016 were effective in reducing U-46619-induced mortality (10% and 15.6% *vs.* 56.6% in controls) as compared to aspirin, which had little effect (80.6%). Mortality induced by injection of a 12.5% suspension of swollen and hardened blood cells was also reduced by NCX-4016 (51.8 *vs.* 81.6%), nicardipine (25%) and ISMN (22%); aspirin had no effect in this model (4).

The antithrombotic effects of NCX-4016 were examined *in vivo* with results showing weak inhibitory activity on thromboxane synthesis. Rats were treated with either aspirin (30, 100 or 200 mg/kg) or NCX-4016 (equimolar doses) and sacrificed 3 h later. Although no gastric damage was observed with NCX-4016, aspirin caused extensive damage at all doses. Thromboxane synthesis of aspirin-treated animals was suppressed by 77% (30 mg/kg) while only a very small inhibition was observed with NCX-4016 (186 mg/kg). No effects of NCX-4016 were observed at doses of 18 and 56 mg/kg, although the latter significantly increased serum nitrate concentrations at 3 and 6 h postdosing. Both agents exhibited enhanced suppression of thromboxane after 5 days of treatment with a 99% and 20-55% suppression of synthesis observed for aspirin (30 mg/kg) and NCX-4016 (10 and 100 mg/kg), respectively; both had similarly decreased thrombus size and attenuated the reductions in blood flow. NCX-4016 may inhibit thrombus formation possibly via nitric oxide release (5).

The effects of NCX-4016 (0.5 mg/kg/h by 2-h i.v. infusion) were evaluated *in vivo* in a rabbit model of acute myocardial infarction induced by permanent coronary artery ligation. Compared to the 24-h mortality rate of 60% obtained in untreated MI animals relative to sham-operated controls, NCX-4016 reduced mortality to 10%. In contrast, the same dose of aspirin had no significant effect on the mortality rate (50% at 24 h). Creatine kinase and myeloperoxidase measurements and ECG recordings also supported the cardioprotectant effects of NCX-4016 in this model (6, 7).

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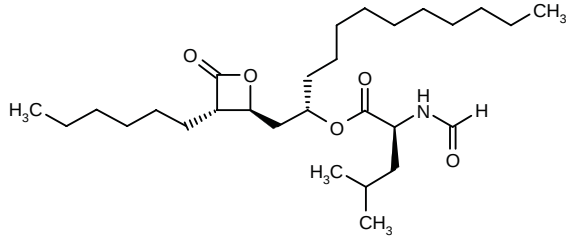

$C_{28}H_{51}NO_5$ **Roche**

Sibutramine (1, 3 and 10 mg/kg p.o.) was shown to be more effective than orlistat (10 and 20 mg/kg b.i.d.) in reducing body weight in rats treated for 15 days. All 3 doses of sibutramine significantly and dose-dependently reduced body weight (4.7, 8.6 and 12.2%, respectively) and food intake, whereas only the high dose of orlistat decreased weight (4.5%) and significantly increased food intake. The ineffectiveness of orlistat was thought to be due to its lack of activity on satiety and energy expenditure (1).

Two randomized, placebo-controlled studies involving 519 overweight patients on a mildly hypocaloric diet given placebo or orlistat (120 mg t.i.d.) reported small decreases in vitamin D levels in both groups after 2 years; the decrease was greater in those patients receiving orlistat (7.9% *vs.* 5.0%). After multivitamin supplementation, vitamin D levels normalized in 64.9 and 57.9% of patients receiving orlistat and placebo, respectively. Vitamin D levels in postmenopausal women not receiving estrogen therapy were similar to the study population as a whole and comparable decreases in levels were observed in both groups. African-American patients had lower vitamin D levels as compared to the study population and after 2 years, decreases of 14.6 and 4.3 nmol/l were observed in patients receiving the placebo and orlistat, respectively (2).

Ingestion of social amounts of ethanol were shown not to affect the inhibition of fat absorption by short-term orlistat treatment. In a randomized, double-blind, placebo-controlled, parallel study, 30 normal weight, healthy males on a standardized diet of 2500 kcal/day (30% fat) received orlistat (120 mg t.i.d.) + ethanol placebo, orlistat + ethanol (40 g/day on days 1 and 6 and 40 g b.i.d. days 1-5) or orlistat placebo + ethanol. Baseline-corrected fecal fat excretions were similar for the orlistat alone (23.7 g) and orlistat + ethanol groups (22.7 g); orlistat had no significant effect on ethanol pharmacokinetics (3).

A placebo-controlled, double-blind study has shown that taking orlistat helps promote weight loss, lessens weight gain and improves some obesity-related disease risk factors. The study evaluated 880 obese patients to determine whether orlistat combined with dietary intervention is more effective than placebo plus diet for losing weight and keeping it off for 2 years. The participants were randomized to treatment with placebo or orlistat (120 mg) 3 times daily for the first year. During the second year, subjects were placed on a weight maintenance diet and the orlistat group was randomized again to receive either placebo or one of two doses of the active drug (60 or 120 mg t.i.d.), while the placebo group remained on the same treatment regimen. The researchers found that, on average, patients taking orlistat in the first year lost more weight (19.31 pounds) than patients taking placebo (12.8 pounds). Patients treated with 120 mg orlistat during the second year also regained less weight (7.05 pounds) than those treated with 60 mg orlistat or placebo (9.39 and 12.41 pounds, respectively) during the second year. Treatment with 120 mg orlistat 3 times daily was associated with improved LDL cholesterol and insulin levels. Furthermore, 34.1% of the patients completing 2 years of treatment with 120 mg orlistat maintained a weight loss of > 10% of their initial body weight, compared with just 17.5% of patients taking placebo (4).

Orlistat (120 mg t.i.d. for 6 days) did not interfere with the pharmacokinetics of pravastatin (40 mg once daily) in a randomized, double-blind, placebo-controlled, 2-way crossover study involving 24 subjects with cholesterol levels of 200-300 mg/dl. Mean half-life for both pravastatin and orlistat + pravastatin was 2 ± 1 h. No significant differences in $AUC_{0\text{-}12h}$ (57.4 ± 24.3 *vs.* 59.7 ± 23.6 ng·h/ml) or C_{max} (29.8 ± 15.9 *vs.* 32.3 ± 15.9 ng/ml) were found for pravastatin alone and in combination with orlistat. Similar decreases in total (23 and 24%) and LDL (34 and 35%) cholesterol were observed with pravastatin alone and in combination with orlistat. No significant adverse effects were reported (5).

The effects of orlistat (120 mg t.i.d.) were examined in 2 multicenter, randomized, double-blind, placebo-controlled trials in 1374 obese patients; all patients were given a mildly hypocaloric diet. After 1 year of treatment,

significantly greater mean weight losses were observed in the orlistat group as compared to placebo (–9.5 *vs.* –6%). A higher proportion of orlistat-treated patients had weight loss of ≥ 5% (63.6 *vs.* 46%) and treatment also decreased mean DBP and SBP by –5.6 and –7.5 mmHg, respectively, as compared to –4.9 and –7.7 mmHg, respectively, in placebo patients (6).

A double-blind study showed that addition of dietary fiber to orlistat treatment may prevent gastrointestinal side effects associated with lipase inhibition. Twenty obese patients were given orlistat with either placebo or Metamucil before meals for 30 days. While no gastrointestinal side effects were observed in the group receiving orlistat + Metamucil, 21% treated with orlistat + placebo had flatulence, abdominal cramps, mild diarrhea and involuntary emission of fecal material (7).

