Drugs of the Future 2001, 26(6): 577-625

CCC: 0377-8282/2001

Information Update

Volume 1-25, Number 6

Estimated developmental phase for this month's updated products:

Preclinical

Emodin (oncolytic; China Pharm. Univ.)

Phase I

Donitriptan mesilate (antimigraine, 5-$HT_{1B/1D}$ agonist; Pierre Fabre)

Phase II

BBR-3438/BBR-3576 (oncolytics; Novuspharma)
DX-9065a (anticoagulant, factor Xa inhibitor; Daiichi Pharm., Beijing General)
(–)-Epigallocatechin gallate (oncolytic, chemopreventive; Natl. Cancer Center Res. Inst.)
Halofuginone hydrobromide (treatment of scleroderma, treatment of restenosis, angiogenesis inhibitor; Collgard, Mayo Clinic)
IY-81149 (treatment of GERD, K^+/K^+-ATPase inhibitor)
JTE-522 (COX-2 inhibitor; Japan Tobacco, R.W. Johnson)
KRN-2391 (antianginal; Kirin Brewery, Nippon Shinyaku)
Lexacalcitol (vitamin D analog; Leo)
Satraplatin (oncolytic; Johnson Matthey, Bristol-Myers Squibb)

Phase III

AE-941 (oncolytic, antipsoriatic, treatment of macular degeneration; AEterna, Alcon, Ferrer, Medac)
Arzoxifene hydrochloride (oncolytic, treatment of postmenopausal syndrome, estrogen receptor modulator; Lilly)
Eniluracil (oncolytic; GlaxoSmithKline)
Huperzine A (cognition enhancer; Hi-Tech Pharmacal, Shanghai Inst. Materia Med., Chin. Acad. Med. Sci.)
Lubeluzole (neuroprotectant; Janssen)
Pirfenidone (treatment of renal failure, antifibrotic; Marnac, Shionogi)
Prasterone (treatment of SLE; Genelabs, Watson)
S-28463 (treatment of hepatitis C, treatment of genital herpes; 3M Pharm., Vernalis)
SB-207499 (treatment of COPD, PDE IV inhibitor; GlaxoSmithKline)

Preregistered

Azimilide hydrochloride (antiarrhythmic; Procter & Gamble, Tanabe Seiyaku)
Rhenium Re-186 etidronate injection (analgesic, diagnostic agent; Mallinckrodt)
Rotraxate hydrochloride (antiulcer; Teijin)
Telithromycin (ketolide antibiotic; Aventis Pharma)

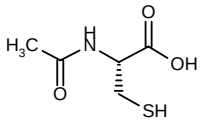
Launched

N-Acetylcysteine (immunostimulant, antioxidant; Zambon)/1968
Alprostadil (treatment of erectile dysfunction, treatment of female sexual dysfunction; Vivus, NexMed, MacroChem, Abbott)/1979
Cevimeline hydrochloride (treatment of Sjögren's syndrome; Snow Brand, Nippon Kayaku, Israel Inst. Biol. Res., Daiichi Pharm.)/2000
Citalopram hydrobromide (antidepressant; Lundbeck, Biovail, Mitsui Pharm.)/1989
Didanosine (anti-HIV; Bristol-Myers Squibb)/1991
Dienogest (hormone replacement therapy, oral contraceptive; Schering AG, Jenapharm)/1990
Dofetilide (antiarrhythmic; Pfizer)/2000
Dornase alfa (treatment of cystic fibrosis; Roche, Genentech)/1994
Eptifibatide (platelet antiaggregatory, fibrinogen gpIIb/IIIa antagonist; COR Therapeutics, Schering-Plough, Essex, Genentech)/1998
Gabapentin (antiepileptic, treatment of neurogenic pain; Pfizer)/1993
Levosimendan (treatment of heart failure; Orion Corp., Abbott)/2000
Loratadine (treatment of allergic rhinitis; Schering-Plough, Essex)/1988
Meropenem (carbapenem antibiotic; Sumitomo, AstraZeneca)/1994
Nateglinide (antidiabetic; Ajinomoto, Aventis Pharma, Novartis, Merck KGaA, Yamanouchi)/1999
Olprinone hydrochloride (bronchodilator, treatment of heart failure; Eisai)/1996
Oxaliplatin (oncolytic; Sanofi-Synthélabo, Yakult Honsha)/1996
Prednicarbate (antipsoriatic, treatment of eczema; Aventis Pharma, Cassella, Camillo Corvi)/1986
Sevoflurane (inhalation anesthetic; Dainabot, Maruishi Pharm., Kodama, Abbott)/1990
Simvastatin (hypolipidemic; Merck & Co.)/1988
Terbinafine hydrochloride (antifungal; Novartis)/1991
Ziprasidone hydrochloride (antipsychotic; Pfizer)/2000

N-Acetylcysteine
Mucomyst®
Fluimucil®

Immunostimulant
Antioxidant

EN: 091298



$C_5H_9NO_3S$

Zambon

The mechanism of action of *N*-acetylcysteine (NAC) was examined in an *in vitro* study using primary human and bovine chondrocytes. Results showed that NAC dose-dependently activated phosphorylation of extracellular signal-regulated kinase-mitogen-activated protein kinase (ERK-MAPK) pathway. The action of ERK was maximum at 15 min and decreased by 180 min. PD-098059, the MAPK inhibitor, antagonized this activation while L-cysteine, reduced glutathione and pyrrolidine dithiocarbamate, but not *N*-acetylalanine, mimicked the effects of NAC (1).

The neuroprotective effects of NAC (20 mg/kg 30 min before and 1, 2 and 6 h after reperfusion) were shown in gerbils subjected to cerebral ischemia. Treatment reduced postischemia brain edema formation and attenuated increases in brain malondialdehyde and hippocampal myeloperoxidase levels. Survival was increased and hyperactivity associated with neurodegeneration was decreased in NAC-treated gerbils. In addition, hippocampal tissue sections from treated animals showed markedly less staining for nitrotyrosine and for poly (ADP-ribose) synthetase and a decrease in neuronal loss was observed in the pyramidal layer of CA1 (2).

The antioxidant effects of NAC (0.2%) were examined on dextran sulfate sodium (DSS; 0.7% in drinking water)-induced and iron-enhanced ulcerative colitis (UC)-associated carcinogenesis in C57BL/6J mice. NAC treatment significantly reduced development of UC-associated adenocarcinomas (68%), tumor multiplicity (1.53 ± 0.62 tumors/mouse) and tumor volume (0.03 ± 0.015 cm^3). The agent was found to reduce oxidative/nitrosative cellular damage to the colon since a significant decrease in nitrotyrosine-positive cells (25.4 ± 10.2 *vs.* 80 ± 26.9 cells/mm^2 epithelium) and a reduction in the PCNA immunostaining index (29.8 ± 4 *vs.* 52.1 ± 9.7% in the distal colon) were observed in NAC-treated animals. No changes in overall inflammatory cell infiltration into the colonic mucosa were observed. Results suggest NAC inhibits reactive oxygen and nitrogen species to prevent UC-associated carcinogenesis (3).

A study in rats continuously exposed to NO_2 (720 ppm/h) showed the efficacy of NAC (200 mg/kg i.p.) in protecting against NO_2-induced impairments in the surfactant system. Results showed that treatment with the agent partially restored BAL components and protected type II pneumocytes against impaired secretory activity. Treatment with NAC decreased both reduced and oxidized glutathione content of BAL and attenuated the NO_2-induced increases in phosphatidylcholine secretion from type II pneumocytes (4).

A study in male ICR mice showed that aerosolized administration of 30 ml NAC (70 mg/ml) twice daily for 28 days significantly attenuated bleomycin (150 mg/kg i.v.)-induced lung fibrosis. NAC inhalation also significantly attenuated the increases in CXC and CC chemokines, macrophage inflammatory protein (MIP)-2, MIP-1α, cytokine-induced neutrophil chemoattractant and lipid hydroperoxide seen on day 7 in the BAL fluid of bleomycin-treated control mice. Aerosolized NAC therefore alleviated bleomycin-induced pulmonary inflammation resulting in a reduction in lung fibrosis (5).

The ability of NAC, administered prophylactically, to prevent iopromide-induced reduction in renal function was examined in 83 patients with chronic renal insufficiency participating in a prospective, randomized, placebo-controlled trial. Participants received either 600 mg oral NAC twice daily plus 0.45% saline i.v. or placebo plus saline. NAC was administered on the day before and on the day of use of the contrast agent, and saline was administered for 12 h before and 12 h after administration of the contrast agent. An increase of at least 0.5 mg/dl in serum creatinine concentration at 48 h after administration of the contrast agent was observed in only 2% (1/41) of the patients in the NAC group *versus* 21% (9/42) of the placebo group. In addition, mean serum creatinine concentration decreased significantly in the NAC group at 48 h after iopromide administration. In contrast, a nonsignificant increase in mean serum creatinine concentration was observed in the control group at 48 h after iopromide administration. These results demonstrate that prophylactic oral administration of NAC in conjunction with hydration is able to prevent iopromide-induced reduction in renal function in patients with chronic renal insufficiency (6).

An open-label pilot study was conducted to determine the efficacy and safety of NAC in patients with mild to moderate Crohn's disease. Eleven patients were treated with NAC at a dose of 800 mg/day orally for 8 weeks in addition to existing medications. Remission was achieved in 4 patients by the fourth week and in 1 by the eighth week, and 3 other patients showed clinical improvement, for an overall response rate at 8 weeks of 72.7%. The treatment was well tolerated. Although blood levels of TNF-α were not found to be elevated in active disease, it was considered that the efficacy of NAC is attributable to its anti-TNF-α activity. The investigators concluded that randomized, controlled trials should be performed to further define the safety and efficacy of NAC in Crohn's disease (7).

A retrospective study based on the hospital charts of 529 patients with paracetamol poisoning determined the risk factors for the development of adverse reactions to NAC. Of these patients, 45 developed side effects to NAC and 18 developed systemic side effects. Serum

paracetamol levels of those patients who developed side effects to NAC were significantly lower as compared to patients who did not develop side effects. Asthmatic patients were discovered to be 2.9 times more likely to develop side effects to NAC. A history of medical allergy was not a risk factor (8).

Results from a double-blind, placebo-controlled study involving 30 patients undergoing elective knee arthroplasty showed the potential renal protective effects of NAC (150 mg/kg i.v. over 30 min before application of the tourniquet and 150 mg/kg/500 ml at 21 ml/h until the tourniquet was released) against reperfusion injury during tourniquet. Patients treated with NAC exhibited significantly higher urine oxygen tension at 3 h postsurgery which reflects medullary perfusion. No changes in serum creatinine, urea or the urine *N*-acetyl-β-D-glucosaminidase/creatinine ratio were observed. Significant increases in serum myoglobin and lactate were observed in both untreated and treated patients during tourniquet release; these levels returned to baseline postsurgery (9).

A randomized, double-blind, placebo-controlled, 8-week trial conducted in 81 HIV-infected patients with low glutathione (GSH) levels and CD4 T cells < 500 cells/μl showed that NAC treatment safely and significantly replenished whole blood (0.88 to 0.98 mM) and T-cell GSH. Treatment caused blood GSH levels to reach within 89% of uninfected controls and also increased β_2-microglobulin levels. Few adverse events were observed and they were not associated with NAC treatment. NAC could therefore be used as an adjunct therapy to provide protection against oxidative stress and improve immune system function and may be effective against other diseases involving GSH deficiency or oxidative stress (*e.g.*, rheumatoid arthritis, Parkinson's disease, hepatitis, liver cirrhosis, septic shock and diabetes) (10).

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AE-941 *Oncolytic*
Neovastat® *Antipsoriatic*
Arthrovas®
Neoretna® *Treatment of Macular Degeneration*
Psovascar®

EN: 232147

Standardized shark cartilage liquid extract comprising the 0-500 kDa molecular fraction

AEterna; Alcon; Ferrer; Medac

An *in vitro* study examined the effects of AE-941 on members of the MMP family of enzymes. The agent potently inhibited the gelatinolytic activity of MMP-2, and the activities of MMP-1, MMP-7, MMP-9 and MMP-13 were also inhibited but to a lesser extent. Inhibition of the elastinolytic activities of MMP-2, MMP-9, MMP-12, porcine pancreatic elastase and human leukocyte elastase was also observed. TIMP-like proteins were detected within AE-941 which may explain the selectivity of the agent for inhibition of MMPs (1).

The effects of AE-941 on VEGF-, histamine-, platelet activating factor (PAF)-, bradykinin- or LPS-induced vascular permeability were examined in mouse capillaries in liver, pancreas, duodenum, ileum, spleen, heart, kidney, stomach, skin, muscle and thyroid gland. AE-941 inhibited VEGF-induced capillary permeability in most tissues and LPS-induced permeability in some tissues. AE-491 had no effect on bradykinin or PAF-induced permeability. It was concluded that the effect of AE-491 on vascular permeability may be via VEGF inhibition (2).

The antitumoral activity of AE-941 was demonstrated in an *in vivo* study using nude mice grafted s.c. with human glioblastoma-derived cells. A significant 61% decrease in tumor volume and a 50% decrease in intratumor vasculature were observed in animals treated with AE-491 at a dose of 30 mcl/day p.o. Higher doses of 150 and 500 mcl/day p.o. resulted in major tumor necrosis and vascular reorganization resulting in cystic formation (3).

Four trials in a total of 482 patients with solid tumors examined the safety of oral AE-941. Of these patients, 146 received the agent for more than 6 months. Treatment with 2.63 ml/kg/day significantly increased survival time (6.15 *vs.* 4.17 months) and decreased death by about 2.5-fold in a subgroup of 47 patients with unresectable non-small cell lung cancer. Results from a multicenter, open-label study in 144 patients with solid tumors refractory to standard therapy indicated efficacy of the agent in patients with renal cell carcinoma. Phase III randomized, double-blind, placebo-controlled trials assessing AE-491 as a monotherapy in 280 patients with metastatic renal cell carcinoma are under way (4).

A pivotal phase II trial, which will take place at approximately 20 sites in Canada, the U.S. and select European countries, will evaluate the efficacy of AE-941 treatment in approximately 120 patients with progressive multiple myeloma. Final results from the trial are expected by the summer of 2002. The study has been designed to determine tumor response based upon commonly used criteria, such as the level of myeloma protein. Other parameters specific to the disease will also be considered (5).

AEterna has signed two agreements for the commercialization of AE-941 with Ferrer and Medac for Europe. According to the new partnerships, AEterna grants the exclusive rights for the commercialization and distribution of the drug in oncology to Ferrer for Southern European countries, including Spain, Greece, Portugal and Italy, while Medac's scope includes Germany, the U.K., Scandinavian countries, Switzerland, Austria and Eastern Europe (6).

AEterna has reported potent antiangiogenic activity in a class of molecules isolated from AE-941. A patent application which covers compositions of matter and methods of use for the treatment of diseases complicated by angiogenesis has been filed in the U.S. relating to this discovery. AE-941 is under evaluation to determine its potential in the fields of oncology, dermatology and ophthalmology. At present, it is being evaluated in 2 phase III trials for the treatment of lung and kidney cancer and a phase II pivotal trial for multiple myeloma at 125 sites in Canada, the U.S. and several European countries (7).

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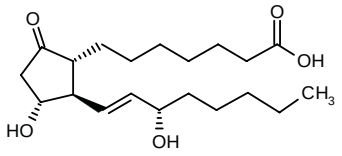
  CCC: 0377-8282/2001

Alprostadil *Treatment of Erectile Dysfunction*
Alprox-TD® *Treatment of Female Sexual Dysfunction*
Topiglan®
Femprox®
Muse®
Befar®
Alista®

EN: 091363



$C_{20}H_{34}O_5$ **Vivus; NexMed; MacroChem; Abbott**

Topically administered alprostadil (Femprox®) has been shown to produce effects on the clitoris and labia similar to following sexual selfstimulation. In this trial, 18 adult women were examined using color duplex ultrasound before and after application of 1 g of 0.2% alprostadil cream. Both peak systolic velocity and end-diastolic velocity significantly increased (135% and 115%, respectively) compared to baseline, and all women had labial and clitoral engorgement. Mild burning was reported by 11% of the women, but no systemic effects were seen. These results indicate that topical alprostadil may be a useful alternative to sexual selfstimulation in the evaluation of the vascular component of female sexual dysfunction (1).

A phase II randomized, parallel, double-blind trial at 12 sites in the U.S. investigated the dose-response relationships of the efficacy and safety of 3 different doses of alprostadil (Alprox-TD®) *versus* placebo in 161 men with mild to moderate ED. The patients were required to apply up to 10 doses at home over a 9-week period and keep a daily diary. The results from this trial indicate that the 3 different dose levels of the drug were more effective than placebo in sexual function endpoint analyses, with the highest dose showing a highly significant increase in erectile function domain scores in the International Index of Erectile Function (IIEF). The response to the global assessment questionnaire, which measures improvement in erectile function, indicated an efficacy rate of 73% in the highest dose group compared to 23% in the placebo group. Other secondary efficacy endpoints also showed statistically significant improvements when the highest dose was compared with placebo (2).

Vivus has signed a distribution and marketing agreement granting Abbott exclusive rights to Muse® in selected markets, including Europe, Japan, Australia, New Zealand and Central and South America. Muse® is a non-injectable, local delivery system consisting of a microsuppository of alprostadil, available in 4 dose strengths, for delivery to the male urethra (3).

Patient enrollment has begun in a phase II trial to evaluate the safety and efficacy of Alista® for the treatment of female sexual dysfunction (FSD). The objective of the multicenter, double-blind, placebo-controlled study is to evaluate the sexual response with the drug in women with a primary diagnosis of female sexual arousal disorder (FSAD), a subcategory of FSD. Results from the trial will provide preliminary data on the drug's efficacy and will assist in designing a larger pivotal study. Alista® is a proprietary formulation of alprostadil which is applied locally to female genitalia (4).

MacroChem has begun an open-label continuation study of Topiglan® for the treatment of ED. In the clinical trial, patients who have completed the randomized and blinded pivotal phase III trial of Topiglan® can elect to receive the agent for an extended period. Topiglan® differs from current and investigational oral drugs for erectile dysfunction in that it is a topical gel that is applied directly to the glans of the penis. In addition, it has no history of interacting with cardiac drugs and can therefore be used in patients currently taking organic nitrate drugs for the treatment of heart disease. The ongoing trial involves 30 clinical trial sites with 460 men randomized to Topiglan® or placebo. Patients are given a preparation to take home and apply to their penis prior to attempting intercourse. In the new study, patients who have completed 16 weeks in the blinded study are offered the opportunity to continue as recipients of the drug regardless of whether they were in an active or the placebo arm of the pivotal trial. Patients who have completed the trial can receive up to 20 doses of Topiglan® per month under the authorized open-label study (5).

NexMed has completed a U.S. phase II safety and efficacy study of Alprox-TD® for the treatment of men with severe ED. The multicenter, double-blind, randomized, parallel, placebo-controlled trial, involving 140 patients at 7 clinical sites, was designed to investigate the dose-response relationships for efficacy and safety of 3 doses of Alprox-TD® *versus* placebo in patients diagnosed with severe ED. The company expects to report results from this trial in mid-April. Pending successful results and FDA approval, the company will include severe ED patients in its phase III trial, which will enroll over 2000 patients at 60 sites in the U.S. (6).

Clinical results have been reported from two U.S. safety trials of Femprox® cream for the treatment of FSAD. In these single-blind, placebo-controlled, dose-escalating studies, 64 healthy women aged 21-60 were divided into 8 groups of 8 women each. Each volunteer received a single dose of placebo or one of 6 different doses of Femprox®. Results indicated that the drug was safe and well tolerated at all doses. No serious adverse effects were reported and no abnormalities in blood pressure or heart rate were observed. These results confirm earlier findings. At present, NexMed is moving Femprox® into a proof-of-concept phase II trial which will enroll over 100 FSAD patients at 11 sites in the U.S. (7).

NexMed has reported that its Asian licensee Vergemont International has filed an NDA in Hong Kong

seeking approval for Befar® cream for the treatment of ED. In February 2001, Befar was approved in China. Befar, which combines alprostadil with NexMed's patented NexACT transdermal penetration-enhancing technology, is incorporated in NexMed's proprietary single-dose dispenser, which is convenient and easy to use. The premeasured dose is applied topically to the tip of the penis with the onset of activity reported at 10-15 min. In the phase III trials conducted in China, Befar® cream was well tolerated with only mild local adverse effects observed (8).