Results from 2 multicenter, randomized, double-blind, placebo-controlled trials in 543 obese patients on a 600 kcal deficit diet with a 4-week lead-in consisting of diet + placebo showed that early weight loss with orlistat (120 mg t.i.d.) predicted 1 year efficacy. Orlistat-treated patients who lost ≥ 5% and < 5% of their body weight at 12 weeks had a mean weight loss of 14.5 and 6%, respectively, after 1 year. Orlistat-treated patients losing ≥ 5% body weight after 12 weeks showed a mean weight loss of 11.3%, reductions in total (–8.9%) and LDL (–9.4%) cholesterol and reductions in systolic and diastolic blood pressure (–7.8 and –6.1 mmHg, respectively) after 1 year of treatment (8).

Orlistat has been evaluated and compared to hypocaloric diet alone for its effects on CVD risk factors by analysis of pooled data from 5 double-blind, randomized, placebo-controlled trials in over 1500 obese patients. In these studies, patients were treated for 1 year with orlistat 120 mg 3 times daily or placebo in addition to a hypocaloric diet. A total of 70% of patients had at least 1 of the following risk factors at entry: elevated LDL cholesterol, elevated blood pressure or hyperinsulinemia. Patients on orlistat lost significantly more weight than those on placebo at the end of the study (9.0% *vs.* 5.6% of initial body weight). Of those with at least 1 CVD risk factor at randomization, significantly more patients on orlistat (27.2% *vs.* 13.9%) had no risk factors at 1 year. Furthermore, the number of risk factors was reduced in 30.5% of those on orlistat compared to 23.4% of those on placebo, and the number of risk factors increased in fewer patients on orlistat (19.1%) compared to placebo (27.4%). Thus, orlistat appears to be a potentially useful adjunctive therapy in obese patients at high risk for CVD (9, 10).

The efficacy and tolerability of combined orlistat (120 mg t.i.d.) and sibutramine (10-20 mg once daily) therapy were demonstrated in a study involving 28 obese patients. At 4 and 12 weeks, the average weight loss was 4.3 and 10 kg, respectively. Side effects were mild and included oily stools (53.6%), oily flatus (17.8%), intestinal obstipation (14.3%), diarrhea (7.1%), insomnia (3.6%), headache (3.6%) and irritability (3.6%). At least 1 side effect occurred in 78.6% of the patients (11).

Results from 5 randomized, placebo-controlled phase II trials in 2675 obese patients on a mildly hypocaloric diet showed that mean weight loss was significantly greater (–8.6 *vs.* –5.7) in patients given orlistat (120 mg t.i.d.) after 1 year; 59% of the orlistat-treated patients achieved weight loss of ≥ 5% as compared to only 41% on placebo. Of these patients, mean diastolic (DBP) and systolic blood pressure (SBP) decreased by –5.4 and –7.1 mmHg, respectively, as compared to –4.5 and –6.7 mmHg, respectively, in placebo; decreases were less in patients losing < 5% of their body weight (–2.6 and –1.1 mmHg *vs.* –2.1 and –1.3 mmHg in placebo, for DBP and SBP, respectively). Similar results were obtained after 2 years of treatment (12).

Results from a 4-week, randomized, double-blind, placebo-controlled study in 23 obese subjects on a hypocaloric diet (1200-1500 kcal/day) showed that orlistat (120 mg t.i.d.) treatment did not increase the risk of developing gallstones. Mean weight loss was 3.8 and 2.3 kg in the orlistat and placebo groups, respectively. Changes in cholesterol saturation index and gallbladder motility parameters were similar in both groups. Bile phospholipids were decreased in both groups with significant reductions observed on placebo. Total bile acids were significantly reduced in the placebo group but were unchanged in the treated group. No cholesterol microcrystals were evident in bile from either group before or after treatment (13).

Orlistat (Xenical®) has been approved in the U.S. and Canada for use in patients with an initial body mass index (BMI) of ≥ 30, or in patients with a BMI of ≥ 27 in the presence of other risk factors such as hypertension, high cholesterol or diabetes. It is indicated for the management of obesity, including weight loss and weight management, when used in conjunction with a modest calorie-reduced diet. As compared to diet alone, weight loss with orlistat also results in measurable improvements in certain obesity-related conditions such as high blood pressure, high cholesterol and diabetes (14, 15).

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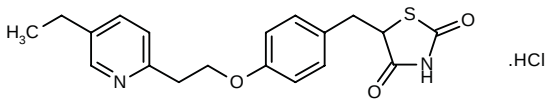

$C_{19}H_{20}N_2O_3S.HCl$ **Lilly; Takeda; Novo Nordisk**

Pioglitazone hydrochloride (Actos™) has been available in the U.S. since August for the improvement of glycemic control in patients with type II diabetes, either as monotherapy or in combination with sulfonylureas, metformin or insulin. Pioglitazone improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. It improves glycemic control while reducing circulating insulin levels. The compound was discovered and developed by Takeda and is copromoted in the U.S. by Lilly. It is supplied as tablets containing 15, 30 and 45 mg pioglitazone (as free base). In related news, Lilly and Takeda have expanded their marketing agreement for pioglitazone to encompass more than 70 countries in Europe, the Middle East, Africa and Asia. The companies have filed an NDA for the drug in the European Union, where it is awaiting final approval. Pioglitazone is under regulatory review in Japan, where it will be copromoted by Takeda and Novo Nordisk (1-6).

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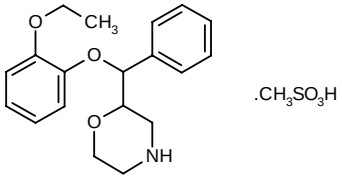

$C_{19}H_{23}NO_3.CH_4O_3S$ **Pharmacia & Upjohn; Janssen**

The FDA has issued an approvable letter for Pharmacia & Upjohn's reboxetine mesilate (Vestra™). The company will continue to work with the FDA to secure final approval for the compound and anticipates a launch in the U.S. during the first half of 2000. Pharmacia & Upjohn has entered into an agreement with Janssen to copromote Vestra™ in the U.S. Under terms of the agreement, Janssen will promote Vestra™ to psychiatrists and Pharmacia & Upjohn will be responsible for promotion to primary care physicians. Vestra™ is currently marketed by Pharmacia & Upjohn as Edronax™ in the U.K. and Germany and as Norebox™ in Spain (1-3).

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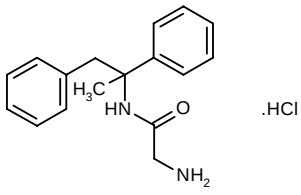

$C_{17}H_{20}N_2O.HCl$ **AstraZeneca**

The pharmacokinetics of remacemide hydrochloride and its active desglycinyl metabolite were evaluated in 18 patients with mild or moderate to severe hepatic impairment and 18 matched healthy controls after administration of a single oral dose of 200 mg remacemide. Changes in the disposition of both remacemide and its metabolite were observed in patients with moderate to severe hepatic impairment. AUC values in patients with mild hepatic impairment were reduced somewhat compared to those in controls (1297 ± 308 ng/h/ml *vs.* 1364 ± 271 ng·h/ml), whereas AUC values in moderately to severely impaired patients were increased compared to controls (1641 ± 426 ng·h/ml *vs.* 1368 ± 203 ng·h/ml). AUCs for the metabolite were increased in all subjects with hepatic impairment (454 ± 133 ng·h/ml in mild impairment *vs.* 357 ± 76 ng·h/ml; 1041 ± 642 ng·h/ml in severe impairment *vs.* 411 ± 100 ng·h/ml). In subjects with more severe impairment, the disposition of the metabolite aappeared to be determined at least in part by CYP3A4. Side effects were similar in all subjects. It was concluded that remacemide may be used safely in patients with mild hepatic insufficiency, but caution should be observed in those with more severe impairment (1).

The pharmacokinetics of remacemide hydrochloride and its desglycinyl maetabolite were also determined in patients with mild to severe renal impairment after a single oral dose of 300 mg remacemide. The AUC for remacemide increased proportionally with the degree of impairment: values of 3450 ± 438, 5038 ± 1771, 6169 ± 1740 and 7524 ± 1944 ng·h/ml were determined in normal controls, mildly, moderately and severely impaired patients, respectively; the respective values for the desglycinyl metabolite were 1381 ± 314, 1471 ± 213, 1298 ± 318 and 1983 ± 400 ng·h/ml. Accumulation of the carbamoyl glucuronide of remacemide, a compound with no known pharmacological activity, was observed with increasing renal impairment. The results from this study indicate that no clinically relevant changes in remacemide exposure occur in mild renal impairment, although caution should be used in more severe cases (2).

Results from a randomized, 12-week, double-blind, placebo-controlled study in 33 parkinsonian patients suffering from "off" periods showed that 400 mg/day remacemide (150 mg p.o. starting dose, increased by 50 mg b.i.d. at 2-week intervals) as adjunct therapy to levodopa was well tolerated. Symptoms tended to improve and levodopa-induced dyskinesia was not aggravated with treatment. At the median maximum tolerated dose (450 mg/day), the Unified Parkinson's Disease Rating Scale (UPDRS) mean motor examination score decreased from 33 to 26; the mean score decreased from 28 to 27 with placebo. A decrease in the UPDRS complications of therapy score from 8 to 6 was also observed in treated patients as compared to no change with placebo. Adverse effects occurring with doses > 200 mg/day included nausea, vomiting, dizziness and hypokinesia. Seventeen patients (77%) discontinued treatment due to adverse effects (3).

The effects of remacemide hydrochloride (300 mg b.i.d. given 1 h before levodopa for 2 weeks) on serum levodopa concentrations were examined in a multicenter, open-label study in 18 patients with mild to moderate Parkinson's disease receiving stable doses of levodopa. The study measured clinical responses using the UPDRS. The AUC values of levodopa were not altered by remacemide. However, mean plasma C_{max} values for levodopa were reduced by 16% and t_{max} was delayed by 20%. It was concluded that these interactions would not impact future trials (4).

Results from 3 placebo-controlled, double-blind, parallel-group, dose-ranging studies involving 518 parkinsonian patients showed that remacemide (75, 150, 300, and 600 mg/day) improved motor performance in levodopa-treated patients. Doses from 75-300 mg/day were well tolerated; dose-related dizziness was the most common side effect observed with 600 mg/day. Although monotherapy with the agent had little effect, 150-300 mg/day given to patients receiving levodopa resulted in improved motor UPDRS scores and percent "on" time. Severity or incidence of levodopa dyskinesia was unaffected by remacemide (5).

Remacemide was evaluated for its ability to protect against cerebral ischemic damage following coronary artery bypass surgery (CABS) in a prospective, double-blind, randomized trial. A total of 171 patients undergoing cardiopulmonary bypass (CPB) were randomized to treatment with placebo or remacemide as successive doses of 25, 50, 100 and 150 mg, followed by 150 mg every 6 h, from 4 days before to 5 days after the surgical procedure. The two patient groups were well matched in terms of age, height, weight, duration of CPB and duration of

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surgery, as well as number of microembolic events. Although the effect was not statistically significant, a lower percentage of patients on remacemide (9% *vs.* 12% for placebo) showed a decrease in performance of at least one standard deviation in 2 or more neuropsychological tests at 8 weeks after surgery. However, significantly greater improvement on a composite measure of neuropsychological performance was observed in the remacemide group, and active drug was also significantly superior to placebo in improving performance in 3/9 tests. Overall, remacemide appeared to be associated with greater preservation of learning ability, as well as fewer or less severe deficits compared to placebo. Plasma levels of remacemide achieved in these patients were similar to those observed when the drug is used as an antiepileptic, but lower than those detected in animal models of neuroprotection, suggesting that efficacy may have been limited in this study (6).

Remacemide (200 mg b.i.d.) administered for 14.5 days for 2 consecutive menstrual cycles was shown to have no effect on the efficacy of oral contraceptives in a randomized, placebo-controlled, double-blind, comparative study in 18 female volunteers. No significant differences were observed in $AUC_{0\text{-}24h}$, C_{max} and t_{max} values between groups and ovulation inhibition was maintained. Hepatic enzyme activity was not stimulated according to levels of 6β-OHC excreted in urine. It was concluded that coadministration was safe (7).

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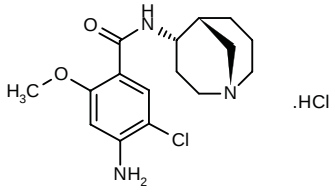
Renzapride Hydrochloride

Treatment of IBS
5-HT_3 Antagonist
5-HT_4 Agonist

EN: 125657



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

The British Medicines Control Agency has granted a Clinical Trials Exemption to Alizyme to undertake a phase II clinical trial of renzapride hydrochloride as a treatment for constipation predominant irritable bowel syndrome. Enrollment for the trial was expected to begin in June 1999. Alizyme has obtained an exclusive option to a worldwide license to renzapride for gastrointestinal disease from SmithKline Beecham (1).

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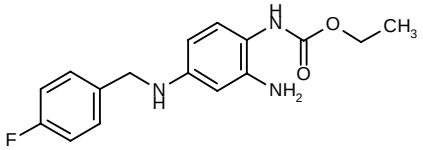
Retigabine

Antiepileptic

EN: 227505



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

A study examining the metabolism of retigabine in several models showed that [^{14}C]-retigabine was metabolized via glucuronidation and acetylation reactions in rats with glucuronides detected in liver microsomes or slices after incubation with the agent and in plasma, bile and feces; none was detected in urine with 67% of the radioactivity excreted in feces as glucuronide (10% of the

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dose). Retigabine (13%), retigabine-*N*-glucuronide (5%) and retigabine-*N*-glucoside (1%) were detected in dog urine at 24 h, with 39% of the unchanged compound excreted in feces. In healthy volunteers given single doses of the agent (600 mg p.o.), acetylation and glucuronidation were found to be the major pathways for retigabine metabolism (1).

A study evaluated the effects of retigabine on GABA-related neurochemical parameters, as potentiation of GABA synthesis has been reported to be involved in its antiepileptic effects. Mice were given a single dose or daily doses over 5 days, followed by removal of brains for neurochemical analysis. Contrary to previous reports, retigabine had no effect on whole-brain GABA levels or the activity of glutamic acid decarboxylase, the enzyme responsible for GABA synthesis, after either single or multiple doses. However, following single, but not repeated, doses, significant decreases in brain concentrations of the excitatory neurotransmitter glutamate and its precursor glutamine were detected. Also, moderate inhibition of GABA-transaminase was observed after repeated dosing. These results suggest that inhibition of GABA metabolism and of glutamate/glutamine may be involved in retigabine's mechanism of action (2).

Retigabine was shown to act on several different epileptiform activities in rat temporal lobe structures which readily develop pharmacoresistant seizures. 4-Aminopyridine (100 μM) treatment of rat entorhinal cortex hippocampal slices induced seizure-like events (SLE) and interictal epileptic discharges (IED) while coadministration of bicuculline (10 μM) changed these activities to recurrent epileptic discharges (RED); IED were isolated after blockade of SLE with glutamate receptor antagonists for AMPA and NMDA. Retigabine dose-dependently and reversibly suppressed all types of epileptic events with suppression of SLE occurring in 71.45% (5 μM) and 100% (10 μM) of the slices and frequency of IED was significantly decreased with 20 μM and blocked with 50 μM; 20 μM blocked isolated IED. RED were suppressed in 71.4% of the slices with 100 μM and a reduction in frequency of 96.1 ± 6.1% was observed in the remaining slices (3).