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4. *Alista enters phase II evaluation for FSD.* DailyDrugNews.com (Daily Essentials) Jan 24, 2001.

5. *MacroChem begins open-label continuation phase III study of Topiglan.* DailyDrugNews.com (Daily Essentials) Jan 26, 2001.

6. *Preliminary U.S. testing of Alprox-TD in severe ED patients completed.* DailyDrugNews.com (Daily Essentials) March 14, 2001.

7. *NexMed's Femprox safe and well tolerated in phase I trials.* DailyDrugNews.com (Daily Essentials) May 4, 2001.

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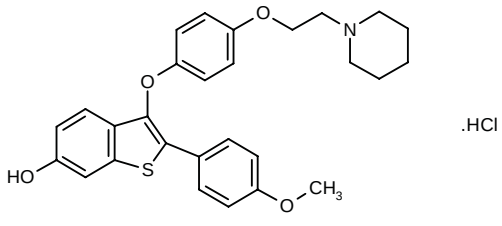
Original monograph - Drugs Fut 1987, 12: 541 (published as Lipo-Alprostadil).

Arzoxifene Hydrochloride

Oncolytic
Treatment of Postmenopausal Syndrome
EN: 249850 *Estrogen Receptor Modulator*



$C_{28}H_{29}NO_4S.HCl$ **Lilly**

The antitumor effects of LY-353381 were shown in a study using a human prostatic cancer cell line (LNCaP) *in vitro* and s.c. LNCaP xenografts in athymic mice *in vivo*. The agent inhibited both estrogen- and androgen-induced cell proliferation *in vitro* and inhibited growth of LNCaP tumors nearly to castrate levels. Since the agent was effective in both vehicle- and sustained-release androgen-treated animals, it was concluded that LY-353381 acts directly on the tumor. No estrogen-induced mammary gland stimulation or testicular or accessory sex organ regression was observed with treatment and no toxicity was seen following high-dose administration for 3 months or longer (1).

A study using ovariectomized rats subjected to 2 h of middle cerebral artery occlusion (MCAO) showed that the neuroprotective effects of LY-353381 (for 5-9 days) against focal cerebral ischemia may be via an increase in BCL-2 expression. Significantly smaller infarct volumes were observed in the caudoputamen in LY-353381-treated rats as compared to controls (49 *vs.* 64%); no difference in cerebral cortical infarct size was observed between treated and control animals. Absolute ischemia cerebral blood flow and tissue volume distribution to low flow zones were also similar between groups. However, LY-353381-treated animals displayed an increase in BCL-2 mRNA expression in both the ipsilateral cerebral cortex and the caudoputamen (2).

A positive impact of estrogen replacement therapy on stroke prevention and stroke severity in postmenopausal women has been suggested but remains unproven. In an attempt to clarify this point, investigators conducted a study of LY-353381 in an experimental model of stroke in estrogen-deficient ovariectomized female rats. In this study, LY-353381 at a dose of 10 mg/kg or vehicle was administered by gavage for up to 8 days to ovariectomized animals, which were then subjected to MCAO and evaluated for infarct volumes and cerebral blood flow. Although pretreatment with LY-353381 reduced infarct volume in the caudoputamen (49 ± 6% of ipsilateral caudoputamen *vs.* 64 ± 4% in vehicle group), no difference was seen in cerebral cortical infarct volumes between the LY-353381 (7 ± 3%) and vehicle groups (13 ± 4%). The protective effect of the drug in the caudoputamen could not be correlated with preservation of regional cerebral blood flow. These findings are encouraging as regards a potential neuroprotective effect for selective estrogen receptor modulators, but further studies will be necessary using different doses and treatment durations and different stroke models (3).

The effects of arzoxifene hydrochloride on human endometrial cancer growth have been compared to those of tamoxifen in ovariectomized athymic mice. The results demonstrated comparable effects on the growth of human endometrial cancer EnCa101 tumor growth. Arzoxifene potentiated the growth of tamoxifen-stimulated tumors, while having no effect on tamoxifen naive tumors, suggesting that it may not be a useful second-line therapy in patients who develop endometrial cancer on tamoxifen (4).

LY-353381 was examined for its long-term effects over 1 year at doses of 0.1 or 0.5 mg/kg/day in ovariectomized rats. Researchers found that the decline in bone mineral density (BMD) was prevented by both doses. Bone loss in the proximal tibial metaphysis was prevented by a reduction in osteoclast number and activation frequency. The study drug maintained bone formation indices at sham level, preserved BMD of lumbar

vertebrae, and resulted in higher vertebral strength than untreated, ovariectomized animals. Additionally, serum cholesterol was reduced 44-59% in LY-353381-treated animals as compared to ovariectomized rats, with uteri 38-40% the weight of those in sham rats (29% of sham in ovariectomized animals) (5).

The pharmacokinetics of single (100 mg) and multiple (100 mg once daily for 4 weeks) doses of LY-353381 were examined in an open-label, 2-period, sequential design trial in 11 healthy postmenopausal women (41-67 years). The pharmacokinetics of LY-353381 were linear and steady state was achieved on day 29. Parameters determined at steady state were comparable to those obtained following single dosing. The $t_{1/2}$ of the agent was 45 h and accumulation (mean accumulation ration = 2.5) of the agent was observed in plasma following multiple dosing. Concentrations of desmethyl metabolites were limited but detected following the first dose (6).

The effects of quinidine (82.5 mg b.i.d. for 7 days) or desipramine (single 75 mg dose) on the pharmacokinetics of single-dose LY-353381 (100 mg) were examined in an open-label, sequential design study conducted in 11 healthy postmenopausal women who were extensive metabolizers. Although quinidine inhibited CYP2D6 and converted extensive metabolizers to poor metabolizers, it had no effect on the pharmacokinetics of LY-353381. Similarly, coadministration of desipramine did not significantly alter the pharmacokinetics of LY-353381. However, the C_{max} and AUC values for desipramine were 14 and 27% lower, respectively, during LY-353381 administration. Further analysis showed that LY-353381 did not decrease the clearance of desipramine (7).

The safety of LY-353381 (10, 20, 50 and 100 mg/day p.o. for 12 weeks) was demonstrated in a phase I trial in 32 patients with recurrent or metastatic breast cancer. Of the patients included, 19 were estrogen receptor (ER) and progesterone receptor (PR) positive, 8 were ER positive and PR negative, 2 were ER positive and PR unknown and 3 were ER and PR unknown; both treatment naive and previously treated patients were included. No dose-limiting toxicity was observed and treatment was well tolerated. Mild to moderate hot flashes were experienced by 56% of the patients at all dose levels. No endometrial thickening was observed after 12 weeks of treatment. Six patients had stable disease for at least 6 months for a median duration of 7.7 months. The pharmacokinetics of the agent were generally linear according to time and dose (8).

Arzoxifene hydrochloride is currently moving into phase III clinical studies for the treatment of metastatic breast cancer. Based on early studies, the compound appears to be an active selective estrogen receptor modulator without any apparent uterine stimulation (9).

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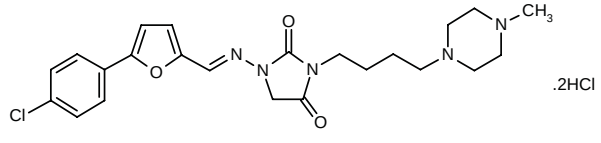
Original monograph - Drugs Fut 1999, 24: 599.

Azimilide Hydrochloride *Antiarrhythmic*
Stedicor®

EN: 195716



$C_{23}H_{28}ClN_5O_3.2HCl$

Procter & Gamble; Tanabe Seiyaku

The effects of azimilide were examined on cardiovascular tissue from normotensive and spontaneously hypertensive (SHR) rats. The agent (30 μM or less) had no effect on resting normotensive aorta or mesenteric and intralobar pulmonary arteries, although concentrations ≥ 30 μM relaxed KCl-contracted aorta and portal vein. Concentrations of 100 nM and 10 μM prolonged normotensive left ventricular action potential and contraction force. Although similar enhancement of contraction force was seen when left ventricular strips from 12-month

SHRs were exposed to azimilide (100 nM and 10 μM), the effect on tissue from 22-month SHRs was less marked. However, 3 and 30 μM azimilide augmented left ventricular force of 22-month SHRs by 40 and 50%, respectively (1).

The effects of azimilide (0.6-54 mg/kg/min i.v. infusion) on cardiac performance, fibrillation threshold and hemodynamics were examined in anesthetized dogs. The agent was well tolerated and effective in increasing contractility. In beagles, while a dose of 2 mg/kg increased QTc to > 20 ms, 8.9 mg/kg increased QTc by 34% and maintained it for at least 60 min postdosing. A dose of 8.9 mg/kg increased heart contractile force (HCF) and +dP/dT by 10 and 34%, respectively, and decreased heart rate by 12%; blood pressure, left ventricular end diastolic pressure, -dP/dT, stroke volume and cardiac output were not affected. The mean maximum dose of 47 mg/kg resulted in a sustained increase in QTc although HCF, +dP/dT, -dP/dT, stroke volume and cardiac output decreased by 27, 24, 32, 16 and 52%, respectively. Cumulative i.v. bolus injections of azimilide (0.3, 1, 3, 10 and 30 mg/kg) administered to mongrel dogs caused an increase in effective refractory period (18%) and +dP/dT (16%) and a decrease in heart rate (22%) at 10 mg/kg; mean blood pressure was significantly decreased only with the 30 mg/kg dose. The highest dose did not alter the ventricular fibrillation threshold (2).

The proarrhythmic effects of dofetilide (0.025 mg/kg/5 min) and azimilide (5 mg/kg/5 min) were shown in a study using anesthetized dogs with a high incidence of torsade de pointes arrhythmias due to chronic complete AV-block and bradycardia-induced volume overload. Dogs were treated with the agents at 4 and 6 weeks of the AV block. Both agents increased monophasic action potential duration, idioventricular rhythm cycle length and QT time. Interventricular dispersion was also significantly increased from 55 to 110 ms after treatment with either agent due to the dissimilar lengthening of the left and right ventricular monophasic action potential duration. Early afterdepolarizations were observed in all animals with ectopic ventricular beats seen in most of them (8/9 and 7/9 animals for dofetilide and azimilide, respectively). Comparable incidence of torsade de pointes arrhythmias was observed with both treatments (6/9 and 5/9 animals for dofetilide and azimilide, respectively) (3).

The antiarrhythmic effects of azimilide (50, 100 or 125 mg or combined 100 and 125 mg once daily) were shown in a randomized, placebo-controlled trial in 384 patients with a history of atrial fibrillation and/or atrial flutter. Treatment with combined doses of 100 and 125 mg azimilide significantly prolonged the time to first symptomatic arrhythmia recurrence; the hazard ratio was 1.58. The hazard ratios for 50, 100 and 125 mg daily doses were 1.17, 1.38 and 1.83, respectively (4).

1. Nand, V., Doggrell, S.A. *Effects of azimilide on cardiovascular tissues from normo- and hypertensive rats.* J Cardiovasc Pharmacol 2000, 36(2): 209.

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3. Van Opstal, J.M., Leunissen, J.D.M., Wellens, H.J.J., Vos, M.A. *Azimilide and dofetilide produce similar electrophysiological and proarrhythmic effects in a canine model of torsade de pointes arrhythmias.* Eur J Pharmacol 2001, 412(1): 67.

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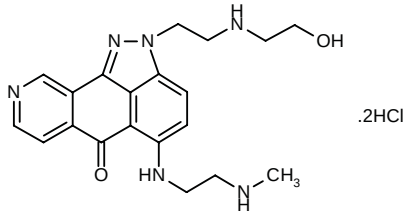
BBR-3438

Oncolytics

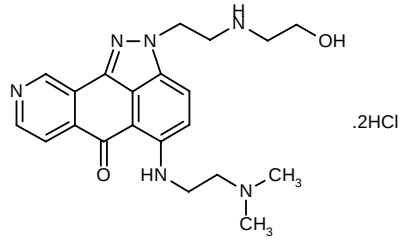
EN: 210576



$C_{20}H_{24}N_6O_2.2HCl$

BBR-3576

EN: 210577



$C_{21}H_{26}N_6O_2.2HCl$ **Novuspharma**

Studies examined the unique mechanism of action of the 9-aza-anthrapyrazoles BBR-3438 and BBR-3576 and compared them to that of the carbocyclic analogs, losoxantrone and mitoxantrone. BBR-3438 and BBR-3576 did not undergo self-aggregation as seen with losoxantrone and mitoxantrone and they were electrochemically reduced at a potential between the latter two. BBR-3438 and BBR-3576 displayed marked affinity for DNA selectively, favoring GC steps in double-helical DNA. In

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contrast, losoxantrone and mitoxantrone showed a lower affinity for GC. Topoisomerase II-mediated DNA cleavage was attenuated with the two compounds, indicating that other nonenzyme-mediated cytotoxic actions are involved in cell killing; the agents may influence free radical production (1).

In September 2000, phase I studies of BBR-3438 began in patients with untreatable solid tumors. The maximum tolerated dose level of 64 mg/m^2 has already been identified and the acute toxicity profile observed is in line with expectations. This compound was developed on the basis of a patent co-owned by Novuspharma and the University of Vermont and Novuspharma holds an exclusive license to the patent. Also in September 2000, phase I studies of BBR-3576 began in patients affected by untreatable solid tumors. Toxicity has turned out to be lower than expected in the phase I studies, which may allow the drug to be administered in much larger doses than first thought. The company is working to establish the maximum tolerated dose (2).

Patient recruitment has begun for an open-label, multicenter phase II trial of BBR-3438 in Germany to evaluate the efficacy of the agent for the treatment of advanced gastric cancer in patients who have already failed one chemotherapy regimen. In addition, patient recruitment for a parallel international trial with BBR-3576, similar in design and scope, in Austria, Germany and the Benelux is about to begin. Both studies will involve gastric cancer patients in order to compare the efficacy and tolerability of the two compounds. In preclinical evaluation, both molecules demonstrated anticancer activity against a broad range of solid tumors, especially prostate and stomach cancers. In the third quarter of 2001, the company intends to begin recruitment for parallel trials of each compound in patients with prostate cancer who have failed to respond to hormone therapy (3).

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2. *Novuspharma makes important progress in clinical programs during past year.* DailyDrugNews.com (Daily Essentials) March 9, 2001.

3. *Two Novuspharma compounds advance to phase II for gastric cancer.* DailyDrugNews.com (Daily Essentials) June 15, 2001.

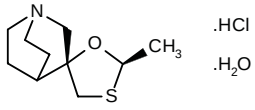
Original monograph - Drugs Fut 1997, 22: 641.

Cevimeline Hydrochloride

AF-102B *Treatment of Sjögren's Syndrome*

Evoxac®

EN: 134916



$C_{10}H_{17}NOS.HCl.H_2O$ **Snow Brand; Nippon Kayaku; Israel Inst. Biol. Res.; Daiichi Pharm.**

Muscarinic M_1 receptor activation has been reported to inhibit the secretion of β-amyloid (Aβ) in cell culture and may therefore represent a therapeutic approach to the treatment of Alzheimer's disease. A recent study assessed the effects of the selective M_1 agonist cevimeline hydrochloride on cerebrospinal fluid (CSF) Aβ levels in 19 Alzheimer's disease patients. A statistically significant decrease in Aβ levels was seen in the group as a whole; specifically, 14 patients showed a 22% decrease in CSF Aβ levels, 2 no change and 3 an increase in total Aβ CSF levels. In contrast, neither the acetylcholinesterase inhibitor physostigmine nor the antiinflammatory agent hydroxychloroquine had a significant effect in Alzheimer's disease patients. These findings point to potential long-term beneficial effects of M_1 agonists in AD (1).

Daiichi Pharmaceutical has launched cevimeline hydrochloride (Evoxac®) as a treatment for Sjögren's syndrome in the U.S. The product is licensed from Snow Brand Milk Products and is available as capsules containing the equivalent of 30 mg of cevimeline (2).

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2. *Cholinergic agonist for Sjögren's syndrome introduced in U.S.* DailyDrugNews.com (Daily Essentials) June 28, 2000.

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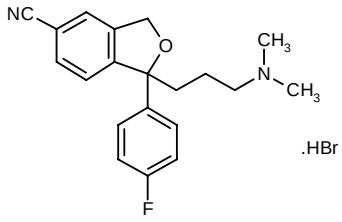
Citalopram Hydrobromide
Celexa®

Antidepressant

EN: 090241



$C_{20}H_{21}FN_2O.HBr$ **Lundbeck; Biovail; Mitsui Pharm.**

Lundbeck and Mitsui Pharmaceuticals (Nihon Schering) have signed a semiexclusive license agreement for the development, registration, sale and marketing of citalopram in the Japanese market. Since several studies in Japanese patients have already been completed, the companies expect only one phase III study (a bridging study) to be completed prior to the submission of the registration application (1).

Biovail successfully completed the development of a novel controlled-release formulation of citalopram (Celexa®) and phase III clinical trials were expected to begin. The successful completion of the technical phase of the development was demonstrated by the results of phase I pivotal bioavailability studies conducted on commercial-scale clinical batches. The controlled-release formulation has been designed to provide further improvements in patient tolerability and features a unique pharmacokinetic profile (2).

1. *Lundbeck and Mitsui establish citalopram collaboration agreement*. DailyDrugNews.com (Daily Essentials) Sept 7, 2000.

2. *Biovail completes development of controlled-release formulation of Celexa.* DailyDrugNews.com (Daily Essentials) July 5, 2000.

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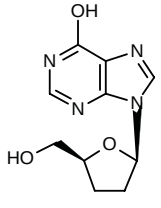
Didanosine
Videx®

Anti-HIV

EN: 143041



$C_{10}H_{12}N_4O_3$ **Bristol-Myers Squibb**

In October 2000, Bristol-Myers Squibb received approval from the FDA for didanosine (Videx® EC) delayed-release capsules with enteric-coated beadlets for the treatment of HIV/AIDS. The first European approval for the formulation was received in February 2000 (1).

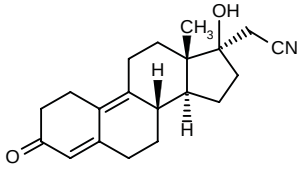
1. *Bristol-Myers Squibb highlights significant developments during 2000.* DailyDrugNews.com (Daily Essentials) Jan 30, 2001.

Original monograph - Drugs Fut 1990, 15: 569.

Dienogest
Climodien®

Hormone Replacement Therapy
Oral Contraceptive

EN: 090248



$C_{20}H_{25}NO_2$ **Schering AG; Jenapharm**

The E.U. has approved Climodien®, a new continuous combination hormone replacement therapy (HRT) for the treatment of symptoms related to the menopause. Climodien®, composed of dienogest and estradiol valerate, was first approved in The Netherlands in December 2000 and the product's first launch is expected to take place in Germany this fall. Climodien® differs from other HRTs, such as sequential or cyclical HRT, in that it is taken without any monthly breaks which usually result in menstruation-like bleeding. Due to this continuous regimen, menstrual bleeding ceases after about 6-8 months (1).

1. *Climodien continuous combined HRT cleared in E.U.* DailyDrugNews.com (Daily Essentials) June 18, 2001.

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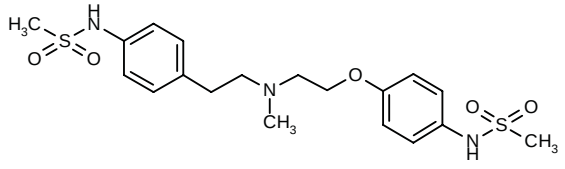
Dofetilide
Xelide®
Tikosyn®

Antiarrhythmic

EN: 138388



$C_{19}H_{27}N_3O_5S_2$ **Pfizer**

An *in vitro* study using HERG1 A channels expressed in *Xenopus* oocytes showed that the Phe-656 residue of HERG determined high-affinity binding of dofetilide. The binding affinity of HERG1 A for dofetilide decreased from 0.125 ± 0.003 μM for the wild-type channels to 15 ± 3 μM for F656V mutated (on the COOH-terminal of S6) channels. Mutations in amino acids in S6 altered deactivation, activation and recovery from inactivation of channels but had no effect on dofetilide affinity. However, an S631A mutation altered the IC_{50} value of dofetilide to 20 ± 3 μM; the IC_{50} for quinidine was unaltered (8 ± 4 and 10 ± 1 μM for wild-type and S631A, respectively). A double mutation of S631A/F656V further increased the IC_{50} of dofetilide to 32 ± 3 μM. It was concluded that allosteric changes during HERG1 A channel inactivation are required for high-affinity dofetilide binding (1).

The clinical efficacy of dofetilide in converting and maintaining sinus rhythm in patients with atrial fibrillation and atrial flutter has been reviewed. The agent was shown to prolong the effective refractory period and dose-dependently prolong the QT and QTc intervals and increase ventricular refractoriness. An elimination $t_{1/2}$ value of 10 h was obtained in patients. Dofetilide exhibited significantly superior activity over flecainide in converting atrial flutter to a normal sinus rhythm (70 *vs.* 9%) and was better than sotalol in converting atrial flutter and atrial fibrillation patients (29 *vs.* 6%) and maintaining them in a normal sinus rhythm for up to 1 year. After dosing, the majority of patients converted to normal sinus rhythm within 24-36 h. The most serious adverse event observed with treatment was dose-dependent torsade de pointes seen in 0.3-10.5% of the patients. Other adverse events were headache, chest pain and dizziness. It was recommended that patients be hospitalized for monitoring for at least 3 days during administration of dofetilide (2).

The pharmacokinetics of oral dofetilide (1000, 1500 or 2500 μg b.i.d. or t.i.d. with a 6-day washout period between treatments) were examined in a randomized, 2-way crossover study conducted in 25 healthy subjects. C_{max} and steady-state plasma dofetilide levels were achieved at 2 h postdosing and on day 3, respectively. The C_{trough} values obtained with both dosing regimens were linear and dose-dependent and $AUC_{0-\tau}$ increased linearly with dose on days 1 and 5. Plasma dofetilide concentrations and prolongation of the QTc interval were linearly correlated with the slope significantly greater on day 1 (12.9-14.2 ms/ng/ml) as compared to day 5 (9.9-12.8 ms/ng/ml) (3).

A randomized, double-blind, placebo-controlled, parallel-group study in 14 healthy male volunteers showed that 5-day dofetilide treatment (250 μg b.i.d. on day 8-12) did not significantly influence the steady-state pharmacokinetic parameters of digoxin (1 mg on day 1 and 2 followed by 250 μg on days 3-12). Thus, dofetilide dose adjustments are not required with concomitant digoxin treatment (4).

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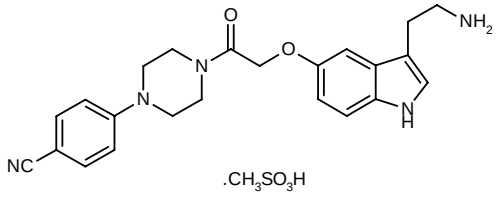
Donitriptan Mesilate
F-12640

Antimigraine
5-HT$_{1B/1D}$ Agonist

EN: 260121



$C_{23}H_{25}N_5O_2.CH_4O_3S$ **Pierre Fabre**

Two different salts of donitriptan have been evaluated, the hydrochloride salt F-11356 and the mesilate salt F-12640. As both salts were shown to be pharmacologically equivalent but the mesilate is associated with improved water solubility and stability, F-12640 was chosen for further development. The results from *in vitro* and *in vivo* studies indicated that donitriptan may provide higher response rates, greater consistency of pain relief, a lower incidence of migraine recurrence, as well as a relatively rapid onset of action and good tolerance (1).

The effects of F-12640, sumatriptan and acetylsalicylic acid (ASA) were compared *in vivo* in a rat model of meningeal calcitonin-related peptide (CGRP) release and protein plasma extravasation. When given 30 min before right trigeminal ganglion stimulation (0.6 mA, 5 ms, 5 Hz), both F-12640 (0.6 mg/kg i.p. 30 min before stimulation) and sumatriptan (0.3 mg/kg) completely inhibited CGRP release; ASA (30 mg/kg) had no effect. All agents were shown to inhibit protein plasma extravasation. Results indicate that F-12640 may be a potential treatment for migraines (2).

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Original monograph - Drugs Fut 1999, 24: 605.

Dornase Alfa
Pulmozyme®

Treatment of Cystic Fibrosis

EN: 188427

Roche; Genentech

Based on a review and prioritization of its development efforts, Genentech has decided to discontinue the development of dornase alfa, the active ingredient in their currently marketed product Pulmozyme® inhalation solution (1).

1. *Aradigm and Genentech discontinue AERx rhDNase development program.* DailyDrugNews.com (Daily Essentials) Feb 6, 2001.

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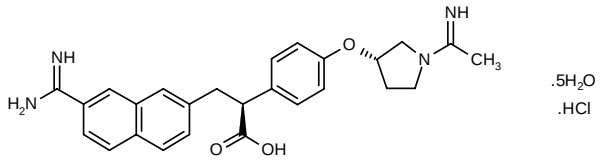
DX-9065a

Anticoagulant
Factor Xa Inhibitor

EN: 199880



$C_{26}H_{28}N_4O_3.HCl.5H_2O$ **Daiichi Pharm.; Beijing General**

The pharmacokinetics of single-dose [^{14}C]-DX-9065a (10 mg 1-h i.v. infusion) were examined in a healthy male volunteer. Mean plasma total radioactivity was 380 ng/ml postinfusion and decreased biexponentially to below detection by 48 h postdosing. The distribution phase $t_{1/2}$ was 6.93 h. By 336 h postinfusion, the total radioactivity recovered in urine and feces was 83.8%. Since 77.6% of the dose was recovered in urine, urinary excretion was concluded to be the major route of elimination; this route was found to be composed of a rapid (0-24 h) and slow (24-336 h) phase and renal tubular secretion was suggested to be involved. Biotransformation of the agent was not significantly involved in elimination since no metabolites were detected in urine (1).

DX-9065a was compared to that of the low-molecular-weight heparin enoxaparin. In an open-label, escalating-dose, crossover study, 6 healthy male volunteers received DX-9065a administered as a 1-mg i.v. bolus + 0.5 mg by infusion over 2 h, followed by an additional 1-mg bolus + 1.25 mg by infusion, followed by a final 1-mg bolus + 2.5 mg by infusion or enoxaparin administered s.c. at 1 mg/kg. Using a perfusion chamber, alterations in platelet thrombus formation before and after drug administration were quantified at high and low shear rates. At a high shear rate, platelet thrombus formation as compared to baseline was 94% for enoxaparin at 4 h after administration and 99% (1 mg + 0.5 mg), 81% (1 mg + 1.25 mg)

and 67% (1 mg + 2.5 mg) for DX-9065a at 2 h following administration of each dose. At a low shear rate, platelet thrombus formation as compared to baseline was 98% for enoxaparin at 4 h following administration and 98% (1 mg + 0.5 mg), 89% (1 mg + 1.25 mg) and 75% (1 mg + 2.5 mg) for DX-9065a at 2 h after administration of each dose. Moreover, unlike enoxaparin, DX-9065a did not produce a significant prolongation of aPTT or bleeding time at any of the doses tested. Therefore, the reduction in platelet thrombus formation under conditions of high and low shear rate on DX-9065a suggests that direct factor Xa inhibition may have a role in the prevention of thromboembolic episodes (2).

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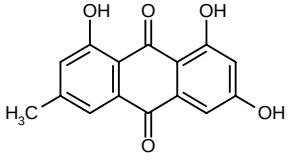
Original monograph - Drugs Fut 1995, 20: 564.

Emodin

Oncolytic

EN: 237157



$C_{15}H_{10}O_5$ **China Pharm. Univ.**

The antiangiogenic effects of emodin were demonstrated using *in vitro* and *in vivo* models. The agent dose-dependently inhibited proliferation of bovine aortic endothelial cells with an IC_{50} value of about 10 μM obtained in MTT and radiolabeled thymidine incorporation assays with or without bFGF or VEGF stimulation. Emodin doses of 10-40 μM blocked the cell cycle at the G_2/M phase, induced apoptosis and increased intracellular free calcium. Results from [^{125}I]-binding assays showed that emodin did not block binding of EGF or VEGF to their receptors. Angiogenesis was also found to be inhibited in an *in vivo* chicken chorioallantoic membrane model. Studies using a metastatic human lung cancer cell line (PG) showed that emodin (10 μM) decreased the secretion of 72 and 92 kD MMPs and inhibited migration and proliferation. A synthetic emodin derivative, EMD-011, was found to be 10-fold more potent than emodin in inhibiting endothelial cell proliferation. Examination of the activity of another analog (C3368-B) is ongoing (1).

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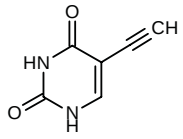
Eniluracil

Oncolytic

EN: 184938



$C_6H_4N_2O_2$ **GlaxoSmithKline**

The preclinical development of eniluracil has been reported in a recent study. The agent was shown to ensure predictable 5-FU dosing thus enabling oral 5-FU administration as opposed to an i.v. bolus followed by continuous infusion. The agent eliminated formation of 5-FU metabolites and new dihydropyrimidine dehydrogenase was produced with a half-life of 2.6 days. Animal studies showed that eniluracil increased the therapeutic index and absolute efficacy of 5-FU (1).

The pharmacology of eniluracil has been summarized. The maximum tolerated dose of oral 5-FU with eniluracil was markedly lower (1-25 mg/m^2) than that observed with conventional 5-FU dosing. Administration of 5-FU with eniluracil resulted in an increase in 5-FU bioavailability of 100%, an increase in the $t_{1/2}$ value of 4-6 h and a decrease in clearance of > 20-fold. The agent was eliminated mainly through renal excretion (about 45-75%). Steady-state concentrations of 5-FU (8-38 ng/ml) were obtained following chronic daily oral dosing with 5-FU (1 mg/m^2 b.i.d.) + eniluracil (20 mg b.i.d.). Following chronic daily administration of oral 5-FU + eniluracil, high 5-FU AUC values were associated with diarrhea as compared to neutropenia observed when 5-FU was administered in a daily times 5 schedule. Moreover, oral eniluracil (10-20 mg b.i.d. p.o.) was shown to completely inactivate dihydropyrimidine dehydrogenase (DPD) in peripheral blood mononuclear cells and

colorectal tumor tissue; eniluracil-induced suppression of DPD was found to be sustained postdosing. The pharmacokinetics of oral eniluracil were comparable to oral 5-FU and, therefore, oral 5-FU administration is possible when given with eniluracil (2).

The clinical development of eniluracil/5-FU has been summarized. Treatment of patients with solid tumors with the agent as a monotherapy for 5 or 28 days resulted in good efficacy. The dose-limiting toxicity was determined to be myelosuppression and diarrhea with the 5- and 28-day schedules, respectively, and a low incidence of hand-foot syndrome was observed with both regimens (3).

An open-label, phase II study in 33 patients with locally advanced or metastatic breast cancer naive to advanced disease chemotherapy showed the efficacy of first-line treatment with combination oral 5-FU (1 mg/m^2 b.i.d.) and eniluracil (10 mg/m^2 b.i.d.) given the first 28 days of a 35-day cycle. Of the 29 evaluable patients, 16 partial responses were seen. Seven patients had stable disease with symptom improvement for at least 3 months. Treatment was tolerated with only 2 cases of grade 3 diarrhea and infection observed. Granulocytopenia, thrombocytopenia and neutropenic sepsis developed in 6, 3 and 3% of the patients, respectively. Other adverse events included grade 1/2 diarrhea (39%), hand-foot syndrome (15%), nausea (27%) and mucositis (18%). Delays and reductions in dosing due to toxicity were required in only 2 and 5% of the courses, respectively (4).

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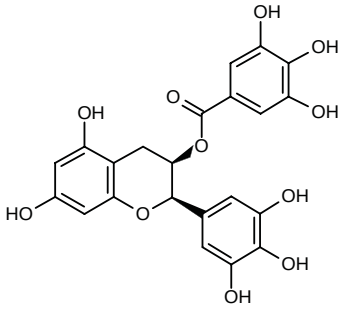
(–)-Epigallocatechin Gallate

Oncolytic
Chemopreventive

EN: 183411



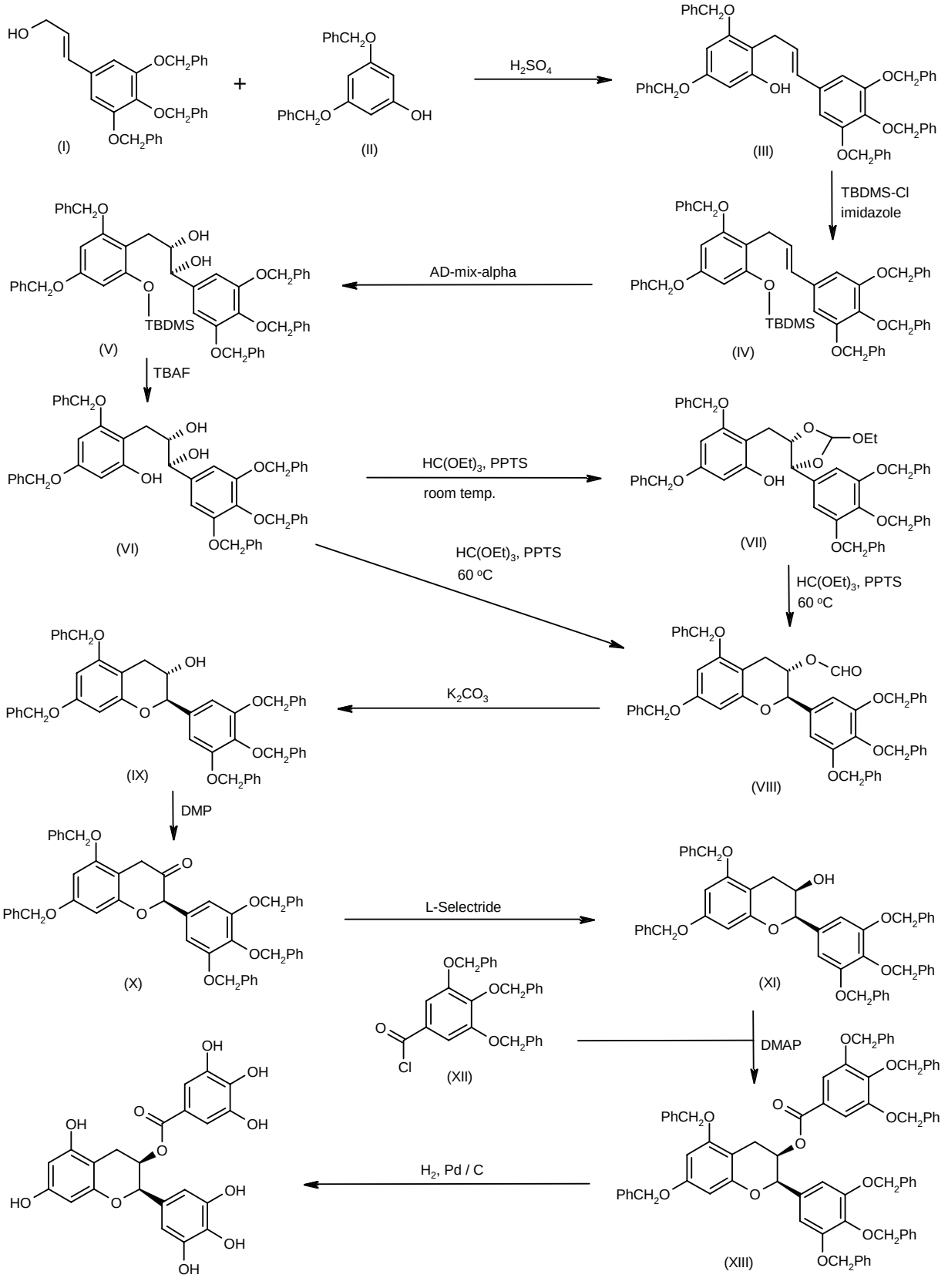
$C_{22}H_{18}O_{11}$ **Natl. Cancer Center Res. Inst. (JP)**

An enantioselective synthesis of epigallocatechin-3-gallate has been reported: The condensation of 3,4,5-tris(benzyloxy)cinnamyl alcohol (I) with 3,5-bis(benzyloxy)phenol (II) by means of H_2SO_4 gives the diphenylpropene derivative (III), which is silylated with TBDMS-Cl and imidazole to yield the silyl ether (IV). The asymmetric dihydroxylation of (IV) with AD-mix-α affords diol (V), which is desilylated with TBAF in THF, providing the trihydroxy compound (VI). Esterification of (VI) with triethyl orthoformate and pyridinium *p*-toluenesulfonate (PPTS) at room temperature gives the cyclic orthoester (VII), which is treated with the same reactants at 60 ºC to yield the benzopyran (VIII). Compound (VIII) can also be obtained directly from (VI) by treatment with triethyl orthoformate and PPTS at 60 ºC. The hydrolysis of the formate group of (VIII) with K_2CO_3 in methanol affords alcohol (IX), which is oxidized to the corresponding ketone (X) with Dess-Martin periodinane (DMP) in dichloromethane. The reduction of (X) with L-Selectride in THF provides the chiral *cis*-alcohol (XI), which is esterified with 3,4,5-tris(benzyloxy)benzoyl chloride (XII) and DMAP in dichloromethane to give the protected ester (XIII). Finally, this compound is debenzylated by hydrogenation with H_2 over Pd/C in methanol/THF (1). Scheme 1.

A study using cDNA microarray analysis incorporating cDNA probes synthesized from untreated and EGCG (12 mcM for 12 h)-treated prostate cancer cells (LNCaP) identified 250 genes whose expression was altered with treatment. Treatment had little or no effect on p38 MAP kinase, phosphatidylinositol 3-kinase, PTEN or PKCβ, -δ, -ε, -μ and -ζ, but significantly suppressed gene expression of PKCα, suggesting that inhibition of PKCα may be involved in the antiproliferative effects of EGCG in prostate cancer cells (2).

An *in vitro* study using human U-87 glioblastoma cells showed that EGCG dose-dependently inhibited proMMP-2 protein secretion. This effect occurred via a brefeldin-A-like mechanism resulting in accumulation of the intracellular pool of proMMP-2 and activation of caspase-3. EGCG also inhibited extracellular secreted proMMP-2 gelatinolytic activity without affecting the intracellular

Scheme 1: Synthesis of Epigallocatechin-3-Gallate



proMMP-2 pool; no changes in MMP-2 transcript levels were observed with treatment (3).

The effects of EGCG (25, 50, 100 and 200 μM for 48 h) were examined in an *in vitro* study using human pancreatic (Panc-1, MIA PaCA-2, BxPC-3) and biliary tract (TGBC-2, SK-ChA-1, NOZC-1) carcinoma cells. EGCG significantly and dose-dependently inhibited growth of all pancreatic (15.4, 26 and 44.6%, respectively) and biliary tract (27.2, 16 and 10.1%, respectively) carcinoma cell lines and significantly suppressed their invasive ability (12, 8.7 and 9.5% and 12.6, 11.2 and 7.9%, respectively) (4).

An *in vitro* study examined the effects of EGCG (20 nM) and theaflavin-3,3'-digallate (TFdiG; 20 nM) on 30.7b Ras 12 cells. EGCG and TFdiG dose-dependently reduced phospho-MEK1/2 protein by 32% at 30 min and 38% at 15 min, respectively. Experiments using lysate from 30.7b Ras 12 cells showed that although EGCG and TFdiG did not alter Raf-1 activity, TFdiG significantly reduced total Raf-1 protein by > 40% at 15 min and > 80% at 120 min; pretreatment with chloroquine (100 mM for 30 min) blocked TFdiG-induced Raf-1 degradation. A decrease in Raf-1 precipitation of > 30% was seen when cells were treated with EGCG for 30 min and Raf-1 was coimmunoprecipitated with Raf-1 and anti-MEK1 antibody. It was concluded that TFdiG-induced rapid lysosome degradation of Raf-1 and EGCG-induced interference with the association of Raf-1 with MEK1 protein were responsible for the inhibition of phospho-ERK1/2 protein levels (5).

An *in vitro* study showed that EGCG (1 mM) protected neonatal rat primary astroglial cultures from 4-hydroxynonenal (HNE)-induced toxicity. While HNE decreased cell viability (80%), EGCG enhanced viability. EGCG was found to significantly reduce (60-80%) the activity and expression of glutathione peroxidase and transferase activity (6).

A study showed that ester-bond containing tea polyphenols such as EGCG at concentrations seen in the serum of green tea drinkers specifically inhibited chymotrypsin-like activity of the proteasome *in vitro* (IC_{50} = 86-194 nM) and *in vivo* (IC_{50} = 1-10 μM). The carbon of the polyphenol ester bond was required for EGCG targeting to inhibit the proteasome in cancer cells. Results from studies using several tumor and transformed cell lines showed that EGCG-induced inhibition of the proteasome caused an accumulation of the proteasome substrates p27(Kip1) and IκB-α and cell growth arrest in the G phase. It was concluded that the proteasome may be the cancer-related target of green tea polyphenols (7).