Retigabine was shown to have neuroprotective effects in acute and chronic models of neuronal impairment including *in vitro* rat hippocampal brain slices exposed to 6 min of hypoxia and hypoglycemia and *in vivo* focal and permanent cerebral ischemia via occlusion of the a. cerebri media and permanent occlusion of the left common artery, respectively, in rats *in vivo*. Improved recovery of pop-spike amplitude was observed in recordings from brain slices pretreated with retigabine (100 μM). Rats pretreated with the agent prior to focal cerebral ischemia showed a 27% reduction in infarct volume without side effects; MK-801 (0.1 mg/kg) had a similar effect although adverse effects were observed. When rats undergoing permanent cerebral ischemia were pretreated with retigabine (0.5, 1 and 2 mg/kg), dose-dependent normalization of chronic ischemia-induced learning and memory deficits was observed (4).

The potent anticonvulsant activity of retigabine was shown to be age-independent in a study using hippocampal brain slices from young (10-17 days postpartum), adult (8 weeks) and old (23 months) rats. Ictal discharges were observed in all slices from young rats and exposure to retigabine converted bursts to interictal activity in 2/7 slices and reduced ictal duration in the remaining slices; all activity was blocked with 10 μM retigabine within 8.1 ± 1.59 min. Although DL-APV (200 μM) also converted ictal to interictal activity, it could not block activity unless retigabine (1 μM) was given in combination. Mg^{2+}-induced interictal activity of adult and old rat slices was inhibited by retigabine (10 μM) at 17 and 13 min, respectively. No spontaneous activity was observed in 8/21 slices of old rats. In the active slices of both old and adult rats, retigabine dose-dependently inhibited the second and third population of orthodromic-stimulated spikes in the CA1 region with no effect on the first population (5).

The *in vivo* and *in vitro* kinetics of retigabine *N*-glucuronidation in humans, dogs and rats were compared, with results showing that the reversible reaction is responsible for enterohepatic circulation of the agent in humans and dogs; a constant ratio between retigabine and retigabine *N*-glucuronide was observed in dogs and humans but not rats. In rats, 90% of retigabine *N*-glucuronidation was catalyzed by UDP-glucuronsyltransferase (UGT)1A1 and UGT1A2, with only 4/10 (1A1, 1A3, 1A4, 1A9) recombinant human UGTs catalyzing the reaction. From activity and inhibition data and the known substrate specificities toward lamotrigine and bilirubin, UGT1A4 was concluded to be the major retigabine UGT *in vivo* (6).

Retigabine has been tested for its effects in the hippocampal kindled rat model of partial seizures and on the acquisition of hippocampal kindling. At doses of 1.25-5 mg/kg i.p., the drug produced time- and dose-dependent reductions in both seizure scores and afterdischarge duration in rats with fully kindled seizures. Pretreatment with retigabine (7.5 mg/kg i.p.) was also able to delay the acquisition of kindling, with effects comparable to those of dizocilpine at a dose (0.5 mg/kg i.p.) that was associated with side effects (7).

The ability of retigabine to suppress epileptiform activity in human neocortical slices from patients undergoing surgery for epilepsy has been evaluated. Retigabine (50-100 μmol/l) was able to suppress both spontaneous field potentials and epileptiform field potentials in Mg^{2+}-free solution in the presence or absence of bicuculline. Its antiepileptic-like effects were reversible (8).

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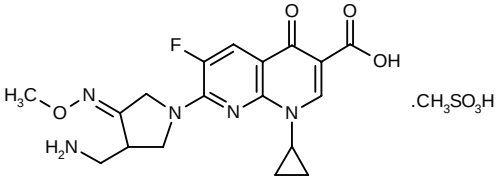
SB-265805/LB-20304a *Naphthyridine Antibacterial*
Gemifloxacin Mesilate
Factive®

EN: 226496



$C_{18}H_{20}FN_5O_4.CH_4O_3S$

LG Chem; SmithKline Beecham

The *in vitro* efficacy of gemifloxacin was shown against *Streptococcus pneumoniae* isolates from patients with community-acquired respiratory tract infections from 14 centers in Spain. Of the 39 strains with high ciprofloxacin MICs, 59, 13 and 28% were penicillin-susceptible, -intermediate and -resistant, respectively. Gemifloxacin had MIC_{90} values 33- and 133-fold lower than trovafloxacin and ciprofloxacin, respectively (1).

The quinolone resistance mechanisms of 17 strains of ofloxacin-resistant *S. pneumoniae* were examined together with their susceptibility to gemifloxacin. Results indicated that at least three antibiotic efflux pumps may be responsible for resistance. Gemifloxacin was the least affected by resistance mechanisms as compared to ciprofloxacin, grepafloxacin, norifloxacin, ofloxacin and trovafloxacin. MIC values for gemifloxacin against all strains were ≤ 0.5 mg/l (2).

Gemifloxacin was shown to have better antimicrobial activity than ciprofloxacin, ofloxacin and levofloxacin against clinical isolates of *S. pneumoniae* and *Chlamydia* spp. Gemifloxacin showed similar activity as the other agents against Gram-negative species and its activity was not affected by penicillin resistance in strains of *Haemophilus influenzae* and *Moraxella catarrhalis* (3).

A study using neutropenic murine thigh and lung infection models showed that the 24 h AUC/MIC required for gemifloxacin activity against 13 isolates of *S. pneumoniae*, 6 isolates of *Enterobacteriaceae* and 1 isolate each of *P. aeruginosa* and *Klebsiella pneumoniae* was similar to other fluoroquinolones and was not affected by infection site or methicillin, penicillin or ciprofloxacin resistance. AUC/dose values and half-lives obtained after treatment with gemifloxacin (0.073-600 mg/kg) were 0.13-0.27 mg/kg/24 h and 0.8-1.2 h, respectively. Mean AUC/MIC values for each dose were 103 and 35 for total and free gemifloxacin (4).

Gemifloxacin was shown to be highly effective *in vitro* against penicillin- and ciprofloxacin-resistant *S. pneumoniae*. MIC values against 2 and 5 *S. pneumoniae* isolates for gemifloxacin were 0.03-0.06 and 0.12 mg/l as compared to 1 and 1-2 mg/l and 64 and 1-4 mg/l for penicillin and ciprofloxacin, respectively (5).

Gemifloxacin was found to be the most active compound *in vitro* against *H. influenzae* (MIC_{90} = ≤ 0.008 mg/l) as compared to trovafloxacin, grepafloxacin, sparfloxacin, ciprofloxacin, ofloxacin, penicillin and erythromycin. Gemifloxacin had comparable activity as ciprofloxacin (MIC_{90} = 0.03 mg/l) and was more potent than the other agents against *H. parainfluenzae* (6).

Gemifloxacin showed excellent *in vivo* activity against *H. influenzae* respiratory tract infection in rats. Administered 24 h postinfection (once or twice daily for 3 days), the compound significantly reduced bacterial numbers and was significantly more effective than cefuroxime and azithromycin. Similar activity was observed with ciprofloxacin, trovafloxacin, grepafloxacin, levofloxacin and tosufloxacin (7).