The apoptotic effects of EGCG were shown *in vitro* against human oral and salivary gland squamous cell carcinoma tumor cell lines. Treatment with the agent resulted in a reduction in bcl-2 and akt expression, activation of DNA fragmentation and activation of caspase-3 and caspase-9 (8).

The metabolism of [4-^{3}H]-EGCG (1 mg p.o.; 50 μCi) was examined in rats. Radioactivity in blood and tissue (except gastrointestinal) peaked at 24 h postdosing. Radioactivity in tissue was 0.8% of the dose or less. No accumulation of EGCG metabolites was observed. The major route of elimination was urinary. Urinary excretion of radioactivity at 48 h postdosing was 30% of the dose and 70% of that radioactivity was identified as the 3',5'-dihydroxyphenyl-gamma-valerolactone conjugate; EGCG, methylated EGCG and their conjugates were not detected in urine (9).

Results from an *in vivo* study using C3H/HeN mice showed that topical EGCG (1 mg/cm^2 skin area) administration prior to a single exposure to UVB radiation (90 mJ/cm^2) inhibited infiltration of leukocytes, particularly CD11b+ cells. Treatment also inhibited UVB-induced myeloperoxidase activity and the depletion of class II MHC+ Ia+ antigen presenting cells in the epidermis. In addition, the number of epidermal and dermal H_2O_2 producing and inducible nitric oxide synthase expressing cells was decreased in the UVB-treated site of EGCG-treated animals (10).

A study using guinea pigs, hairless mice and human dermal fibroblast cultures showed the efficacy of EGCG in protecting against UV-induced skin damage. Treatment of guinea pigs with the agent significantly decreased lipid peroxidation as compared to controls (286 ± 57 *vs.* 838 ± 144 nmol/mg at 18 h post-UV exposure) and UVB-induced erythema was also decreased (erythema relative index = 191 ± 49 *vs.* 311 ± 45 at 16 h post-UV exposure). The agent decreased UVA-induced skin damage (*i.e.*, roughness and sagginess) and protected against UV-induced dermal collagen loss in hairless mouse skin. Treatment of fibroblast cultures with the agent protected against UV-induced increases in collagen secretion and collagenase mRNA levels and inhibited NF-κB and AP-1 binding activities (11).

A study has successfully used liquid chromatography with multichannel electrochemical detection to determine levels of EGCG in rat blood taken using an automated sampler. EGCG was detected within 10 min. The limit of detection was 2 ng/kg. EGCG (2 mg/kg) was rapidly absorbed following i.p. administration and blood concentrations declined in a biexponential manner (12).

A randomized, crossover phase I trial conducted in 20 healthy subjects examined the pharmacokinetics of single oral doses of EGCG (200, 400, 600 and 800 mg based on EGCG content) and polyphenon E. No significant differences were observed between the pharmacokinetics obtained for the two formulations. The mean AUC values of unchanged EGCG for the respective doses following administration of EGCG and polyphenon E, respectively, were 22.5 and 21.9, 35.4 and 52.2, 101.9 and 79.7 and 167.1 and 161.4 μg·min/ml. Epigallocatechin or epicatechin levels in plasma were undetectable or low/undetectable following EGCG and polyphenon E administration, respectively. The AUC and C_{max} values for 800 mg EGCG were significantly higher than those obtained with the 200 and 400 mg doses (13).

The pharmacokinetics of i.v. (–)-epicatechin (EC) and EGCG were compared following administration to rats as a combination in green tea extract or as individual agents.

Significantly different pharmacokinetics were obtained for pure formulations *versus* the extract, indicating that an additional substance(s) in the extract exerts pharmacological effects. The clearance (l/min/kg), V_c (l/kg), V_d (l/kg), $t_{1/2\alpha}$ (min) and $t_{1/2\beta}$ (min) for extract/pure EC formulations were 0.04/0.04, 0.5/1.6, 2.4/4.6, 3.1/10.6 and 49/83, respectively; all parameters except clearance were significantly different for the two formulations. The same parameters obtained for extract/pure EGCG formulations were 0.02/0.03, 0.4/0.7, 3.1/3.8, 9.3/9.1 and 140/95, respectively; all parameters except V_d and $t_{1/2\alpha}$ were significantly different in the two formulations (14).

The efficacy of EGCG (2% cream b.i.d. for 5 days/week for 4 weeks) was demonstrated in a randomized, placebo-controlled, parallel-group study involving 60 young subjects (12-30 years) with acne vulgaris (10-150 mild to moderate open or closed comedones including cystic acne lesions). Of those subjects treated with EGCG cream, 70% were cured of acne lesions as compared to 6.6% on placebo. Only 5% of the subjects reported adverse events with either EGCG cream or placebo. The study included a 12-month follow-up with no subjects discontinuing (15).

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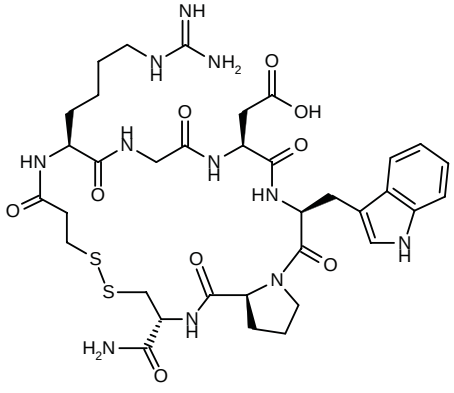

$C_{35}H_{49}N_{11}O_9S_2$

COR Therapeutics; Schering-Plough; Essex; Genentech

Researchers have completed an analysis of the subgroup of 4035 patients from the U.S. from the multinational Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) study, which investigated the use of eptifibatide in patients presenting with chest pain within the previous 24 h and with ischemic ECG changes or creatine kinase-MB elevation. Enrolled patients were randomized to placebo or eptifibatide infusion for up to 72-96 h. Treatment reduced the rate of death or myocardial infarction over 30 days from 15.4% to 11.9%. An absolute treatment effect of 3.5 events prevented per 100 patients treated was achieved early and was maintained over 6 months. A higher incidence of bleeding events was found in the eptifibatide group, but these were mostly associated with invasive procedures. While all patient subgroups within the U.S. appeared to benefit similarly from treatment, patients in the U.S. derived greater clinical benefit than those in other parts of the world (1).

Encouraging findings have been presented from the first phase of the INTEGRITI (INTEGRIlin and Tenecteplase in acute myocardial Infarction) study, a phase II collaborative effort between the Thrombolysis In Myocardial Infarction (TIMI) research network at Harvard University and Duke clinical research networks. The results in patients with S-T segment elevation myocardial infarction showed that eptifibatide combined with a half-dose of tenecteplase was able to fully restore blood flow through blocked arteries in 70% of patients within 60 min of initiating therapy. For comparison, previous studies of full-dose fibrinolytic agents have reported restoration of blood flow within this time frame in < 50% of heart attack patients. The combination also restored blood flow to some degree in 96% of patients over 60 min, whereas previous studies of full-dose fibrinolytics have reported some restoration of blood flow through blocked arteries in < 80% of patients. This first phase of INTEGRITI included nearly 190 patients presenting to the hospital with an ECG-confirmed heart attack, who were administered various combination doses of eptifibatide and tenecteplase in a stepwise fashion to determine their effect on opening blocked coronary arteries within 60 min of initiating therapy. The final studied combination of eptifibatide consisted of a bolus dose of 180 μg/kg followed by an infusion of 2.0 μg/kg/min and a second bolus of 180 μg/kg 10 min later with a single half-dose bolus of tenecteplase. This combination restored TIMI 3 (normal) blood flow through blocked arteries in 70% of patients and TIMI 2 or 3 (some) blood flow in 96% of patients at 60 min. The incidence of major and minor bleeding events was similar to that previously reported for full-dose fibrinolytic therapy. A second phase of INTEGRITI is under way to compare the effects of this combination of eptifibatide and half-dose tenecteplase with full-dose tenecteplase alone on coronary blood flow (2).

Results from the ESPRIT (Enhanced Suppression of Platelet Receptor gpIIb/IIIa using Integrilin Therapy) study have shown that patients who received eptifibatide during coronary stent procedures continued to benefit from a statistically significant reduction in the combined incidence of death or heart attack at 1 year compared to patients who received placebo. The 1-year analysis indicated that the combined incidence of death or heart

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attack was significantly reduced from 12.4% on placebo to 8.0% on eptifibatide. The combined endpoint of death, heart attack or target vessel revascularization at 1 year was also significantly reduced from 22.1% on placebo to 17.5% on eptifibatide. Benefit for all components of the study endpoint was demonstrated at 48 h, 30 days, 6 months and 1 year, without any attenuation of effect. The incidence of heart attack at 1 year was reduced from 10.7% on placebo to 7.2% on eptifibatide, results consistent with those from 30 days and 6 months. The incidence of death at 1 year was reduced from 2.0% on placebo to 1.4% on eptifibatide, a 0.6% reduction as compared to a 0.2% reduction in death at 30 days and identical to the reduction reported at 6 months (3).

Cor Therapeutics and Schering-Plough have announced that the FDA has approved revised prescribing information for eptifibatide to include a new dosing regimen for patients undergoing percutaneous coronary intervention and specific reference within the product's indications for use in patients undergoing intracoronary stenting. Most of the labeling changes are reflective of the results of the ESPRIT study in patients undergoing non-emergency PCI with intended intracoronary stent placement. ESPRIT demonstrated that patients who received eptifibatide, dosed as an initial 180 μg/kg bolus injection immediately followed by a 2.0 μg/kg/min infusion and a second 180 μg/kg bolus 10 min after the first bolus, experienced a highly statistically significant reduction in the combined endpoint of death, heart attack, urgent target vessel revascularization, or need for thrombotic bailout versus those receiving placebo at 48 h and at 30 days. This is now the recommended dosing regimen in patients undergoing PCI. Other labeling changes reflect new dosing guidelines in renally impaired patients, revised heparin dosing recommendations in PCI, and updates to the safety-related sections of the prescribing information (4).

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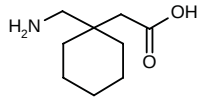

$C_9H_{17}NO_2$ **Pfizer**

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

Gabapentin may be useful as a treatment for hot flashes, according to 6 case studies. The frequency of hot flashes in 6 patients was reduced by an average of 87% after gabapentin administration. In some cases, gabapentin appeared to stop the occurrence of hot flashes completely. The drug's apparent effect on temperature-regulating centers was also noted in a separate case of a patient with known hypothalamic dysfunction, in

whom gabapentin use was associated with a marked increase in the number of hypothermia episodes. Gabapentin is currently under clinical evaluation as a treatment for hot flashes (2).

Higher strengths of gabapentin have been approved for marketing in the U.K. for the treatment of neuropathic pain. The 600- and 800-mg tablets were previously approved only for the adjunctive therapy of partial seizures. The product is now available in all formulations (capsules of 100, 300 and 400 mg; tablets of 600 and 800 mg) for both indications (3).

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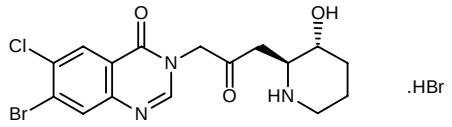

$C_{16}H_{17}BrClN_3O_3.HBr$ **Collgard; Mayo Clinic**

The influence of halofuginone on various stages of the angiogenic process was examined using several experimental systems. Halofuginone was found to inhibit the proliferation of actively growing bovine aortic endothelial cells (BAEC), with about 80% inhibition at a concentration of 400 ng/ml. It almost completely inhibited the gelatinolytic activity of MMP-2 in BAEC at a concentration of 100 ng/ml, and endothelial cell invasion through Matrigel-coated filters was inhibited by 60% in the presence of 50 ng/ml halofuginone. Capillary tube formation, mimicking invasion, migration and differentiation steps in angiogenesis, was completely inhibited by halofuginone at 50 ng/ml. Further studies demonstrated the ability of the compound (100 ng/ml) to completely inhibit microvessel formation (endothelial cell sprouting) *in vitro* using rat aortic rings embedded in collagen gel. The last stage of angiogenesis is characterized by deposition of new basement membrane-like extracellular matrix, and halofuginone inhibited its deposition by vascular endothelial cells by 80-85% at a concentration of 50 ng/ml. Lastly, the *in vivo* antiangiogenic activity of halofuginone was demonstrated using a murine corneal micropocket angiogenesis model, where the compound produced almost complete inhibition of neovascularization following oral (5 mg/kg diet) or i.p. administration (2 μg/day). Based on this profile, its oral bioavailability and proven safety as an antiparasitic agent, halofuginone is considered a promising new treatment for diseases associated with pathological angiogenesis (1).

The effects of halofuginone (40 μg/kg) and epidermal growth factor (EGF; 40 μg/kg) injections for 14 days as adjuncts to ureteral healing following endopyelotomy and

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endoureterotomy were examined in a study using pigs subjected to bilateral uretoureteral anastomosis. The ureter lumens of animals receiving either agent were significantly larger than control animals on day 30. Halofuginone-treated animals had significantly thicker epithelium as compared to controls and animals treated with EGF. No changes in the thickness of smooth muscle and adventitia were observed between groups. Stenting was found to improve results (2).

The efficacy of halofuginone (1 and 5 ppm in the diet or 0.03% injection into the urethra for 7 days) in preventing urethral stricture formation was shown in an *in vivo* study using rats. Coagulation current was applied to rats to induce urethral strictures. Halofuginone injection of 5 ppm was found to normalize urethrograms and inhibited increases in collagen α_1(I) gene expression and collagen content. *In vitro* studies using male rat urethral fibroblasts showed that the agent (10 nM) inhibited collagen secretion by fibroblasts via inhibition of collagen α1(I) gene expression (3).

Results were reported from a porcine coronary stent injury model in which pigs were given placebo, oral halofuginone (0.2 mg/kg/day) or i.v. halofuginone (0.1 mg/kg b.i.d.) starting 7 days before coronary artery balloon injury and stenting, and continuing until the animals were killed at 28 days. Using regression lines to plot neointimal thickness as a function of injury score, it was shown that i.v. halofuginone was the most effective treatment and placebo the least effective in limiting neointimal hyperplasia. Serum drug levels were also significantly higher in the i.v. group than in the oral halofuginone group (4).

Low doses of halofuginone, administered either in the diet or by i.p. injection, have been shown to significantly decrease prostate tumor weight and volume in a mouse model. SCID mice were injected s.c. with human androgen-independent WISH-PC-2 prostate cancer cells and treated with i.p. halofuginone (4 mcg every other day for 21 days) or drug given in the feed (1 and 2 ppm 1 week before injection of tumor cells). Both groups of halofuginone-treated mice showed a 4- to 5-fold decrease in tumor weight and volume compared to untreated controls, and low levels of tumor cell invasion were seen in the treated animals compared to the complete invasion in controls. Tumor growth following orthotopic injection of cells was also reduced by oral halofuginone and, in contrast to untreated controls, little tumor cell invasion of prostate tissue was seen. Halofuginone is an extremely potent inhibitor of collagen type I synthesis in soft tissue and an inhibitor of the matrix metalloproteinase MMP-2 at the transcriptional level. It affects tumor growth by a novel mechanism of action which results in the inhibition of tumor stromal support, angiogenesis, invasion and cell proliferation. The first clinical trial in cancer is expected to commence in the near future (5).

Collgard has entered a second collaborative research and licensing agreement with the Mayo Clinic to further develop halofuginone for the treatment of coronary restenosis. The goal of the second agreement is to achieve certain clinical milestones testing the efficacy of halofuginone to prevent restenosis. Halofuginone selectively blocks two pivotal events involved in restenosis in the nanomolar range: extracellular matrix deposition and smooth muscle cell migration and proliferation. Halofuginone is also in phase II clinical development for the treatment and prevention of scleroderma (6).

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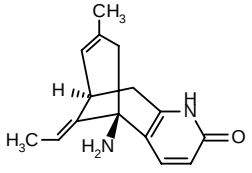

$C_{15}H_{18}N_2O$

Hi-Tech Pharmacal; Shanghai Inst. Materia Med.; Chin. Acad. Med. Sci.

The neuroprotective effects of huperzine A and tacrine (0.1-10 μM) were shown *in vitro* in a study using rat PC12 and primary cultured cortical neurons. Pretreat-ment of cells with either agent before exposure to the active fragment of amyloid β-peptide significantly increased cell survival, glutathione peroxidase activity and superoxide dismutase activity and decreased malondialdehyde levels (1).

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IY-81149

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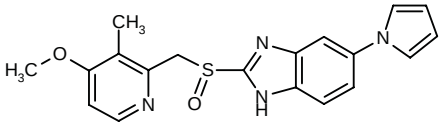

$C_{19}H_{18}N_4O_2S$ **Il-Yang; Axcan**

IY-81149 was compared to omeprazole in terms of their respective effects on gastric acid secretion *in vitro* and *in vivo*. In a rabbit parietal cell preparation, IY-81149 inhibited H^+/K^+-ATPase about 17 times more potently than omeprazole at a pH of 7.4. Similarly, in histamine-stimulated rabbit and human parietal cells, IY-81149 inhibited the accumulation of [^{14}C]-aminopyrine more potently than omeprazole. *In vivo* studies in pylorus-ligated rats, anesthetized rats, fistular rats and Heidenhain pouch dogs demonstrated that oral IY-81149 had inhibitory effects on acid output that were 2-3 times more potent than those of oral omeprazole. These *in vivo* studies assessed inhibitory activity both under conditions of normal gastric acid secretion and of acid secretion increased by secretagogues such as histamine and pentagastrin. Finally, the shorter duration of action observed with IY-81149 may translate into fewer adverse events such as elevation of plasma gastrin concentration (1).

General pharmacological studies were conducted on IY-81149 to test its effects on the central nervous, cardiovascular, respiratory and other organ systems in mice, rats, guinea pigs and dogs given oral doses ranging from 0.3-1000 mg/kg. Whereas at doses of 1-3 mg/kg p.o. the compound produced a significant and dose-dependent gastric antisecretory effect in pylorus-ligated rats, no notable effects on the other systems were seen at doses below 100 mg/kg, which is 20 times higher than the estimated clinically effective dose. The only effects on general behavior in mice were a decrease in locomotor activity at the highest dose and signs of impairment of motor function at 300 and 1000 mg/kg. At doses of 100 mg/kg and above it prolonged hexobarbital sleeping time in mice, a dose-dependent hypothermic effect was seen in mice at 300 and 1000 mg/kg and an analgesic effect was observed at the highest dose in mice. However, no anticonvulsant activity (mice), no cardiovascular or respiratory effects (rats, dogs) and no effect on smooth muscle contraction (guinea pigs), intestinal transport (mice) or renal function (mice) were seen (2).

A randomized, double-blind, 2-way crossover study examined the pharmacodynamic efficacy of IY-81149 (5, 10 or 20 mg once daily for 5 days) as compared to omeprazole (20 mg once daily for 5 days) in 60 subjects with gastroesophageal reflux disease. No significant differences in AUC_{0-24}, AUC_{0-8}, AUC_{8-16}, median pH in a 24-h interval and the percent time in a 24-h period in which gastric pH was greater than 4 were observed between the 5 mg dose of IY-81149 and omeprazole. Values for all parameters measured indicated that 10 mg IY-81149 suppressed gastric acid significantly more than omeprazole and that the 20 mg dose of IY-81149 was significantly superior to omeprazole in suppressing gastric acid. All IY-81149 doses were significantly more effective than omeprazole at 16-34 h postdosing (3).

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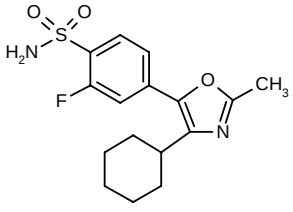
JTE-522

COX-2 Inhibitor

EN: 239031



$C_{16}H_{19}FN_2O_3S$ **Japan Tobacco; R.W. Johnson**

The antiproliferative effects of JTE-522 (30 mg/kg/day p.o. for 3 weeks) were examined in an *in vitro* study using 5 metastatic (HT-29, WiDr-meta, WiDr-wild, SW1116, HCT-15) and nonmetastatic (Colo 201, Colo 205) human colon carcinoma xenografts in SCID mice. In contrast to the nonmetastatic carcinomas, all metastatic cell lines were found to express COX-2 protein and mRNA. Treatment with the agent did not inhibit s.c. growth of

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HT-29 and Colo 205 tumors but prevented hepatic metastasis of HT-29 when administered on day 1 after tumor injection. JTE-522 dose-dependently inhibited VEGF expression in HT-29 tumors but did not affect MMP activity (1).

A study using a mouse strain with a truncated ApcΔ474 showed that treatment with JTE-522 (20 mg/kg p.o.) suppressed polypogenesis. Mice treated with 20 mg/kg JTE-522 had significantly less intestinal polyps/mouse (83.8 ± 12.3) as compared to controls (123.3 ± 9.3) and animals treated with 2 mg/kg JTE-522 (111.6 ± 6.7). Results indicated that the agent may be effective in preventing colorectal tumors (2).

An *in vivo* study examined the effects of JTE-522 (3, 9 or 30 mg/kg/day p.o. for 15 weeks or 9 mg/kg for 24 weeks) on NMBA-induced esophageal tumorigenesis in F344 rats. A dose of 30 mg/kg was shown to significantly decrease the number but not the size of NMBA-induced tumors/rat. However, a dose of 9 mg/kg/day for 24 weeks significantly reduced both tumor number and size by 29 and 44%, respectively. Although JTE-522 treatment did not affect NMBA-induced upregulation of COX-2 expression, a significant reduction in PGE_2 synthesis was seen with treatment. It was concluded that COX-2-mediated PGE_2 production plays a role in tumorigenesis and may be a potential therapeutic target for prevention of esophageal cancer (3).

An *in vivo* study using a rat model of postoperative pain (skin incision on the footpad) showed the efficacy of JTE-522 (1-100 mg/kg p.o. 5 min postsurgery) and indomethacin (1-30 mg/kg) as compared to FR-173657 (10 and 100 mg/kg). Mechanical allodynia was determined by measuring the frequency of foot withdrawal in response to a Frey filament (12.5 g). Both JTE-522 and indomethacin significantly and dose-dependently attenuated the response while FR-173567 had no effect (4).

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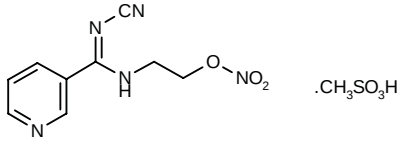
KRN-2391 *Antianginal*

EN: 163803



$C_9H_9N_5O_3.CH_4O_3S$ **Kirin Brewery; Nippon Shinyaku**

The effects of KRN-2391 (10 or 20 μg/kg i.v. over 5 s after hemodynamic stabilization) on circulation and renal sympathetic nerve activity (RSNA) were examined and compared to sodium nitroprusside (SNP; 10 μg/kg) in nerve-intact and baroreceptor-denervated rabbits. In intact animals, the mean arterial pressure (MAP) decreased to 84.1 ± 2.2, 87.2 ± 1.5 and 80.1 ± 4.1% of the controls following treatment with SNP, 10 μg and 20 μg KRN-2391, respectively; the time to reach the lowest MAP for these groups was 29.6 ± 3.2, 52.9 ± 3.3 and 65.6 ± 6.7 s, respectively, and all 3 treatment groups exhibited similar increases in heart rate (HR) and RSNA. In denervated animals, none of the agents altered HR or RSNA but MAP was decreased with treatment to 72.9 ± 2.1, 74.5 ± 2 and 66.8 ± 2%, respectively. Thus, results showed that KRN-2391 like SNP is a highly selective vasodilator of vascular smooth muscle without affecting HR, RSNA or baroreflex sensitivity. However, KRN-2391 was less effective than SNP in reducing blood pressure (1).

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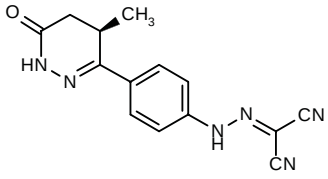
Levosimendan
(–)-OR-1259
Simdax®

Treatment of Heart Failure

EN: 189761



$C_{14}H_{12}N_6O$ **Orion Corp.; Abbott**

Levosimendan was reported to be useful for the treatment or prevention of coronary graft vasospasm after coronary artery by-pass surgery. Preferably, levosimendan is administered intravenously, starting after the coronary bypass is completed and continuing throughout the early recovery period (1).

A study using isolated intact rabbit ventricular papillary muscles loaded with aequorin examined the mechanism of action of OR-1896, the active metabolite of levosimendan. Results showed that the positive inotropic effects of the metabolite are partially due to an increase in myofibrillar Ca^{2+} sensitivity. A biphasic concentration-response curve was obtained with peaks observed at 10 μM and 1 mM. The maximal response and increase in Ca^{2+} transients seen during the first phase were 11 and 5%, respectively, of those seen with isoproterenol. The positive inotropic effects of OR-1896 did not alter relaxation and were blocked by carbachol (2).

A study using isolated guinea pig aortas precontracted with phenylephrine compared the effects of levosimendan and milrinone and showed that levosimendan induced vasorelaxation via the opening of K channels and stimulation of the Na^+/Ca^{2+} exchanger and not through phosphodiesterase inhibition. Contraction was inhibited by about 80% with both agents. While addition of $NiCl_2$ (1 mM) and $BaCl_2$ (0.5 mM) antagonized the effects of levosimendan (–50 ± 5% and –40 ± 4%, respectively), they had little effect on milrinone-induced vasodilation; verapamil did not significantly influence the vasodilating effects of either agent. Milrinone but not levosimendan was found to relax aorta during washout when it was not precontracted with phenylephrine (3).

An open, randomized trial conducted in 10 healthy subjects showed that concomitant levosimendan administration (0.5 mg q.i.d. p.o. for 9 days) did not influence the pharmacodynamics of warfarin (25 mg p.o. on day 4). Although the volume of distribution of warfarin was higher and the elimination half-life was shorter with levosimendan treatment, the latter agent did not enhance the effects of warfarin as assessed using activated thromboplastin time (APTT) and thromboplastin time (TT-SPA) assays. In addition, levosimendan administered alone was found to have no effect on APTT or TT-SPA assays, indicating a lack of effect on blood coagulation. Headache was reported with continuous levosimendan dosing, possibly due to cerebral vasodilation (4).

A multicenter, randomized, double-blind, placebo-controlled study conducted in 146 patients with severe heart failure (NYHA class III of IV; mean ventricular ejection fraction = 21 ± 1%; pulmonary capillary wedge pressure = 15 mmHg or more; cardiac index = 2.5 l/min/m^2 or less) demonstrated the acute hemodynamic effects and clinical efficacy of levosimendan (0.1 μg/kg/min increased up to 0.4 μg/kg/min over 4 h followed by 2 h at the maximum tolerated infusion rate). Dose-dependent increases in stroke volume and cardiac index were observed with the lowest infusion rate; the maximum increases were 28 and 39%, respectively. Only a modest increase in heart rate of 8% was observed with the maximum infusion rate; heart rate was not affected at lower infusion rates. Treatment with levosimendan also dose-dependently decreased pulmonary capillary wedge, right atrial, pulmonary arterial and mean arterial pressures. According to patient and physician assessments, the agent did not increase adverse events and appeared to improve dyspnea and fatigue (5).

Results from a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in 151 adult patients with congestive heart failure of ischemic origin showed the efficacy of treatment with a 10-min levosimendan bolus (6-24 μg/kg) followed by 24-h infusion with 0.05-0.2 μg/kg/min. Dobutamine (6 μg/kg/min) was administered to some patients in an open-label manner for comparison. The response rates for levosimendan at the lowest and highest doses were 50 and 88%, respectively, as compared to 14 and 70% in placebo and dobutamine groups, respectively. Dose-dependent effects were observed with levosimendan, including significant increases in cardiac output and stroke volume and decreases in pulmonary capillary wedge pressure during infusion with the agent. Treatment was well tolerated. The most common adverse events seen with the higher doses were headache (9%), nausea (5%) and hypotension (5%) (6).

The effects of levosimendan administered as a short-term i.v. infusion were examined in 10 patients with normal cardiac function. Infusion of the agent resulted in plasma concentrations of 110 ± 22 μg/l. Treatment significantly increased heart rate (by 9 beats/min) and shortened the sinus node recovery time and AH interval in addition to decreasing the effective refractory periods in the atrioventricular node (by 40-63 ms), atrium (by 22-33 ms) and ventricle (by 5-9 ms). The agent also significantly increased the duration of ventricular monophasic action potentials by 9-17 and 5-15 ms at 50 and 90% levels of repolarization, respectively; the QT interval was unchanged during spontaneous rhythm and atrial pacing. Since the effects on the ventricle were not marked, it was concluded that the agent has a low potential for inducing serious cardiac arrhythmias (7).

Results from a randomized, double-blind, placebo-controlled study in 24 patients with acute myocardial

infarction who underwent angioplasty (PCTA) showed that levosimendan (24 mg/kg) improved function of stunned myocardium. Treatment with the agent significantly decreased the number of hypokinetic segments (–2.4 *vs.* +0.8) and caused a leftward and/or upward shift in the systolic pressure-volume (PV) relationship in 50% of the patients *versus* 12% on placebo. In addition, end-systolic (–14.6 *vs.* +11 mmHg) and volume indices (–9.5 *vs.* +4.1 ml/m) significantly decreased with treatment. No changes in the end-systolic PV ratios were observed. Levosimendan significantly improved the index of active isovolumic relaxation Tau as compared to placebo (–14.5 *vs.* +11.5 ms). Similar changes in the PV ratios and in the index of chamber compliance during late diastole were observed for both groups (8).

Orion has received favorable mutual recognition decisions for levosimendan (Simdax®) in eight European countries: Finland, Spain, Italy, Iceland, Greece, Luxembourg, Norway and Portugal. Marketing authorizations are expected in the coming months. Although the company had originally solicited mutual approval in all E.U. countries, applications were withdrawn in The Netherlands, Ireland, Great Britain, France, Germany, Denmark and Belgium. Levosimendan was launched in Sweden in October 2000. In addition to Sweden, Orion will market the drug in Finland, Iceland and Norway, while marketing partner Abbott will lead product introduction in Italy, Spain, Greece, Luxembourg and Portugal. Applications for additional marketing authorizations have been or will be submitted in several countries in South America, Asia and Europe's non-E.U. area in 2001. Levosimendan is indicated for short-term treatment of acutely decompensated severe chronic heart failure when conventional heart failure medications alone are not sufficient (9).

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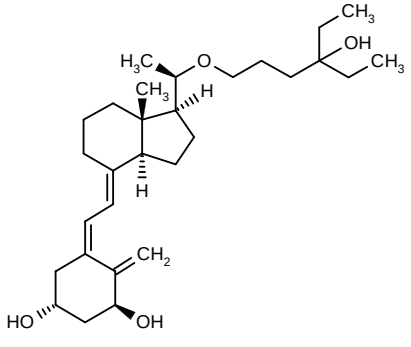
Lexacalcitol

Vitamin D Analog

EN: 166325



$C_{29}H_{48}O_4$ **Leo**

The antiproliferative effects of KH-1060, EB-1089 (1 nM for 72 h) and 9-*cis* or all-*trans* retinoic acid (100 nM

for 72 h) alone or in combination were shown in a study using the C2C12 mouse myoblast cell line. Incubation of cells for 72 h with 1,25-dihydroxyvitamin D_3 had no effect on proliferation. KH-1060 was more effective than EB-1089 (about 62% inhibition) and 9-*cis* retinoic acid (about 53%) more potent than all-*trans* retinoic acid in decreasing cell number. Synergistic activity was observed when KH-1060 was combined with either 9-*cis* or all-*trans* retinoic acid (77 and 76% inhibition, respectively). [^{3}H]-Thymidine incorporation was significantly increased by approximately 250 and 260% when KH-1060 was combined with 9-*cis* or all-*trans* retinoic acid, respectively (1).

An *in vitro* study examined the mechanism of regulated receptor degradation of KH-1060 and MC-1288 using human wild-type and mutated (point mutations + helix 12 deletion) vitamin D receptors (VDR) and MG-63 cells. Both analogs protected VDR against degradation more effectively than calcitriol and EB-1089. KH-1060 and MC-1288 also prevented formation of a RXRβ-VDR-VDRE-Sug-1 complex in nuclear extracts of MG-132-treated cells. KH-1060 and MC-1288 dose-dependently arrested the cell cycle of MG-63 cells in the G_0/G_1 phase earlier and at lower concentrations as compared to calcitriol. Inhibition of cell cycle progression with KH-1060 and MC-1288 was associated with hypophosphorylation of Rb and marked inhibition of Cdk2 activity which correlated with increased p27 levels; downregulation of Cdk2 protein and cyclin E were observed with no changes in p21 and cyclin D1 levels detected (2).

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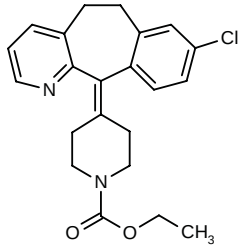
Loratadine Claritin®

Treatment of Allergic Rhinitis

EN: 090791



$C_{22}H_{23}ClN_2O_2$ **Schering-Plough; Essex**

Scientists have described the use of antiallergic drugs for the treatment of mental and vascular disorders, particularly depression, alcoholism, weight control, sexual dysfunction, panic and obsessive/compulsive disorder, migraine, stroke, orthostatic hypotension, gastrointestinal stasis, nausea, dizziness and jet lag. Preferably useful are non-sedating or low-sedating antihistamines such as loratadine or its metabolite desloratadine. It is believed that they exert their effects by interacting with the 5-HT_7 receptor as demonstrated in a binding assay where desloratadine gave a K_i value of 204 nM for displacement of [^{3}H]-LSD (1).

Loratadine has been examined for its effects in patients with active Crohn's disease. Nineteen patients were randomized to receive prednisolone/5-ASA plus placebo or loratadine (10 mg/day) for 6 months, with steroid tapering over 12-16 weeks. The most significant effect of loratadine was a reduction in the cumulative prednisolone dose as compared to placebo-treated patients, with mean cumulative steroid doses of 28, 32 and 38 mg/kg, respectively, at 2, 4 and 6 months, compared to respective doses of 28, 38.6 and 52.8 mg/kg on placebo. Also, remission rates at 1, 2, 4 and 6 months were greater in loratadine-treated patients (60, 30, 30 and 20%, respectively) than in placebo-treated patients (37, 25, 25 and 12%, respectively). These findings support a role for adjunctive therapy with antihistamines in the treatment of Crohn's disease (2).

The FDA has approved Claritin® (loratadine) Syrup 10 mg/10 ml for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis and for the treatment of chronic idiopathic urticaria (CIU) in children 2-5 years old. Claritin® Syrup 10 mg/10 ml was previously indicated for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis and for the treatment of CIU in patients 6 years of age or older. The recommended dose for children 2-5 years of age is 5 mg once daily and the recommended dose for patients 6 years of age and older is 10 mg once daily. Two studies evaluated the safety of 5 mg loratadine syrup in children aged 2-5 years. A single-dose, open-label bioavailability study characterized the pharmacokinetic profile of loratadine. A randomized, double-blind, placebo-controlled, parallel-group study assessed the tolerability of 5 mg of loratadine syrup after

multiple doses; loratadine syrup or placebo was given once daily for 15 days to children with a history of allergic rhinitis or CIU. Single and multiple doses of Claritin® Syrup were well tolerated (3).

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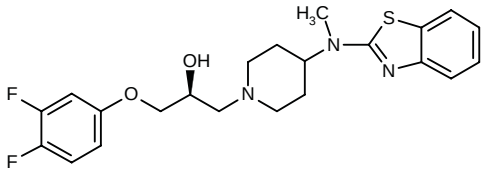
Lubeluzole
Prosynap®

Neuroprotectant

EN: 211576



$C_{22}H_{25}F_2N_3O_2S$ **Janssen**

A new synthesis of lubeluzole has been reported: The condensation of 3,4-difluorophenol (I) with racemic glycidol (II) by means of PPh_3 and DEAD in THF gives 2-(3,4-difluorophenoxymethyl)oxirane (III), which is opened by means of Li_2CuCl_4 in THF, yielding racemic 1-chloro-3-(3,4-difluorophenoxy)-2-propanol (IV). Racemic compound (IV) is kinetically resolved by transesterification with vinyl butyrate using *Rhizomucor miehei* lipase (RML) as catalyst, providing a mixture of (*R*)-1-chloro-3-(3,4-difluorophenoxy)-2-propanol (V) and the (*S*)-butyrate (VI). This mixture is easily separated by column chromatography. Finally, the (*R*)-alcohol (V) is condensed with *N*-methyl-*N*-(piperidin-4-yl)benzothiazol-2-amine (VII) by means of $NaHCO_3$ in hot DMF. The key intermediate *N*-methyl-*N*-(piperidin-4-yl)benzothiazol-2-amine (VII) has been obtained as follows: Reductive amination of 4-oxopiperidine-1-carboxylic acid ethyl ester (VIII) with methylamine and borane/pyridine complex in methanol gives 4-(methylamino)piperidine-1-carboxylic acid ethyl ester (IX), which is condensed with isothiocyanatobenzene (X) in isopropyl ether to yield the thiourea (XI). Cyclization of compound (XI) by means of Br_2 in refluxing CCl_4 affords the benzothiazole derivative (V), which is finally decarboxylated by means of HBr in refluxing water, followed by treatment with NaOH (1). Scheme 2.

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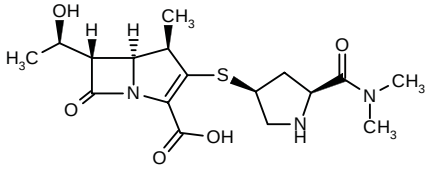
Meropenem
Merrem®

Carbapenem Antibiotic

EN: 136278



$C_{17}H_{25}N_3O_5S$ **Sumitomo; AstraZeneca**

AstraZeneca has filed an sNDA for meropenem for injection (Merrem® I.V.) for the treatment of hospital-acquired pneumonia and hospitalized patients with community-acquired pneumonia. The drug is already approved in the U.S. as single-agent therapy for the treatment of intraabdominal infections in adults and children, and bacterial meningitis in children 3 months of age and older (1).

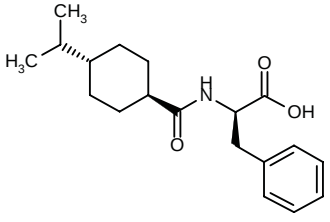
1. *AstraZeneca files sNDA seeking new indications for Merrem I.V.* DailyDrugNews.com (Daily Essentials) June 28, 2001.

Original monograph - Drugs Fut 1988, 13: 534.