Gemifloxacin as compared to ciprofloxacin, grepafloxacin, moxifloxacin, levofloxacin and trovafloxacin was the only compound to show good *in vitro* activity against ciprofloxacin-resistant *S. pneumoniae* strain 502226. Gemifloxacin was also the most bactericidal agent against quinolone-susceptible *S. pneumoniae* strain C3LN4 (8).

The efficacy of gemifloxacin was examined against *Streptococcus pyogenes*, *Staphylococcus epidermidis* and *S. aureus* skin and soft tissue infections in rats and compared to amoxycillin/clavulanate, ciprofloxacin, cefuroxime, azithromycin, trovafloxacin, grepafloxacin, levofloxacin and tosufloxacin. Agents were given orally 1 h postinfection (once or twice daily) for 3 days. No other compound was found to have greater activity than gemifloxacin against *S. pyogenes* and *S. aureus* infections (9).

Gemifloxacin was shown to be the most active agent against Gram-positive streptococci clinical isolates *in vitro* as compared to trovafloxacin, moxifloxacin, grepafloxacin and clinafloxacin. Gemifloxacin was as potent or less potent than ciprofloxacin against most Gram-negative aerobes with the exception of *Acinetobacter* spp. and *Stenotrophomonas maltophilia*; clinafloxacin and trovafloxacin were the most active against Gram-negative

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anaerobes except for *Fusobacterium* spp., where gemifloxacin was more active than trovafloxacin (10).

Gemifloxacin was shown to be the more active agent *in vitro* against 50 recent *S. pyogenes*, *Streptococcus agalactiae* and viridans streptococci isolates as compared to other antimicrobials including nalidixic acid, ofloxacin, ciprofloxacin, levofloxacin, trovafloxacin, grepafloxacin, penicillin, ampicillin and gentamicin; MIC_{50} and MIC_{90} values for gemifloxacin were 1-2 dilutions lower. MIC values against 4 ofloxacin-intermediate or -resistant *S. agalactiae* isolates and 3 ofloxacin-intermediate *S. pyogenes* isolates were 0.03-0.06 (11).

The *in vitro* activity of gemifloxacin was compared with levofloxacin, trovafloxacin, moxifloxacin, grepafloxacin, gatifloxacin and sparfloxacin against 20 *S. pneumoniae* isolates with reduced susceptibility to ciprofloxacin (MIC = ≥ 16 mg/l). In contrast to gemifloxacin, the fluoroquinolones showed reduced activity against strains with increasing ciprofloxacin resistance. One strain with no amino acid substitutions in the QRDR region of GyrA was susceptible to all agents. The remaining strains had substitutions in ParC, GyrA and/or GyrB (12).

In a rabbit model of *S. pneumoniae* meningitis, the mesylate salt of gemifloxacin (5 mg/kg/h) given between 12 and 24 h after infection, with or without dexamethasone, was almost as effective as ceftriaxone (10 mg/kg/h) in reducing CSF bacterial counts. Whereas serum levels were similar or lower at 24 h than at 14 h, CSF concentrations were significantly higher at this dose, with or without dexamethasone. A dose of gemifloxacin of 1 mg/kg/h was less effective and serum and CSF concentrations were lower (13).

The activity of gemifloxacin was compared to gatifloxacin, moxifloxacin, trovafloxacin, ciprofloxacin and ofloxacin against 367 clinical isolates from the urine of patients with complicated and/or hospital-acquired urinary tract infections. Gemifloxacin inhibited 80.7-95.4% of all strains at MICs of 0.5-4 mg/l. At an MIC of ≤ 1 mg/l, 85.3, 84.5, 82.0, 80.9, 60.5 and 52.9% of pathogens, respectively, were susceptible to gemifloxacin, trovafloxacin, moxifloxacin, gatifloxacin, ciprofloxacin and ofloxacin; at an MIC breakpoint of 4 mg/l, the rates of resistance for gemifloxacin, moxifloxacin, gatifloxacin, trovafloxacin, ciprofloxacin and ofloxacin were 9.5, 13.1, 13.6, 13.9, 18.0 and 42.4%, respectively (14).

The activity of gemifloxacin was tested against *H. influenzae* and *M. catarrhalis* isolates and compared to the activities of ciprofloxacin, levofloxacin, sparfloxacin, grepafloxacin, trovafloxacin, ampicillin, amoxycillin/clavulanate, cefixime, cefuroxime and azithromycin. Results from this study demonstrated that gemifloxacin and grepafloxacin had the lowest MICs of all agents tested against both β-lactamase-positive and β-lactamase-negative *H. influenzae* and *M. catarrhalis*. The MIC_{50} and MIC_{90} values for both quinolones ranged from 0.008-0.16 mg/l (15).

The *in vitro* activity of gemifloxacin was tested against *S. pneumoniae* and compared to moxifloxacin, grepafloxacin, sparfloxacin, levofloxacin, ciprofloxacin, ofloxacin, erythromycin, tetracycline and penicillin G. Gemifloxacin demonstrated the highest activity of all fluoroquinolones tested against 200 susceptible and intermediately resistant isolates (MIC_{50} = 0.016 mg/l, MIC_{90} = 0.03-0.06 mg/l) (16).

The *in vivo* efficacy of gemifloxacin was examined in the rat model of respiratory tract infection against *S. pneumoniae* strains and compared to those of amoxycillin/clavulanate, ciprofloxacin, cefuroxime, azithromycin, trovafloxacin, grepafloxacin and levofloxacin. The agents were given orally (once or twice daily) 24 h postinfection for 3 days. Gemifloxacin was as effective as amoxycillin/clavulanate and no other agent was more active. Trovafloxacin, ciprofloxacin, grepafloxacin and levofloxacin were significantly less effective (17).

A study comparing the effects of gemifloxacin, trovafloxacin and ciprofloxacin on spontaneous antimicrobial resistance *in vitro* using 10 Gram-positive and Gram-negative isolates showed that repeated exposure to subinhibitory concentrations of the agents resulted in a decrease in bacterial susceptibility. This effect was more rapid with ciprofloxacin and trovafloxacin, with gemifloxacin displaying the lowest selection frequency (18).

A study using the neutropenic murine thigh infection model showed that the activity of gemifloxacin against ciprofloxacin-resistant strains of *S. pneumoniae* was similar to activity observed against sensitive strains when isolates contained gyrase, ParC and ParE mutations. The MIC values were 0.03-0.5 mg/l. However, efflux of gemifloxacin was not as active *in vivo* as observed *in vitro* (19).

The *in vitro* activity and postantibiotic effects of gemifloxacin were compared to those of trovafloxacin, moxifloxacin, grepafloxacin, levofloxacin, ofloxacin, ciprofloxacin, azithromycin, clarithromycin, erythromycin and rifampicin against isolates of *Legionella pneumophila* and other *Legionella* spp. Rifampicin and trovafloxacin were the most active (MIC_{90} = ≤ 0.008 mg/l) and gemifloxacin showed high potency (MIC_{90} = 0.016 mg/l) similar to levofloxacin, grepafloxacin and moxifloxacin and greater than ciprofloxacin and ofloxacin (MIC_{90} = 0.03 mg/l). Gemifloxacin had the longest postantibiotic effect against erythromycin-resistant *L. pneumophila* (4.65 h), which was superior to rifampicin (0.9 h), clarithromycin (1.9 h) and levofloxacin (2.59 h) (20).