Nateglinide
Fastic®
Starsis®
Starlix®

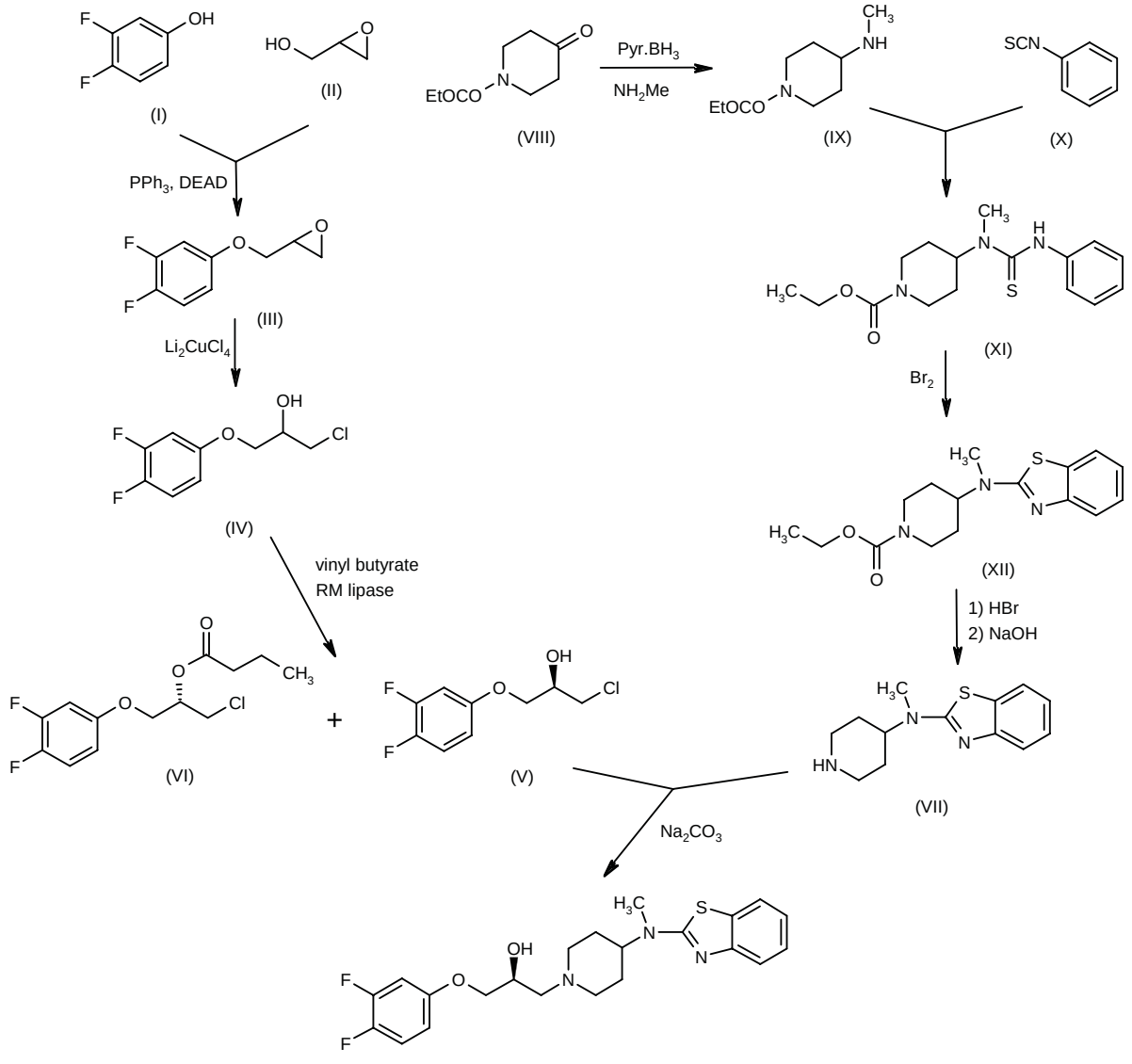
Antidiabetic

EN: 127137



$C_{19}H_{27}NO_3$ **Ajinomoto; Aventis Pharma; Novartis; Merck KGaA; Yamanouchi**

Scheme 2: Synthesis of Lubeluzole



A double-blind, placebo-controlled, single-center crossover study conducted in 10 patients with type 2 diabetes examined the efficacy of nateglinide (30, 60 or 120 mg t.i.d. or 120 mg q.i.d. 10 min before meals for 7 days). Significant dose-dependent increases in plasma insulin and reductions in plasma glucose levels were observed following treatment with all doses as compared to placebo; the 60 and 120 mg doses showed similar efficacy and were superior to the 30 mg dose. When the agent was administered a fourth time (120 mg), reductions in plasma glucose were maintained throughout the night. No serious adverse events were reported and no hypoglycemic events occurred (1).

A partnership for the joint promotion and marketing of nateglinide in Europe and parts of Africa, Southeast Asia and Latin America has been established between Merck KGaA and Novartis (2).

Novartis has launched nateglinide (Starlix®) in the U.S. and the European Commission has granted marketing approval for the drug in the European Union for the treatment of type 2 diabetes. Specifically, the product has been approved in combination with metformin in type 2 diabetes patients inadequately controlled despite a maximally tolerated dose of metformin alone. This approval was based on data from clinical trials involving more than 3100 patients with type 2 diabetes. In the trials, the nateglinide/metformin combination therapy induced a clinically relevant improvement in glucose control assessed by relevant HbA1c (hemoglobin A1c) reductions at all baseline HbA1c levels. Nateglinide has been

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approved in a 60-mg starting dose, which can be increased to 120 mg if necessary. The maximum recommended single daily dose is 180 mg taken before three main meals (3, 4).

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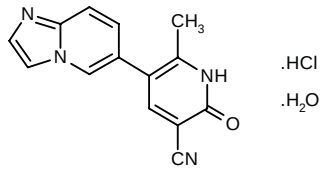

$C_{14}H_{10}N_4O.HCl.H_2O$ **Eisai**

Olprinone hydrochloride was shown to improve pulmonary hypertension without adverse cardiac events in a dog model of hypertension. In this study, hypoxic pulmonary hypertension was induced in adult dogs which were then administered single i.v. bolus injections of olprinone at doses of 10, 30 and 100 mg/kg at 5-min intervals. At the higher doses, heart rate was increased by olprinone, but it remained the same at the lowest dose. Significant reductions in mean aortic pressure, mean pulmonary arterial pressure, pulmonary vascular resistance, systemic vascular resistance and right ventricular stroke work index were seen with the highest dose, but these parameters remained unchanged at the lower doses. No significant changes were seen with any dose in cardiac index or the first derivative value of the left ventricular pressure. The results indicate the potential application of the drug in the treatment of primary pulmonary hypertension and associated right heart failure (1).

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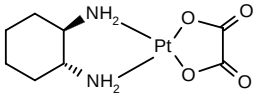

$C_8H_{14}N_2O_4Pt$ **Sanofi-Synthélabo; Yakult Honsha**

An ongoing phase I trial in 20 patients with metastatic solid tumors is attempting to determine the maximum tolerated dose (MTD) of combination pemetrexed sodium and oxaliplatin. Patients received pemetrexed sodium (300-500 mg/m^2 = dose levels 1-5) as a 10-min i.v. infusion on day 1 of a 21-day cycle followed by a 2-h i.v. infusion of oxaliplatin (85-120 mg/m^2 = dose levels 1-5) 30 min later. Dose-limiting toxicities (DLTs) were defined as only those toxicities occurring within the first cycle and included grade 4 neutropenia for more than 7 days, febrile neutropenia, grade 4 thrombocytopenia and > grade 3 nonhematologic toxicity (except alopecia, nausea and vomiting). Patients have received 82 courses so far and no DLTs were observed at dose levels 1-5. The toxicities observed related to treatment were grade 3 (35.8%) and 4 (19.4%) neutropenia, grade 3 (3.8%) and 4 (1.3%) anemia, grade 3 thrombocytopenia (10.4%) and grade 3 elevated transaminases (12.5%). Nonhematologic toxicities reported were neurologic toxicities, fever with or without infection, nausea and skin toxicity. Unconfirmed partial responses were noted in 1 patient with esophageal cancer at dose level 1 and in 1 patient with colon cancer at dose level 5. Accrual is ongoing at 500/300 mg/m^2 pemetrexed/oxaliplatin (dose level 6). Three DLTs have been seen at this level (1).

Sanofi-Synthélabo has purchased Lilly's share of their U.S.-based joint venture Sanofi Lilly Oncology and has thereby recovered full rights to oxaliplatin in the U.S. Following the negative recommendation of the Oncologic Drugs Advisory Committee in March of last year, the FDA informed Sanofi Lilly Oncology that additional studies would be required before approval in the U.S. for this indication. As a result, Sanofi-Synthélabo is initiating two phase III studies for an NDA as second-line treatment of metastatic colorectal cancer (2).

Yakult Honsha has begun phase II trials of oxaliplatin in Japan. The company obtained Japanese development and marketing rights to the water-soluble platinum complex from Debiopharm (3).

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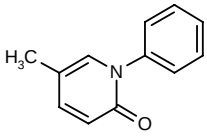

$C_{12}H_{11}NO$ **Marnac; Shionogi**

The effects of pirfenidone were examined *in vitro* using stimulated (PDGF or TGFβ1) rat hepatic stellate cells. The agent (1, 100 and 100 μM) significantly inhibited PDGF-induced cell proliferation with peak effects seen at the highest dose (7 ± 1.6 and 1.9 ± 0.4 BrdU positive cells with the 1 and 100 μM doses, respectively). No cytotoxic effects were observed at these doses and inhibition was not associated with PDGF receptor autophosphorylation or PDGF-induced ERK1, ERK2 or p70S6 kinase activation. However, pirfenidone significantly inhibited PDGF-stimulated Na^+/H^+ exchanger activation (JH+ = 16.5 ± 4.4 *vs.* 8.5 ± 2.4 *vs.* mmol/min with 1000 μM), TGFβ1-stimulated type I collagen accumulation in media (54 and 92% with 100 and 1000 μM, respectively) and TGFβ1-induced α1(I) collagen mRNA expression (1).

A study using salt-depleted rats with chronic ciclosporin nephrotoxicity showed that pirfenidone (250 mg/kg/day for 28 days) significantly decreased mRNA TGFβ1 (0.82 ± 0.10 *vs.* 2.12 ± 0.47) and PAF-1 (0.11 ± 0.02 *vs.* 0.59 ± 0.20) expression and reduced ciclosporin-induced (7.5 mg/kg/day for 28 days) intestinal fibrosis (by 50%). Ciclosporin-induced decreases in glomerular filtration rates were also ameliorated with treatment. A significant correlation between intestinal fibrosis and the number of apoptotic cells was also observed with treatment (2).

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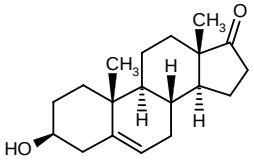

$C_{19}H_{28}O_2$ **Genelabs; Watson**

An *in vitro* study using cocultured TF228.1.16 and SupT1 cells showed that DHEA and dexamethasone (15-45 μg/ml) inhibited fusion between the cell types. Results indicate that activation of host cell phospholipase A_2 may be important for HIV-1 transmission (1).

A study in rats treated with a carcinogen (MNU) to induce 1-6 hyperplastic and premalignant mammary gland tumors showed that DHEA or DHEA-8354 (125 or 1000 mg/kg in the diet for 6 weeks starting 5 weeks after tumor induction) inhibited tumor progression via induction of alveolar differentiation in tumors. A significant decrease in the number of mammary tumors was observed with treatment (3.1 and 2.6 tumors for the 125 and 1000 mg/kg groups, respectively, *vs.* 4 in controls) and the high dose significantly reduced tumor burden (2.3-2.6 g *vs.* 3.4-3.6 g in controls). Treatment also changed tumor morphology in that 90% of the tumors from treated animals contained highly differentiated alveolar structure as compared to only 25% of the control tumors (2).

A study using a rat model of global cerebral ischemia (4-vessel occlusion for 10 min) examined the efficacy of DHEA (25, 50 or 100 mg implanted s.c. in the neck prior to ischemia induction) in reducing hippocampal CA neuronal injury. Animals treated with 100 mg DHEA had significantly less hippocampal CA neuronal injury (60 ± 7%) on day 7 after ischemia induction as compared to 88 ± 13% observed in controls and 84 ± 8 and 82 ± 6% seen in animals treated with 25 or 50 mg DHEA, respectively (3).

An *in vivo* study conducted in rats with polymicrobial sepsis induced by cecal ligation and puncture showed the efficacy of DHEA (30 mg/kg s.c.) in decreasing mortality and improving cellular immune function. After sepsis onset, rats were treated with the agent and killed 48 h later. DHEA significantly increased survival rate (87 *vs.* 53%), restored depressed delayed-type hypersensitivity reaction and decreased serum TNF-α levels (307 ± 1.4 *vs.* 32.4 ± 6.6 pg/ml) (4).

DHEAS (30 mg/kg b.i.d. i.p. for 5 days) was shown to improve learning (days 1-4) and enhance memory (day 5) in mature (7-9 months) but not young (2 months) OF1 mice in a study using the hidden platform test (5).

The neuroprotective effects of DHEAS (50 mg/kg i.v.) were shown in a study using a reversible spinal cord ischemia (15-60 min occlusion of the infrarenal aorta) rabbit model. The P_{50} values (*i.e.*, the duration of ischemia [min] resulting in a 50% probability of permanent paraplegia) for animals treated with DHEAS 5 min after occlusion onset were significantly prolonged (36.8 ± 3.9 *vs.* 28.8 ± 2 min) in DHEAS-treated animals. The effects of DHEAS were sustained since differences in P_{50} values were significant even at 4 days (38.6 ± 5.9 *vs.* 26.1 ± 2.2 min). The agent had no effect when administered 30 min after occlusion (6).

A 1-year, double-blind, placebo-controlled study in 280 elderly (60-79 years old) men and women showed the efficacy and safety of long-term treatment with DHEA (50 mg/day). DHEAS levels increased and were significantly higher in DHEA-treated subjects at 6 months as compared to 12 months, indicating no accumulation. Although androstenedione, androstanediol glucuronide and estradiol levels increased in DHEA-treated men, testosterone did not. In DHEA-treated women, only androstenedione and androstanediol glucuronide levels were increased at 12 months. Significantly improved bone turnover and skin status were observed with DHEA treatment, especially in women. Treatment was concluded to be safe (7).

The effects of DHEA (50 mg twice daily) were evaluated in 58 subjects with probable Alzheimer's disease, according to NINCDS-ADRDA criteria. This randomized, double-blind, placebo-controlled trial showed a significant improvement at 3 months in Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) scores in patients receiving DHEA as compared to those receiving placebo. However, no significant difference between groups was noted using the Clinician's Interview-Based Impression of Change with Caregiver input (CIBIC-Plus) (8).

Results from a study conducted in 17 psychiatric patients and 25 healthy control subjects suggest that increased DHEAS levels could predict suppressed GABAergic transmission resulting in anxiety and hyporesponsiveness in response to electroconvulsive therapy (ECT). Basal and post-ECT DHEA and cortisol plasma levels were significantly higher in patients as compared to control subjects (218 *vs.* 150%). After 6 ECT sessions, plasma DHEAS levels were significantly higher than levels in patients after 1 ECT session (125%) and levels in controls (165%). Patients classified as ECT nonresponders showed significantly increased DHEAS levels (208%) after 6 ECTs as compared to ECT responders.

Of the patients with increased DHEAS levels, only 1/8 responded as compared to 8/9 in the group with nonelevated DHEAS levels (9).

The effects of DHEA replacement were assessed in 24 women with primary and secondary adrenal insufficiency. In this randomized, double-blind, placebo-controlled, crossover trial, patients received DHEA (50 mg) or placebo for 4 months, with a 1-month washout period between treatments. DHEA raised the initially low serum concentrations of DHEA, DHEA sulfate, androstenedione and testosterone into the normal range. In addition, improved overall well-being and sexual satisfaction were noted after 4 months of DHEA replacement therapy. Further study is needed to determine whether these beneficial effects of DHEA are due to a direct effect of DHEA on the CNS or an indirect effect via the increase in peripheral androgen synthesis (10).

Data from a double-blind, placebo-controlled trial of DHEA in 22 subjects diagnosed with major depression using DSM-IV criteria have been reported. DHEA was administered at 30 mg once daily for the first 2 weeks, twice daily for the second 2 weeks, and 3 times daily for the final 2 weeks. After a total of 6 weeks of therapy, subjects treated with DHEA showed a 30.5% improvement in HDRS ratings, as compared to a 5.3% response in the placebo group. Therefore, significant antidepressant effects were achieved with DHEA therapy in subjects with major depression; however, more study is needed to determine the long-term risk/benefit profile of this agent (11).

A study conducted in 184 women (35-48 years) in their late reproductive years with regular menses showed that 26% of the subjects reported a decreased libido. Plasma testosterone and FSH levels did not correlate with libido although there may be a correlation between low DHEAS levels and decreased libido. A significant relationship between DHEAS and libido was observed in African-American women but not in Caucasians (12).

A randomized, double-blind, placebo-controlled study conducted in 381 women with mild to moderate systemic lupus erythematosus (SLE) examined the efficacy of treatment with oral GL-701 (200 mg/day for 12 months). Baseline DHEAS levels were found to be low in those patients also receiving steroids. More responders and fewer SLE flares were observed in the groups receiving GL-701 as compared to placebo. In addition, patients treated with the agent tended to show improvements in patient VAS and other scores. The greatest responses were observed in those patients also receiving steroids. BMD was also found to significantly improve and HDL-cholesterol, total triglycerides and C3 were reduced in patients treated with the agent. Treatment was well tolerated although a higher incidence of mild acne (33 *vs.* 14%) and hirsutism (16 *vs.* 2%) was seen as compared to placebo. Myalgia (22 *vs.* 36%) and mucosal ulcers (15 *vs.* 23%) were more frequent on placebo. Four deaths, all possibly related to SLE, were seen in placebo patients (13).

Genelabs Technologies and Watson have entered into a collaboration and license agreement pertaining to prasterone (Aslera®) for the treatment of SLE. Under the terms of the agreement, Watson has been granted an exclusive license to North American rights to prasterone (14).

The FDA has deemed the NDA for prasterone as first-line therapy for the treatment of women with mild to moderate systemic SLE not approvable. This decision was based on several issues, mainly relating to efficacy and safety data. Genelabs expects to work closely with the FDA in order to address these concerns with the goal of ultimately attaining FDA marketing approval (15).

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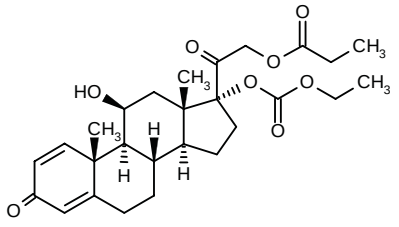
Prednicarbate
Hoe-777
S-770777
Dermatop®

Antipsoriatic
Treatment of Eczema

EN: 117492



$C_{27}H_{36}O_8$

Aventis Pharma; Cassella; Camillo Corvi

Dermik, the dermatology division of Aventis, has launched Dermatop® (prednicarbate 0.1%), a new topical corticosteroid for the treatment of eczema and psoriasis, in Canada. The product is available in two formulations: an ointment and an emollient cream. Clinical studies revealed that prednicarbate emollient cream was significantly more effective than hydrocortisone cream 1% in the treatment of children with atopic dermatitis, one of the most common forms of eczema. The cream was also shown to be at least as effective as betamethasone valerate cream 0.1% in the treatment of adults with atopic dermatitis. Due to its favorable safety profile, the product may be especially useful for the long-term treatment of chronic dermatoses and for the treatment of geriatric patients (1).

1. *Dermik launches new eczema and psoriasis product in Canada.* DailyDrugNews.com (Daily Essentials) April 11, 2001.

Original monograph - Drugs Fut 1986, 11: 460.

Rhenium Re-186 Etidronate Injection

Analgesic
Diagnostic Agent

EN: 183269

Mallinckrodt

The toxicity and efficacy of Re-186-HEDP (1295 MBq) were evaluated in a phase II trial involving 12 men with prostate cancer and 16 women with breast cancer. Objective responses were observed in 67 and 36% of the prostate and breast cancer patients, respectively, with a mean duration of response of 45 and 24 days, respectively. No serious adverse events were seen and marrow toxicity was not more than grade 2 for white blood cells and grade 3 for platelets (1).

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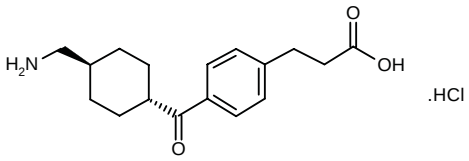
Rotraxate Hydrochloride
TEI-5103
Cumelon®

Antiulcer

EN: 090563



$C_{17}H_{23}NO_3.HCl$

Teijin

Teijin reported that the development of TEI-5103 has stopped (1).

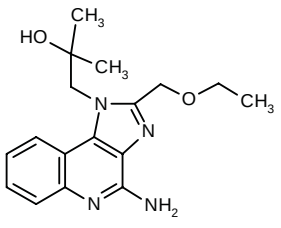
1. *TEI-5103 development status.* Teijin Company Communication 2000, Dec 27.

Original monograph - Drugs Fut 1985, 10: 485.

S-28463
R-848
Resiquimod

Treatment of Hepatitis C
Treatment of Genital Herpes

EN: 221036



$C_{17}H_{22}N_4O_2$

3M Pharm.; Vernalis

  CCC: 0377-8282/2001

A study using cDNA gene array analysis to screen 588 genes found in macrophages identified 13 genes induced by S-28463. These 13 genes are all known to be involved in macrophage activation and inflammatory responses (1).

The effects of R-848 on IgE production were recently reported. R-848 was tested at concentrations of 0.1-10 ng/ml in peripheral blood mononuclear cells (PBMCs) from normal and allergic human donors. Strong inhibition of anti-CD40 + IL-4-stimulated IgE production was seen in both groups, with maximal inhibition of 99% in PBMCs from normal donors and of 86% in cells from allergic donors at the highest concentration. On the contrary, the compound had no effect on spontaneous IgE production, and no effect on proliferation was seen at any concentration in PBMCs from normal donors. Although reductions in CD23 expression and induction of interferon γ (normal donors) were seen in stimulated cells in the presence of R-848, its mechanism of action remains to be clarified in further studies (2).

Results from a randomized, double-blind, vehicle-controlled study in 52 patients with herpes genitalis showed that treatment with R-848 gel for 3 weeks significantly reduced recurrence as compared to the vehicle (169 *vs.* 57 days). Dose-limiting local adverse events requiring dose reductions were seen in 2 patients treated with R-848 and in 1 vehicle-treated patient. Of the R-848-treated patients, 32% had no recurrence as compared to only 6% in the vehicle group. Based on these promising results, phase III clinical trials for recurrent genital herpes have been initiated in both the U.S. and Europe (3, 4).

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4. *Phase III trial of 3M's genital herpes Rx begin.* DailyDrugNews.com (Daily Essentials) Nov 3, 2000.

Original monograph - Drugs Fut 1999, 24: 622.

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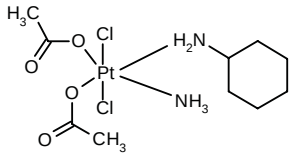
Satraplatin

Oncolytic

EN: 185356



$C_{10}H_{22}Cl_2N_2O_4Pt$

Johnson Matthey; Bristol-Myers Squibb

The additive effects of JM-261 combined with ionizing radiation (2 Gy) were shown against human lung carcinoma cells (H460) *in vitro* and H460 s.c. xenografts in nude mice *in vivo*. *In vitro* cologenic survival studies revealed a dose enhancement ratio of 1.23 with combination JM-216 (15 μM for 1 h) + irradiation treatment. Oral administration of the agent (30 mg/kg) followed by radiation 1 h later for 5 days resulted in tumor growth delays in mice; an enhancement ratio of 1.24 was obtained *in vivo* (1).

A phase I, escalating-dose trial conducted in 23 patients with solid tumors (*e.g.*, non-small cell lung cancer, breast cancer, head and neck cancer) examined the pharmacokinetics and efficacy of oral JM-216 (50, 75, 100 and 20 mg/m^2 once daily for 5 days every 26 days). The maximum tolerated dose (MTD) was determined to be 120 mg/m^2/day; the dose-limiting toxicities were leukopenia, thrombocytopenia, anemia and diarrhea. Two patients resistant to doxorubicin with breast cancer showed tumor shrinkage with JM-216 treatment. The AUC and peak C_{max} values for total platinum on days 1 and 5 and ultrafiltered platinum on day 1 increased in proportion to JM-216 dose. Total platinum and ultrafiltered platinum AUC values on day 5 were higher than values seen on day 1. The AUC value for ultrafiltered platinum obtained on day 5 correlated best with decreases in leukocyte counts and absolute neutrophil counts. The recommended dose for phase II studies was 100 mg/m^2/day every 4-6 weeks (2).

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Original monograph - Drugs Fut 1993, 18: 551.

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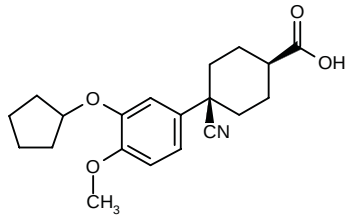
SB-207499
Cilomilast
Ariflo®

Treatment of COPD
PDE IV Inhibitor

EN: 204973



$C_{20}H_{25}NO_4$

GlaxoSmithKline

Results from an *in vitro* study using human peripheral blood neutrophils showed that SB-207499 selectively and significantly inhibited agonist-induced neutrophil effector functions such as oxidative burst (> 90%), adhesion 60%) and exocytosis of primary and secondary granules (50%) and F-Met-Leu-Phe-induced chemotaxis (50%). The agent (up to 10 μM) had no effect on phagocytosis of IgG opsonized red blood cells or serum opsonized zymosan or on bacterial killing (1).

Results from an *in vitro* study using human polymorphonuclear neutrophils (PMNs) pretreated with TNF-α (100 U/ml for 15 min) and activated with fMLP (10 nM for 30 min) showed that cilomilast (10 nM-100 μM) significantly and dose-dependently inhibited migration and extracellular proteolysis by PMNs. The agent (10 μM) inhibited PMN polarization in response to fMLP and actin (by 61.2 ± 1.2%). PMN release and cell surface expression of human leukocyte elastase was also significantly inhibited by 46.3 ± 4.4 and 63.8 ± 2.5%, respectively, with 1 μM cilomilast (2).

An *in vitro* study using bronchial epithelial cells (BEC) and sputum cells (SC) isolated from 10 COPD patients examined the efficacy of cilomilast (10 μM) in inhibiting TNF-α, IL-8 and GM-CSF release. TNF-α was significantly decreased from 139 ± 59 to 97 ± 50 pg/ml in BEC and from 1485 ± 440 to 1080 ± 354 pg/ml in SC. GM-CSF was significantly reduced from 546 ± 230 to 302 ± 149 pg/ml in SC. The agent had no significant effect on IL-8 release from either cell type. Results indicate that cilomilast may be effective in resolving COPD-associated neutrophilic inflammation (3).

Results from a study using rabbits showed that administration of cilomilast (10 mg/kg i.v. 1 min before LPS) inhibited LPS-induced pulmonary trapping of [^{111}In]-labeled polymorphonuclear leukocytes (4).

Results from a study in guinea pigs showed the antitussive effects of SB-207499 (1 or 10 mg/kg i.p. 24 and 1 h before inhalation of capsaicin), suggesting that the agent may be effective as a treatment for eosinophilic bronchitis. Treatment significantly decreased capsaicin-induced increases in coughing in sensitized animals and cough responses in nonsensitized animals. The antigen-induced increase in eosinophils in bronchoalveolar lavage fluid was not altered by treatment (5).

A randomized, double-blind, placebo-controlled, multiple-dose, 4-way crossover study conducted in 18 subjects showed no pharmacokinetic or pharmacodynamic interaction of cilomilast (15 mg b.i.d. p.o.) and theophylline (individualized dosing to achieve steady-state plasma levels of 10-15 μg/ml) when given concomitantly for 4 days (6).

A randomized, double-blind, placebo-controlled, multiple-dose, 4-way crossover study conducted in 18 subjects showed that no cardiovascular interaction occurred when cilomilast (15 mg b.i.d. p.o.) was coadministered with theophylline (individualized dosing to achieve steady-state plasma levels of 10-15 μg/ml) for 4 days. Combination treatment was well tolerated and no significant changes in supine or erect blood pressure, ECG time intervals or morphology, hand tremor or tachycardia were observed. No differences were seen in the QTc in subjects treated with cilomilast alone or in combination with theophylline (7).

A randomized, placebo-controlled study with a 1 month run-in period conducted in 647 patients with stable COPD (FEV_1 = 30-70%; ≤ 15% response to a β_2 agonist) showed the efficacy of maintenance cilomilast (15 mg b.i.d. p.o. for 6 months) therapy in improving health status. A significant reduction of 4.1 points in St. George's Respiratory Questionnaire (SCRQ) scores that were maintained throughout the 6-month dosing period was observed in treated patients. Significant improvements in symptom (–5.1 points), impact (–3.7 points) and activity (–4.1 points) SGRQ subscales were observed with treatment. Cilomilast-treated patients also displayed significant improvements in SF-36 physical function (difference of 3.6 points over placebo) and general health perception scores at week 24 (8).

A randomized, placebo-controlled study with a 1-month run-in period conducted in 647 patients with stable COPD showed the efficacy of cilomilast (15 mg b.i.d. p.o. for 6 months) in reducing exacerbations including acute worsening of COPD (level 1), acute worsening requiring additional treatment as an outpatient (level 2) and acute worsening requiring hospitalization (level 3). Treatment with cilomilast significantly decreased the risk of all levels by 39% and levels 2 and 3 by 45% as compared to placebo (9).

Results from a multicenter 6-week trial in patients with COPD showed the efficacy of SB-207499 (15 mg b.i.d). Treatment with the agent resulted in consistent and significant improvements in pulmonary function. Trough FEV_1 significantly improved by 130 and 160 ml over baseline and placebo, respectively (10).

A randomized, multicenter, placebo-controlled phase III trial conducted in 2058 patients with stable COPD showed the safety and efficacy of cilomilast (15 mg b.i.d. p.o. for 6 months). Fewer adverse events were observed in the cilomilast group as compared to placebo. Acute exacerbation of COPD (30.7 *vs.* 38.9% in placebo) was the most common adverse event and the gastrointestinal

side effects seen in the cilomilast group were only mild to moderate and self-limited. No significant effects were observed on Holter and 12-lead ECGs, vital signs and laboratory parameters (11).

A randomized, placebo-controlled study with a 1-month run-in period conducted in 647 patients with stable COPD showed the efficacy of cilomilast (15 mg b.i.d. p.o. for 6 months) in improving lung function. Treated patients showed a significant average improvement in FEV_1 of 40 ml as compared to placebo; an 80 ml difference was observed between treated and placebo groups at the end of treatment. Treated patients also exhibited significant improvements as compared to placebo in FVC (mean difference = 110 ml), clinic trough FEV_6 (mean difference = 90 ml) and clinic trough FEF_{25-75} (mean difference = 40 ml/s) (12).

Cilomilast is in phase III clinical trials with an NDA planned for the second half of 2002 (13).

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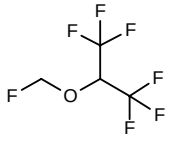
Sevoflurane
Sevofrane®
Sevorane®
Ultane®

Inhalation Anesthetic

EN: 090235



$C_4H_3F_7O$

Dainabot; Maruishi Pharm.; Kodama; Abbott

A new method for the preparation of sevoflurane has been described: Reaction of 1,1,1,3,3,3-hexafluoro-2-propanol (I) with 1,3,5-trioxane (II) and $AlCl_3$ gives the chloromethyl ether (III), which is then fluorinated with KF in hot polyethylene glycol (PEG-400) (1). Scheme 3.

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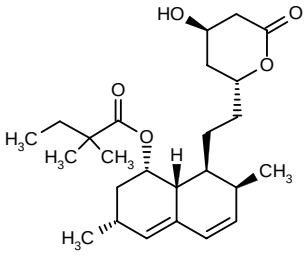
Original monograph - Drugs Fut 1976, 1: 307.

Simvastatin
Zocor®

Hypolipidemic

EN: 122234



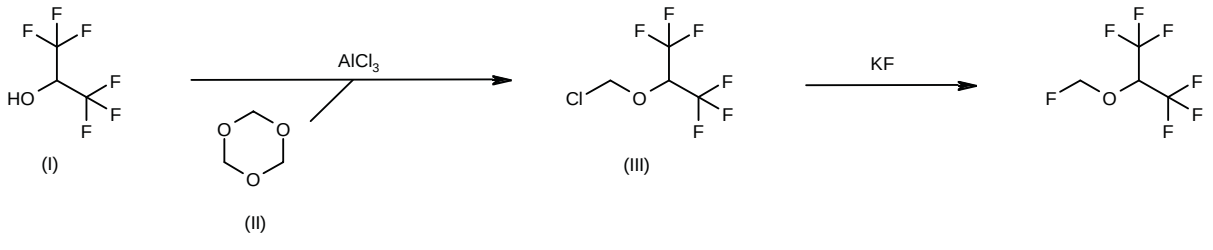
$C_{25}H_{38}O_5$

Merck & Co.

Two recent independent, retrospective, epidemiological studies have shown a greatly decreased incidence of Alzheimer's disease (AD) and dementia in patients treated with HMG-CoA reductase inhibitors, also known as statins. A research team postulated that the reduced risk of AD observed in patients prescribed statins to lower their elevated serum cholesterol levels could be due to a reduction in Aβ42, a β-amyloid isoform linked to all inherited forms of AD. Tesearchers examined the effects of simvastatin and lovastatin – alone or in combination with methyl-β-cyclodextrin (CDX), a compound that physically removes cholesterol from the plasma membrane – on intracellular and secretory β-amyloid levels. In primary cultures of hippocampal neurons and mixed cortical neurons, both simvastatin and lovastatin reduced intracellular and extracellular levels of Aβ42 and Aβ40 peptides. Similarly, a strong, reversible decline in cerebral Aβ42 and Aβ40 levels was observed in the cerebrospinal fluid and brain homogenate of guinea pigs treated with high doses of simvastatin. The cholesterol-extracting toxin CDX also induced a strong reduction in intracellular and secretory neuronal Aβ42 and Aβ40 levels *in vitro*. Since statins and CDX reduce cholesterol levels through entirely different mechanisms, it is possible that the observed reductions in β-amyloid levels are due to cholesterol depletion or to a change in lipid ratio. Based on the results of this study, the researchers suggest that cholesterol-lowering therapy may have a role to play in the prevention of AD (1).

Statins have been found to produce beneficial effects unrelated to the lipid-lowering activity for which they are prescribed, including improved endothelial function, enhanced tissue perfusion and reduction in cardiovascular events. Now researchers have found that activation of protein kinase Akt/PKB in endothelial cells by simvastatin may provide a possible explanation for such effects. *In vitro*, Akt activation by simvastatin induced endothelial nitric oxide synthase phosphorylation and nitric oxide production, inhibited endothelial cell apoptosis and accelerated endothelial tube formation. Simvastatin and enhanced Akt signaling in the endothelium also promoted blood vessel growth in ischemic limbs of normocholesterolemic rabbits. Statin therapy may therefore be useful in conditions where angiogenesis is desired, regardless of cholesterol status, including peripheral ischemic disease (2).

Scheme 3: Synthesis of Sevoflurane



A study examined the effects of simvastatin on coronary endothelial function in hypercholesterolemic pigs and showed that the drug preserves endothelial-dependent relaxation in the absence of an effect on lipids. Pigs were randomly allocated to receive a normal diet, a high-cholesterol diet with no treatment, or a high-cholesterol diet with simvastatin for 12 weeks. No significant differences in lipid levels were seen in the hypercholesterolemic groups. However, in epicardial vessels and arterioles there was a significantly attenuated endothelium-dependent vasorelaxation in the hypercholesterolemic pigs compared with animals fed a normal diet, which was significantly reversed by simvastatin treatment. This impaired vascular response was associated with a decrease in coronary endothelial nitric oxide synthase levels in the hypercholesterolemic animals compared to controls, which was normalized by simvastatin. Simvastatin was also able to reverse the increase in markers of oxidative stress seen in the untreated hypercholesterolemic animals. Thus, statins may be useful for reducing cardiac morbidity independent of their lipid-lowering effects (3).

In a study of acute inflammation, normal mice were given oral simvastatin or indomethacin 1 h before foot pad injection of carrageenan. Simvastatin-treated mice showed significantly reduced edema and a similar reduction in inflammation compared to mice given oral indomethacin. Mice given either simvastatin or indomethacin 24 h before carrageenan, however, showed no reduction in the inflammatory response. These findings strongly suggest an acute antiinflammatory action of simvastatin, independent of its effect on plasma cholesterol levels, which requires several days of therapy. The effect of simvastatin on atherosclerosis was then examined in apolipoprotein E-deficient (apoE–/–) mice fed a high-fat Western-type diet. There was no effect on plasma lipids in mice given simvastatin for 6 weeks. However, mice treated with a dose of 100 mg/kg showed a decrease of 23% in total aortic cholesterol content compared with controls, as well as a 19% reduction in free cholesterol and a 34% reduction in cholesteryl ester content in aorta (4).

A study investigated the effects of simvastatin and atorvastatin on HDL cholesterol subfractions. This 36-week dose-escalation study assigned about 800 patients to simvastatin (40 mg and 80 mg) or atorvastatin (20 mg and 40 mg) for successive 6-week periods, then simvastatin 80 mg or atorvastatin 80 mg for 24 additional weeks. Study results demonstrated that the greater increases in HDL cholesterol and Apo A-I observed for simvastatin as compared to atorvastatin were consistently reflected in the changes in HDL subfractions (5).

In 18 patients with documented ischemic heart disease and hypercholesterolemia, the effects of simvastatin on endothelial function were assessed and compared to the effects of a lipid-lowering diet. The researchers examined brachial artery responses to reactive hyperemia and to nitroglycerin at baseline, after 3 months of dietary modification and at 1 and 3 months of simvastatin (40 mg/day) therapy. During the diet phase of the study, no significant changes were observed in triglyceride levels, in contrast to the significant drop in triglyceride levels after 1 month of simvastatin therapy. In addition, simvastatin, but not diet, was shown to improve endothelium-dependent vasodilatation after several weeks of therapy. Neither endothelium-independent responses nor reactive hyperemic stimulus changed significantly during the study period (6).

Simvastatin may offer additional protective effects against cardiovascular disease above and beyond its lipid-altering effects. Simvastatin was found to lower plasma levels of C-reactive protein (CRP) in hyperlipidemic patients. These findings suggest that the compound may have direct antiinflammatory properties. This study used archived plasma samples from 2 multicenter, randomized, double-blind, placebo-controlled studies of simvastatin in patients with hyperlipidemia. Pooled results from the two studies showed significant decreases in CRP levels among patients treated with 40 mg or 80 mg simvastatin as compared to placebo, although no dose-response was observed (7).

Statin therapy may also have a role to play in the prevention of stroke, according to a recent study. This study involved 318 internal carotid artery (ICA) stenoses in 230 patients referred for examination over a period of 3.5 years. Of the 318 stenoses examined, 147 had been exposed to simvastatin and the remaining 171 had never been exposed to a lipid-lowering drug. Over a 20-month period, total mean stenosis increased from 59.0% to 63.9% in untreated arteries, in contrast to the decrease from 59.8% to 49.8% observed with simvastatin. These results point to a reversal in the progression of carotid artery stenosis over time with simvastatin therapy, a finding which suggests that this drug may serve to reduce stroke risk in patients with known carotid artery disease (8).

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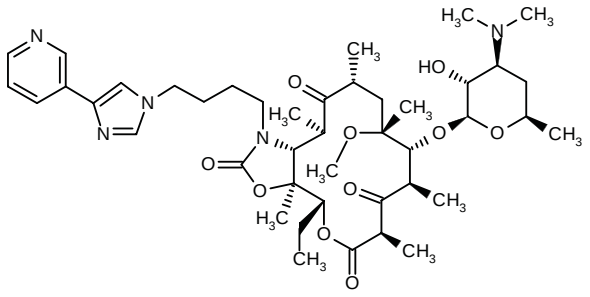

$C_{43}H_{65}N_5O_{10}$

Aventis Pharma

The *in vitro* activity of telithromycin was compared to amoxycillin, cefdinir, levofloxacin, clarithromycin, azithromycin and erythromycin A against Gram-positive clinical isolates in Japan. Telithromycin was the most active compound against erythromycin A-susceptible and -resistant *Streptococcus pneumoniae* with mefA, mefE or ermB genes. Telithromycin was also very active against erythromycin A-susceptible or inducibly-resistant *Staphylococcus aureus* and erythromycin A-susceptible and -intermediate *Enterococcus faecalis* (1).

Results from a study using 23S ribosomal RNA from *Escherichia coli* showed that telithromycin unlike erythromycin and clarithromycin interacted directly with the base of A752 in domain II of 23S rRNA. Thus, telithromycin can still bind to ribosomes mutated at A2058. This may explain the efficacy of the agent observed against erythromycin-resistant pneumococcal infections (2).

The *in vitro* activity of telithromycin and HMR-3004 were compared to clarithromycin against 34 strains of slowly growing mycobacteria at pH 6.8 and 7.4. The MICs obtained at pH 7.4 were found to be 1-2 dilutions lower than at pH 6.8. Clarithromycin was the most potent agent followed by HMR-3004 which was more potent than telithromycin. While moderate susceptibility was observed for *Mycobacterium bovis* BCG, *M. ulcerans*, *M. avium* and *M. paratuberculosis* with HMR-3004 and telithromycin (MIC at pH ≤ 7.4, 5 and ≤ 20 μg/ml, respectively, *vs.* ≤ 1.25 μg/ml for clarithromycin), *M. tuberculosis*, *M. africanum*, *M. bovis* and *M. simiae* were resistant (MIC at pH 7.4, ≥ 10 and ≥ 40 μg/ml, respectively) to these agents. A high degree of intracellular phagocyte accumulation was observed with both telithromycin and HMR-3004 (3).

The *in vitro* activity of telithromycin was examined against 100 strains of erythromycin-resistant *S. pneumoniae* and *Streptococcus agalactiae* and compared to the activities of erythromycin, roxithromycin, azithromycin, miocamycin, clindamycin, quinupristin-dalfopristin and tetracycline. The resistance rates for clindamycin were 56 and 78% for *S. agalactiae* and *S. pneumoniae*, respectively. More than 70% of the strains were resistant to tetracycline. All *S. agalactiae* and *S. pneumoniae* strains were inhibited with 0.5 and ≤ 1 μg/ml quinupristin-dalfopristin, respectively. Telithromycin was active against all strains (MIC = 0.008-0.1 μg/ml and 0.008-1 μg/ml for *S. agalactiae* and *S. pneumoniae*, respectively), showing the lowest $MIC_{50/90}$ values as compared to the other agents. Strains bearing the constitutive MLSB phenotype were highly resistant to all macrolides and clindamycin. The inducible MLSB and M phenotypes were seen in 10 and 2%, respectively, of the *S. pneumoniae* strains and 28 and 6%, respectively, of the *S. agalactiae* strains (4).