The *in vitro* activity of gemifloxacin (MIC_{90} = 0.06 mg/l) was superior to that of ciprofloxacin, ofloxacin, levofloxacin, grepafloxacin, moxifloxacin and sparfloxacin (MIC_{90} = ≥ 0.25 mg/l) against *S. pneumoniae*. Gemifloxacin and grepafloxacin (MIC_{90} = ≤ 0.02 mg/l) were the most effective agents against *M. catarrhalis* and *H. influenzae*. Greater activity was observed for gemifloxacin, trovafloxacin and moxifloxacin (MIC_{90} = 0.06 mg/l) against *S. aureus* as compared to ciprofloxacin, amoxycillin and amoxycillin/clavulanate (MIC_{90} = ≥ 1 mg/l). Gemifloxacin had activity similar to moxifloxacin (MIC_{90} = 0.25 mg/l) against anaerobic strains and to ofloxacin, trovafloxacin, moxifloxacin and sparfloxacin (MIC_{90} = 0.5 mg/l) against several other strains, including *Enterobacteriaceae* and nonfermentative Gram-negative bacilli (21).

Gemifloxacin was more active *in vitro* than trovafloxacin against fusobacteria, peptostreptococci and *P. asaccharolytica* and displayed similar activity against *Clostridia* spp. Similar activity was observed for gemifloxacin and DU-6859 against peptostreptococci, *C. perfringens*, *C. ramosum* and fusobacteria. Sparfloxacin, grepafloxacin and levofloxacin were less active than gemifloxacin against the test anaerobes (22).

A study examining the efficacy of gemifloxacin against 782 recent Gram-positive and Gram-negative isolates showed that the agent was more potent than trovafloxacin, levofloxacin, ciprofloxacin, amoxycillin/clavulanate, cefixime and nalidixic acid against respiratory tract pathogens (23).

Gemifloxacin was compared to ciprofloxacin, levofloxacin, sparfloxacin, grepafloxacin, trovafloxacin, amoxicillin, cefuroxime, azithromycin and clarithromycin against susceptible and resistant pneumococci and was found to have the lowest MIC values (0.004-0.5 mg/l) (24).

The antimicrobial activities of gemifloxacin and ciprofloxacin were compared over a wide range of the AUC/MIC ratio using a clinical isolate of *S. aureus*. It was concluded that results from quinolone pharmacodynamic studies are dependent on the obtained simulated AUC/MIC ratios and gemifloxacin may be more effective against *S. aureus* since there are differences between the MICs for gemifloxacin and ciprofloxacin (25).

The pharmacokinetics of gemifloxacin (160, 320, 480 and 640 mg once daily for 7 days) characterized in healthy male subjects were found to be linear and dose-independent. The agent was well tolerated; 1 subject given 640 mg discontinued after 6 days because of mild, transient elevations of ALT/AST (26).

The pharmacokinetics of single oral doses of gemifloxacin (20, 40, 80, 160, 320, 600 and 800 mg) were examined in healthy males. Results showed that the compound was rapidly absorbed, with plasma C_{max} being reached 1 h postdosing. Pharmacokinetics increased linearly with dose although terminal half-life (7.4 ± 2 h) and renal clearance (150 ml/min) were dose-independent; 25-40% of the dose was excreted as unchanged compound in urine. No adverse effects were observed (27).

Gemifloxacin has shown strong activity against Gram-positive and Gram-negative bacteria and favorable pharmacokinetics compared to ciprofloxacin. Against a range of pathogens causing respiratory infections, including streptococci, methicillin-susceptible and -resistant staphylococci, *Escherichia coli*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Klebsiella* spp., *Proteus vulgaris*, *Proteus mirabilis*, *Morganella morganii*, *Serratia* spp., *Citrobacter* spp. and *Salmonella* spp., it gave MIC_{90} values of < 0.06-0.5 mg/l. Bactericidal activity was observed against *S. pneumoniae*, *H. influenzae*, *S. aureus*, *E. coli* and *P. aeruginosa*, and it displayed good postantibiotic effect against *S. aureus* and *E. coli*. Gemifloxacin is reported to be more active than grepafloxacin, levofloxacin and trovafloxacin against quinolone-resistant *H. influenzae* and *S. pneumoniae* (28).

The pharmacokinetics of single doses of the (+)- and (–)-enantiomers of gemifloxacin (320 mg p.o.) were examined in healthy male subjects. Results showed that lower $AUC_{0-\infty}$ values were obtained for the (+)-enantiomer (3.21 *vs.* 4.56 mg·h/l); however, this slight difference would not affect the clinical efficacy of the racemic formulation. No differences were observed in elimination (6.3 *vs.* 7.2 h), absorption or urinary excretion rates between the enantiomers (29).

A double-blind, randomized, parallel-group, comparative study in 30 healthy subjects showed that treatment with gemifloxacin (320 mg once daily) for 7 days had low phototoxic potential. Similar mild photosensitivity was observed with ciprofloxacin (500 mg b.i.d.) (30).

A double-blind, randomized, placebo-controlled, 2-way, crossover study in 14 healthy elderly subjects has shown that gemifloxacin (320 mg once daily on days 8-14) and digoxin (0.25 mg once daily on days 1-14) can be coadministered without dose adjustments. Gemifloxacin dosing did not alter the steady-state pharmacokinetics of digoxin (31).

Results from a double-blind, randomized, placebo-controlled, 2-way, crossover study in 12 healthy males showed that gemifloxacin and omeprazole can be coadministered without dose adjustments. Gemifloxacin (320 mg fasted) was given after 4-day dosing with omeprazole (40 mg once daily). A modest increase in systemic exposure to gemifloxacin was observed with C_{max} values increasing by 10%; however, these results were not considered clinically significant (32).

Results from a randomized, 4-way, crossover study in 14 healthy males showed that gemifloxacin (320 mg) should be administered 2 h before or 3 h after the antacid Maalox®. Marked reductions of 85% were observed in gemifloxacin AUC values when Maalox® was given 10 min after gemifloxacin (33).

A double-blind, placebo-controlled, parallel-group study in 35 healthy males showed that gemifloxacin (320 mg on days 18-24) did not affect the steady-state pharmacodynamics of warfarin given as a loading dose on days 1 and 2 and as a fixed dose on days 14-24. Therefore, coadministration is possible without dose adjustments (34).

Gemifloxacin mesilate is the proposed international nonproprietary name for SB-265805/LB-20304a (35).

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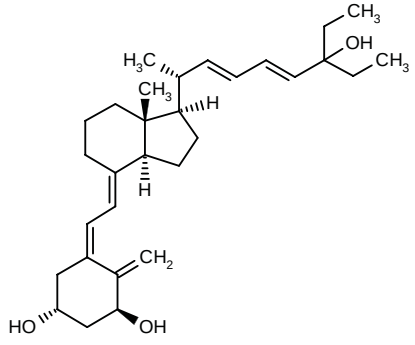

$C_{30}H_{46}O_3$ **Leo**

An *in vitro* study using MG-63 cells grown on a slow rotating lateral vessel to simulate microgravity showed that EB-1089 partially reversed decreases in vitamin D receptor activity. EB-1089 was more potent than calcitriol (100 nM) in stimulating alkaline phosphatase activity, osteocalcin secretion and vitamin D receptor and collagen Iα_1 mRNA expression. The agent also activated MAP

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kinase, increasing its activity for the duration of the 3-day experiment. Thus, EB-1089 may be a potential treatment to reduce the effects of microgravity on vitamin D receptor activity (1).

A study using MCF-7 breast cancer cells has shown that EB-1089 alters the IGF-receptor signaling pathway via attenuation of IGF-1-induced tyrosine phosphorylation of IRS-1 and IRS-2; the agent did not affect des(1-3)IGF-I-induced tyrosine phosphorylation of IRS-1. Since EB-1089-induced inhibition of IGF-I-stimulated phosphorylation of IRS-1 was attenuated by an antisense IGFBP-5 oligodeoxynucleotide, IGFBP-5 may be involved in the mechanism of action of EB-1089 (2).

Antileukemic effects of EB-1089 were shown to occur via activation of the cyclin-dependent kinase inhibitor (CDK), p21, with CDK2 and CDK6 potential target molecules. HL-60 cells treated with EB-1089 (10 nM) for 3 days showed the G1 block and time-dependent increases in p21 and p27 levels; no effects on p15 or p16 were observed. EB-1089 treatment also downregulated CDK2 and CDK4 although protein levels of CDK4 increased. Although antibodies to CDK2, CDK4 and CDK6 immunoprecipitated with p27 protein from control cells but not from EB-1089-treated cells, treated cells with CDK2 and CDK6 antibodies had higher levels of p21 protein; anti-CDK4 had no effect. Thus, p21 is a potential candidate for the control of G1 progression in EB-1089-treated cells (3).

Rats treated with EB-1089 for 10 days showed a 30% loss in ventral prostate weight, as well as apoptosis in the prostate sections and histological changes indicative of pressure-induced atrophy. EB-1089 also induced ventral prostate regression associated with dose-dependent increases in the expression of IGF binding proteins. No effect was seen on levels of dihydrotestosterone or free testosterone in serum. Thus, the prostate regression-inducing activity of EB-1089 does indeed appear to be linked to increased production of IGFBPs, leading to alterations in the availability of IGF-1 (4).

An *in vivo* study has suggested that EB-1089-induced prostate regression may be due to increased expression of IGFBPs. A 25% decrease in ventral prostate weight was observed in rats treated with the agent for 14 days with apoptosis detected in prostate sections. EB-1089 treatment was accompanied by a 15- to 25-fold increase in expression of IGFBPs, in addition to a 40-fold increase in prostatic TGF-1 mRNA levels; no effects on serum dihydrotestosterone or free testosterone were observed (5).

The safety and efficacy of EB-1089 (15 μg/day with dose escalations every 2 weeks) were examined in an open, uncontrolled phase II study in 35 patients with non-resectable pancreatic cancer. The median individual dose was 15 μg/day. Although 51 adverse effects were observed, all but 3 cases of reversible hypercalcemia and 1 episode of confusion were considered related to disease progression and not EB-1089 treatment. No objective responses were observed and median survival was 107 days with 6 patients surviving for > 6 months and 2 patients > 2 years. It was concluded that the agent was safe with limited efficacy in patients with advanced pancreatic cancer (6).

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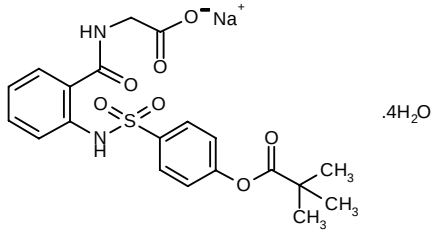

$C_{20}H_{21}N_2O_7S.Na.4H_2O$ **Ono**

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Ono-5046 (2-20 mg) was shown to attenuate phorbol myristate acetate (PMA; 13.3 μg)-induced injury in isolated blood-perfused dog lungs. PMA-induced increases in vascular permeability as determined by the capillary filtration coefficient and decreases in solvent-drag reflection coefficient were dose-dependently attenuated by Ono-5046 (1).

The hepatic clearance of Ono-5046 was found to be relatively low in a study in rats. Although Ono-5046 was hydrolyzed to its inactive metabolic (EI-601) in liver homogenates and erythrocyte suspensions, the agent was stable in plasma or whole blood *in vitro*. Scatchard analysis revealed that > 99% of 100 μM of the agent would bind to plasma proteins at physiological plasma protein concentrations. Total plasma clearance was constant (9 ml/min/kg) with different plasma steady-state concentrations (5-50 μM). The hepatic extraction ratio of Ono-5046 was significantly reduced by addition of BSA in perfused liver experiments due to high protein binding of the agent (2).

The role of neutrophil elastase in acid-induced acute lung injury has been examined using Ono-5046. Conscious hamsters administered a single intratracheal instillation of HCl died following the development of severe lung injury manifested by hemorrhage and increase in protein levels in bronchoalveolar lavage fluid (BALF). Continuous infusion of Ono-5046 (0.01-1 mg/kg/h) for 48 h following HCl instillation dose-dependently reduced mortality and significantly improved these BALF parameters and PaO_2, effects associated with inhibition of neutrophil elastase in BALF (3).

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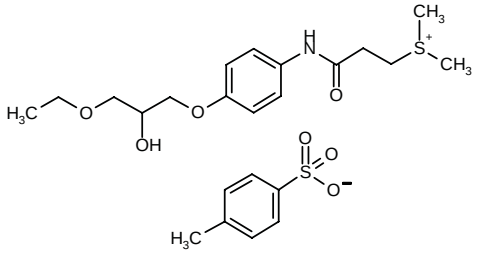

$C_{16}H_{26}NO_4S.C_7H_7O_3S$ **Taiho**

Four women with T-cell-dominant interstitial cystitis who had symptoms of frequency, nocturia and suprapubic pain were administered oral suplatast tosilate (300 mg/day) for 6-14 months. Clinical response appeared after 4 months of treatment, with no apparent adverse effects. Improvements in frequency, nocturia and suprapubic pain were observed in 2/4 patients, and all 4 patients had improvements in blood examination and urinalysis as well as improved bladder capacity and bladder compliance. All patients had elevated levels of eosinophils, IgE and IL-4 at baseline. Following 4 months of treatment, eosinophils decreased from 8.5% to 1%, IgE decreased from 1420 to 620 IU/ml, IL-4 decreased from 25.8 to 3.0 pg/ml and CD45R0-positive T-cells in urine disappeared completely. Voiding bladder capacity increased from a baseline value of 50 ml to 150 ml after 4 months of treatment. These preliminary findings support the therapeutic efficacy of suplatast tosilate in the treatment of interstitial cystitis (1).

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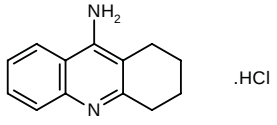

$C_{13}H_{14}N_2.HCl$ **Alza; Parke-Davis**

A significant reduction in the symptoms of Tourette syndrome was reported in a study of 9 adults treated with tacrine hydrochloride. Low doses of tacrine reduced involuntary movements and vocalizations (motor and vocal tics), while higher doses were ineffective or, in some cases, aggravated the symptoms. Tacrine also produced dose-related improvements in comorbid symptoms of Tourette syndrome, including attentional difficulties, hyperactivity, impulsivity and obsessive thinking. Current treatments for Tourette syndrome include dopamine antagonists (*e.g.*, haloperidol), which can alleviate tics but are often accompanied by a number of side effects, and serotonergic drugs (*e.g.*, fluoxetine and sertraline), which lessen obsessive-compulsive symptoms associated with Tourette but may aggravate tics. Other useful drug classes include antihypertensive drugs such as clonidine, botulinum toxin injections to relieve facial tics, and psychostimulants such as methylphenidate to relieve attention deficit hyperactivity disorder-like symptoms (1).

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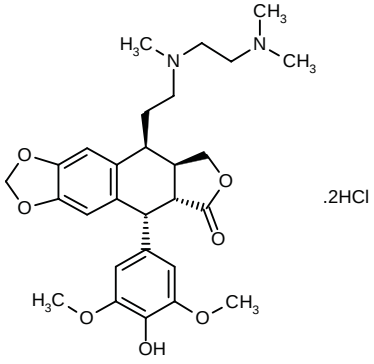
1. *Tacrine may reduce symptoms of Tourette syndrome.* DailyDrugNews.com (Daily Essentials) June 16, 1999.

Original monograph - Drugs Fut 1987, 12: 1032.

TOP-53

Antineoplastic

EN: 188095



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

The antitumor activity of TOP-53 was demonstrated against micro cell colonies from human surgical specimens of non-small cell lung cancer, gland cancer, squamous cell carcinoma and large cell cancer. The cytocidal effective rate for TOP-53 (10 μg/ml) was 57% as compared to 12% for UP-16 and 11-29% for MMC, PEP, CPM, BLM, 5-FU, ADM, VDS, CDDP, SN-38 and ACNU (1).

No differences in leukocyte counts were observed after multiple (1 dose/8 h x 5) or single doses of TOP-53 to mice, although platelet counts and body weight were slightly decreased in animals receiving multiple doses. The optimal dosing schedule was concluded to be intermittent administration at 1-week intervals. Recovery period of bone marrow suppression in mice was approximately 7-10 days (2).

A phase I study of TOP-53 (5.7-143.1 mg/m^2) in 24 patients used an integrated Bayesian approach involving animal toxicity data, predictions of posterior distribution of AUC, hybrid use of dose escalation and a modified continual reassessment method to estimate the maximum tolerated dose as 107.2 mg/m^2. Dose-limiting toxicity was grade 4 hematological and grade 3 or more nonhematological toxicities which occurred in 3/9 patients (3).

The clinical pharmacokinetics of TOP-53 (5.7-143.1 mg/m^2 i.v.) in 24 patients were compared to those in dogs and mice in a phase I dose escalation study where the dose-limiting toxicity was leukopenia. Linear pharmacokinetics of TOP-53 included clearance, distribution volume and half-life of 3.3 ± 1.4 l/h/m^2, 190 ± 75 l/m^2 and 50 h, respectively. Relationships between dosage or leukopenia and unbound AUC were similar in humans, mice and dogs. However, these values differed when total AUC was considered, possibly due to interspecies variability of protein binding. Six to 16-fold species differences in clearance for total drug were observed as compared to only 0.7- to 1.5-fold for unbound drug. The unbound fraction in humans correlated with α_1-acid glycoprotein and varied considerably (2-10% and 5.5 ± 2.1%). Unbound fraction was 53% and 41% for dogs and mice, respectively (4).

1. Fujimoto, S. et al. *Antitumor activity of TOP-53 against non-small cell lung cancer with human surgical specimens.* Jpn J Cancer Res 1998, 89(Suppl.): Abst 2278.

2. Kobunai, T. et al. *Optimal dosing schedule of TOP-53, a novel podophillotoxin derivative.* Jpn J Cancer Res 1998, 89(Suppl.): Abst 2284.

3. Ohashi, Y. et al. *A hybrid design of pharmacokinetically guided dose escalation (PGDE) and continual reassessment method (CRM) in a phase I trial of TOP-53 integrated approach using Bayesian concepts.* Proc Amer Assoc Cancer Res 1999, 40: Abst 545.

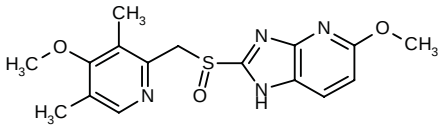
4. Minami, H., Sasaki, H., Ohashi, Y., Tsuda, M., Bando, T., Fuiji, H., Ohtsu, T., Igarashi, T., Itoh, K., Watanabe, Y., Onozawa, Y., Kodama, K., Sugiyama, Y., Suzuki, T. *Clinical pharmacokinetics and pharmacodynamics of TOP-53 in comparison with dogs and mice.* Proc Amer Assoc Cancer Res 1999, 40: Abst 607.

Original monograph - Drugs Fut 1996, 21: 1136.

TU-199
Tenatoprazole

Gastric Antisecretory
H^+/K^+-ATPase Inhibitor

EN: 205401



$C_{16}H_{18}N_4O_3S$ **Tokyo Tanabe; Hokuriku**

Single dose TU-199 (0.1, 0.2 and 0.4 mg/kg p.o.) was shown to dose-dependently inhibit histamine-stimulated gastric acid secretion through inhibition of H^+/K^+-ATPase in dogs. Carbachol- and tetragastrin-stimulated gastric acid secretion were also dose-dependently inhibited by TU-199, which was more potent than omeprazole. Histamine gastric acid secretion was significantly and more potently suppressed by TU-199 (0.2 mg/kg) than by omeprazole or lansoprazole when the agent was given once daily for 7 days; maximum effects were observed after 3-4 doses. The duration of intragastric pH elevation was longer in gastric fistula dogs treated with TU-199 (0.3 mg/kg) than with omeprazole (0.6 mg/kg) or lansoprazole (0.9 mg/kg). IC_{50} values for the inhibition of H^+/K^+-ATPase activity were 8.6, 8.8 and 9.9 μM for TU-199, omeprazole and lansoprazole, respectively, in *in vitro* studies using dog gastric mucosal microsomes (1).

TU-199 was shown not to cause mutations. In a reverse mutation study using *Salmonella typhimurium* and *Escherichia coli*, TU-199 did not increase revertant colonies. Treatment of a Chinese hamster lung fibroblast cell line with TU-199 decreased the incidence of cells with

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structurally aberrant chromosomes to less than 5% and oral administration to ICR mice showed that TU-199 did not induce micronuclei (2).

A teratological study in rabbits showed that the nontoxic dose of TU-199 was 10 mg/kg for dams, 50 mg/kg for dam reproduction and 250 mg/kg for fetuses. TU-199 was administered orally (2, 10, 50 and 250 mg/kg) once daily on days 6-18 of gestation. Side effects with 250 mg in dams included a decrease in feces, reddish brown urine, abortions and increased stomach weights. No effects on fetal survival or growth were observed (3).

A 13-week oral toxicity study in which beagle dogs were administered TU-199 (0.5, 5, 50 and 500 mg/kg p.o.) daily followed by a 5-week washout period showed that the nontoxic dose was 0.5 mg/kg/day. Adverse effects included a high incidence of vomiting with the highest dose and increased levels of urea nitrogen. Dilatation and hypertrophy were observed in the stomach and dilatation and partial necrosis in the fundic glands. Hypertrophy of thyroid follicular epithelial cells was also observed. During the 5-week washout period, all adverse effects were reversed except stomach dilatation and hypertrophy of the mucous membrane (4).

A 13-week oral toxicity study in which rats were orally administered TU-199 (10, 30, 100 and 500 mg/kg) followed by a 5-week washout period showed that the nontoxic dose in males and females was 30 and 10 mg/kg or less. Adverse effects were observed in the stomach, liver and thyroid and included increased stomach and liver weights, single-cell necrosis in the chief cell region, decreases in transaminases, increases in total cholesterol, thyroid colloid, slight anemia and decreases in T3 levels (5).

A teratological study in rats has shown that the nontoxic dose of TU-199 was 100 mg/kg for dams and 500 mg/kg for dam reproduction, fetuses and newborns. TU-199 was administered by gavage (4, 20, 100 and 500 mg/kg) on days 7-17 of gestation. Side effects with the high dose included reddish brown urine, mild decreases in body weight gain and decreased food consumption in dams. No premature or aborted births or effects on parturition or lactation were observed. No changes in implantation indices or viability of fetuses were observed and the agent had no effect on external, visceral and skeletal properties of fetuses or newborns (6).

Tenatoprazole is the new proposed international nonproprietary name for TU-199 (7).

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7. *Proposed international nonproprietary names (Prop. INN): List 80.* WHO Drug Inf 1998, 12(4): 279.

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