Results from the multicenter PROTEKT (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin) study showed that telithromycin was highly active as compared to penicillin, ceflacor, cefuroxime, erythromycin, clarithromyin, azithromycin, levofloxacin and moxifloxacin against the 1327 *S. pneumoniae* strains examined. Strains were isolated from patients with pneumonia, acute bacterial exacerbation of chronic bronchitis, COPD, sinusitis, tonsillitis/pharyngitis or otitis media. The susceptibility obtained for telithromycin as compared to the respective agents was 99.8, 57.7, 49.4, 65.8, 57.3, 57.5, 57.6, 98 and 98.9, respectively. The mode MICs for telithromycin against penicillin- or macrolide- susceptible, -intermediate and -resistant strains were 0.015, 0.015 and 0.06 mg/l, respectively (5).

An *in vitro* study examined the resistance of groups A, C and G β-hemolytic *Streptococcus pyogenes* to telithromycin with results showing that 99.3% of strains tested were susceptible to the agent ($MIC_{50/90}$ = 0.012/0.25 μg/ml). Of the strains from groups A, C and G, 21.32, 41.6 and 10.5%, respectively, were erythromycin-resistant. In addition, 55.1% of all erythromycin-resistant strains were found to carry the ermA gene while the remaining erythromycin-resistant strains carried the mefA gene; both genes occurred simultaneously in only 1 erythromycin-resistant strain (6).

The *in vitro* activity of telithromycin was compared to those of 8 other antibiotics against 77 strains of viridans group streptococci (40.3 and 35.1% resistant to penicillin G and erythromycin A, respectively) isolated from

neutropenic cancer patients. Telithromycin was the most active agent examined (MIC range = ≤ 0.03-1 μg/ml). The agent may therefore be effective as a treatment for viridans streptococcal bacteremia in neutropenic cancer patients (7).

The *in vitro* efficacy of telithromycin was shown against erythromycin-susceptible *S. aureus* and erythromycin-resistant *S. pneumoniae* and *Haemophilus influenzae* strains. The concentrations of the agent used were comparable to free serum concentrations resulting from repeated oral administration of 800 mg to adults for 10 days. Bacteriostatic activity of the agent was seen against all 3 strains (8).

The *in vitro* efficacy of telithromycin was compared to azithromycin, clarithromycin, erythromycin and roxithromycin against 502 strains of anaerobic bacteria. Telithromycin inhibited 10, 50, 93, 100, 98, 85-96, 100, 46-56 and 90% of *Bacteroides fragilis*, other *B. fragilis* group strains, other *Bacteroides* spp., *Porphyromonas* spp., *Prevotella* spp., *Bilophila wadsworthia*, *Clostridium perfringens*, *Clostridium difficile* plus *Clostridium ramosum* and non-spore-forming Gram-positive bacilli, respectively. No activity was observed against strains from the *Fusobacterium mortiferum/varium* group (9).

The *in vitro* activities of telithromycin and levofloxacin were compared to those of ofloxacin, doxycycline and several macrolides against 99 human mycoplasma strains. The MIC values for telithromycin and levofloxacin for all isolates were ≤ 0.52 μg/ml (except for *Mycoplasma hominis*) and ≤ 1 μg/ml, respectively (10).

The activity of telithromycin and HMR-3004 were examined against 2 strains of *Chlamydia pneumoniae* in an intracellular (Hep-2 cells) *in vitro* kinetic model. The MICs for telithromycin and HMR-3004 for both strains were 0.039 and 0.0156 mg/l, respectively. The killing effects were time-dependent when agents were used at concentrations 10 times the MIC (1 log unit decrease in the number of inclusions/well at 48 h *vs.* 2.8 log unit decrease after 96 h). If cells were pretreated with telithromycin at 10 times the MIC for 12 h and then exposed to a concentration 0.5 times the MIC, an increased killing effect was observed. It was concluded that both agents have bactericidal activity against *C. pneumoniae* and significant sub-MIC effects were evident (11).

The *in vitro* activity of telithromycin and HMR-3004 was examined against erythromycin-susceptible and -resistant strains of *S. pyogenes* and *S. pneumoniae*. Comparable high activity was observed for the 2 agents against erythromycin- and penicillin-susceptible and -resistant *S. pneumoniae* and erythromycin-resistant *S. pyogenes* with the M, iMLS-B or iMLS-C phenotypes. The agents were less active against erythromycin-resistant *S. pyogenes* with the cMLS or iMLS-A phenotype (12).

The *in vitro* activity of telithromycin was compared to erythromycin and levofloxacin against intracellular *Legionella pneumophila* (strain L-1033) in an assay using human monocytes exposed to the bacteria for 1 h. The agent exhibited concentration- and time-dependent antibacterial effects. Telithromycin at a concentration 10 times the MIC was significantly more active than erythromycin but less active than levofloxacin. The antibacterial activity of telithromycin was not affected when the agent was removed from assays at 24 h. No synergy or interference was observed when cells were treated with a combination of telithromycin and rifampicin (13).

The *in vitro* activity of telithromycin was compared to the activity of 7 other antimicrobial agents against 292 strains of obligately anaerobic bacteria. The MIC_{50} and MIC_{90} values for telithromycin were: both 4 mg/l for *B. fragilis*, *Bacteroides ovatus* and *Bacteroides thetaiotaomicron*; 2 and 4 mg/l, respectively, for *Fusobacterium* spp. and *B. wadsworthia*; both 2 mg/l for *Bacteroides caccae*; 1 and 4 mg/l, respectively, against *Bacteroides vulgatus*; 0.25 and 4 mg/l, respectively, for *Prevotella* spp.; less than or equal to 0.03 and 0.5 mg/l, respectively, for *Clostridium* spp.; and 0.125 and 4 mg/l, respectively, for *Peptostreptococcus* spp (14).

The *in vitro* efficacy of telithromycin was shown against erythromycin-resistant *S. pyogenes* (111 strains), group C streptococcus (18), group G streptococcus (18) and *S. pneumoniae* (18) strains. The MICs for 103 *S. pyogenes* strains were ≤ 0.5 μg/ml. Those strains that were inhibited by MICs of ≥ 1 μg/ml and ≥ 4 μg/ml were found to carry an ermB and a constitutive ermB gene, respectively. However, telithromycin inhibited *S. pneumoniae* strains also carrying the constitutive ermB gene with MICs of ≤ 0.25 μg/ml (15).

An *in vitro* study examined the activity of telithromycin against 202 isolates of *S. pyogenes* collected in Spain. Of all strains, 88 and 76% were susceptible to telithromycin (≤ 0.5 μg/ml) and erythromycin (≤ 0.25 μg/ml), respectively. Of all erythromycin-intermediate and -resistant strains, 1.5 and 22.3%, respectively, carried the mefA efflux related gene; mefA was also seen in 6 and 2 isolates also bearing ermTR and ermB genes, respectively. The MICs for erythromycin against strains with only the mefA gene were 8- to 16-fold higher (1-16 *vs.* 0.01-0.25 μg/ml) while the MICs for telithromycin were lower (0.03-2 *vs.* 0.008-0.25 μg/ml, respectively). MICs for telithromycin (0.06-1 μg/ml), erythromycin (0.5-1.6 μg/ml) and clindamycin (0.03-0.06 μg/ml) did not increase in strains bearing both mefA and ermTR. However, the simultaneous presence of mefA and ermB increased the MICs to 8-32, 128 and 128 μg/ml, respectively. Of those mefA positive isolates, 85 and 95.8% showed MICs of less than or equal to 1 and 2 μg/ml, respectively, for telithromycin (16).

A study using rabbits with pneumonia due to *S. pneumoniae* (strains 195, 16089 and 11724) showed the efficacy of telithromycin (800 mg b.i.d.) and compared its activity to amoxycillin (1 g i.v. t.i.d.) and erythromycin (500 mg once daily). The MIC values (mg/l) for telithromycin, amoxycillin and erythromycin (respectively) were 0.02, 0.01 and 16 for strain 195, 0.02, 2 and 0.25 for strain 16089 and 0.02, 8 and > 64 for strain 11724. Results showed that telithromycin caused significant bacterial clearance in animals infected with the penicillin- and

erythromycin-resistant strains but was less active against the highly erythromycin-resistant strain. Significant bacterial clearance in the lungs and spleen of animals infected with strains 195 and 16089 was observed 48 h posttreatment with both telithromycin and amoxycillin; erythromycin was only active against the erythromycin-susceptible strain. When the time above MBC was > 33%, all agents caused significant bacterial clearance although failure was seen when this value was < 25%. The MIC for telithromycin did not correlate with microbiological outcome (17).

The plasma and saliva pharmacokinetics of telithromycin (800 mg once daily p.o. for 10 days) were determined as well as its effects on normal oropharyngeal and intestinal microflora as compared to clarithromycin (500 mg b.i.d. for 10 days) in a study involving 20 healthy volunteers. The mean C_{max} and AUC values for telithromycin in saliva were higher than those obtained in plasma. Both saliva and serum telithromycin were similar to those obtained for clarithromycin. Moderate and similar ecological disturbances in normal microflora were observed for both agents. No yeast or *C. difficile* overgrowth was seen. Although treatments resulted in emergence of resistant strains, telithromycin exhibited a more favorable profile. Significant increases in the MIC for intestinal *Bacteroides* isolates lasting for 2 weeks after treatment cessation were observed with both telithromycin and clarithromycin. Highly clarithromycin-resistant alpha-hemolytic streptococci, intestinal enterococci and *Enterobacteriaceae* were identified on day 10 in the clarithromycin group (18).

The population pharmacokinetics of telithromycin (800 mg once daily for 5 or 7-10 days) were determined from results of 7 studies involving 1590 patients with community-acquired pneumonia, acute exacerbations of chronic bronchitis, sinusitis or pharyngitis/tonsillitis. Results revealed that no dosage adjustments are required due to patient gender, age, body size, renal function, smoking status or infection severity (19).

A nonblind, parallel-group study conducted in 24 healthy Japanese subjects showed that telithromycin penetrated the epithelial lining fluid (ELF) and alveolar macrophages following multiple dosing (600 or 800 mg p.o. once daily for 5 days). Concentrations of the agent in macrophages and ELF were higher than in plasma, indicating good penetration of the agent into pulmonary tissue (20).

A study in 18 healthy male volunteers evaluated the dose proportionality of telithromycin pharmacokinetics following a single p.o. dose (day 1) and multiple daily dosing (days 5-11). Telithromycin was well tolerated and reached steady state 2-3 days after dosing. An accumulation ratio of 1.4-1.5 was found. Renal clearance did not change with dose. However, $t_{1/2}$ values were found to increase (21).

A randomized study conducted in 12 young (18-40 years) and 12 elderly (> 65 years) volunteers evaluated the influence of age on the oral bioavailability of telithromycin following single oral (800 mg) and intravenous (400 mg [young] or 800 mg [elderly] as 2.5-h infusion) doses separated by 1 week. Telithromycin bioavailabity was 57% regardless of the age group and was well tolerated. Total clearance tended to decrease in the elderly (22).

Results from an open-label, randomized, 2-period, crossover study in 12 healthy male subjects showed that telithromycin (800 mg/day on days 5-10) does not affect the pharmacokinetics of paroxetine (30 mg once daily for 10 days). From these results, it was concluded that telithromycin has a low potential to interact with other CYP2D6 substrates (23).

Results from an open-label, 3-way crossover study conducted in 15 healthy males showed that the bioavailability of telithromycin (800 mg) was not altered by coadministration with gastric pH altering agents such as Zantac® (300 mg p.o. 1 h before telithromycin) or Maalox® (20 ml p.o. 15 min before telithromycin) (24).

A study conducted in 19 patients undergoing routine fiberoptic bronchoscopy showed that telithromycin penetrated the bronchial mucosa, epithelial lining fluid (ELF) and alveolar macrophages following multiple dosing (800 mg once daily for 5 days). The agent could be detected in bronchial mucosa, ELF and macrophages for more than 24 h postdosing. Results indicate that telithromycin may be effective as a treatment for community-acquired pneumonia and acute exacerbation of chronic bronchitis (25).

The tissue distribution of single-dose telithromycin (600 mg p.o. 3-4 h before tissue resection) was examined in a trial involving 26 patients undergoing tissue resection as a treatment for chronic otitis media, chronic paranasal sinusitis, chronic tonsillitis, palatine tonsil hyperplasia or tonsillar infection. The concentrations of telithromycin and distribution ratios in the mucous membranes of the middle ear, paranasal sinuses and tonsils were 0.119-2.49 mg/kg and 0.465-3.822, 1.390-2.31 mg/kg and 2.558-6.353, and 0.241-6.25 mg/kg and 5.165-16.856, respectively. Results demonstrated good distribution of the agent, indicating its efficacy as a treatment for otorhinolaryngological infections (26).

Results from a randomized, double-blind, parallel group study in 404 adults with mild or moderate community-acquired pneumonia showed that telithromycin (800 mg once daily for 7-10 days) was at least as effective and safe as amoxycillin (1000 mg t.i.d. for 10 days). Better rates for clinical cure (94.6 *vs.* 90%) and bacteriological outcome (90 *vs.* 87.5%) were obtained for telithromycin as compared to amoxycillin More patients receiving amoxycillin required additional respiratory tract infection-related antibiotics for clinical failure or unresolved symptoms in the first 5 treatment days (16 *vs.* 8 patients) and on days 11-15 and 16-20 (27).

Results from a randomized, double-blind, multicenter trial conducted in 396 patients (15-65 years) with acute pharyngitis or tonsillitis caused by group A beta-hemolytic streptococci (GABHS) showed that telithromycin (800 mg once daily for 5 days followed by placebo for 5 days) was as safe and effective as penicillin V (500 mg t.i.d. for 10 days). Clinical cure rates for the 234 evaluable

patients administered telithromycin or penicillin were 94.8 and 94.1%, respectively. Satisfactory bacteriological outcome was seen in 84.3 and 89.1% of the patients, respectively. Treatments were well tolerated, with mild to moderate gastrointestinal adverse events being the most commonly reported. Diarrhea and nausea were more frequent in the telithromycin groups while a higher incidence of elevated transaminases and vaginal moniliasis was seen in the penicillin group (28).

Results from a randomized, double-blind, multicenter trial conducted in 248 adult patients with community-acquired pneumonia showed that telithromycin (800 mg once daily for 7-10 days) was as safe and effective as trovafloxacin (200 mg once daily for 7-10 days). Clinical cure rates for the 186 evaluable patients administered telithromycin or trovafloxacin were 91.1 and 94.8%, respectively. Of the 43 patients in whom the pathogen was identified, eradication was seen in 94.1 and 1005, respectively, with pathogen eradication rates of 95.5 and 100%, respectively. Treatment was generally well tolerated with treatment-related adverse events reported in 42.1 and 30.6% of the patients in the telithromycin and trovafloxacin groups, respectively. The majority were mild and the most common were diarrhea (16.5 and 5.8%), nausea (8.3 and 4.1%), dizziness (1.7 and 7.4%) and headache (4.1 and 6.6%) (29).

Results from a randomized, double-blind, multicenter trial conducted in 463 adolescents (13 years or older) and adults with acute pharyngitis or tonsillitis caused by group A beta-hemolytic streptococci (GABHS) showed that oral telithromycin (800 mg once daily for 5 days) was as safe and effective as oral clarithromycin (250 mg b.i.d. for 10 days). Treatments were generally well tolerated. Clinical cure rates for the 285 evaluable patients administered telithromycin or clarithromycin were 92.7 and 91.1%, respectively. Satisfactory bacteriological outcome (*i.e.*, eradication of the pathogen or appearance of a new serotype of GABHS without clinical signs or symptoms) was seen in 91.3 and 88.1% of the patients, respectively, and pathogen eradication rates were 91.3 and 88.9%, respectively. Treatment-related adverse events were reported in 43.2 and 26.3% of the patients in the telithromycin and clarithromycin groups, respectively. The most common adverse events were diarrhea (16.6 and 7.5%), nausea (10.5 and 3.9%) and dizziness (6.1 and 1.3%) (30).

Results from a randomized, double-blind, multicenter trial conducted in 496 patients with acute exacerbations of chronic bronchitis showed that telithromycin (800 mg once daily for 5 days) was as safe and effective as cefuroxime axetil (500 mg b.i.d. for 10 days). Clinical cure rates for the 375 evaluable patients administered telithromycin or cefuroxime axetil were 89.2 and 86.3%, respectively. Of the 115 patients in whom the pathogen was identified, eradication was seen in 87.9 and 86%, respectively, and the pathogen eradication rates were 89.6 and 84.9%, respectively. No significant difference was observed in treatment-related adverse events between the telithromycin and cefuroxime groups (28.2 and 28.3%). Most were mild, with the most common being diarrhea (10.9 and 10.2%) and nausea (9.2 and 2.9%) (31).

Results from a randomized, double-blind, multicenter trial conducted in 448 patients with community-acquired pneumonia showed that oral telithromycin (800 mg once daily for 10 days) was as safe and effective as oral clarithromycin (500 mg b.i.d. for 10 days). Clinical cure rates for the 318 evaluable patients administered telithromycin or clarithromycin were 88.3 and 88.5%, respectively. Of the 56 patients in whom the pathogen was identified, eradication was seen in 89.3 and 96.4%, respectively, and pathogen eradication rates were 87.5 and 96.7%, respectively. No significant difference was observed in treatment-related adverse events between the telithromycin and clarithromycin groups (38.5 and 27.9%). The most common were diarrhea (12.7 and 7.2%), nausea (8.6 and 5.0%), dizziness (4.1 and 1.8%) and headache (4.1 and 5.4%) (32).

Results from a randomized, double-blind, multicenter trial conducted in 790 patients with acute maxillary sinusitis showed that oral telithromycin (800 mg once daily for 5 or 10 days) was as safe and effective as amoxicillin/clavulanic acid (500/125 mg t.i.d. for 10 days). Clinical cure rates for the 434 evaluable patients administered telithromycin for 5 or 10 days or amoxicillin/clavulanic acid were 78.8, 74.1 and 74.6%, respectively. Out of the 22 patients in whom the pathogen was identified, eradication was seen in 85.7, 85.7 and 75%, respectively, and pathogen eradication rates were 85.7, 85.7 and 80%, respectively. Adverse events of which the most common were diarrhea (19.1, 19.9 and 23.9%, respectively) and nausea (11.7, 9 and 7.5%, respectively), were reported in 42, 45.9 and 43.9% of the patients, respectively. It was concluded that the 5-day telithromycin regimen was as effective as the 10-day regimen (33).

The efficacy of telithromycin (800 mg once daily for 7-10 days) was shown from results of 4 ongoing phase III trials conducted in a total of 755 patients with community-acquired pneumonia. The clinical cure rates for patients with documented infections due to *C. pneumoniae* (30 patients), *Mycoplasma pneumoniae* (28 patients), *L. pneumophila* (4 patients) and *Coxiella burnetti* (5 patients) were 83.3, 96.4, 100 and 80%, respectively (34).

The efficacy of telithromycin (800 mg once daily for 7-10 days) in treating bacteremia was shown from results of 4 ongoing phase III trials conducted in a total of 755 patients with community-acquired pneumonia. Of these patients, 4.6% had documented bacteremia at baseline, most of which were due to *S. pneumoniae*, including 3 penicillin-resistant and 2 erythromycin A-resistant strains. Of the 30 evaluable patients with bacteremia, 90% had a clinical cure and an eradication rate of 90%. Of those 26 patients with confirmed pneumococcal bacteremia, 88.5% had a clinical cure and the pathogen eradication rate was 88.5% (35).

An open-label study conducted in 240 patients with mild or moderate community-acquired pneumoniae

showed the efficacy and safety of telithromycin (800 mg once daily for 7-10 days). Treatment was generally well tolerated. Clinical cure rates were 92.9 and 79.6% in the per protocol (PP) and modified intent-to-treat populations, respectively. The most common pathogen was *S. pneumoniae*. Satisfactory bacteriological outcome was seen in 88.9% of the patients in the PP population and the overall eradication rate was 82.7%. Clinical cures and bacteriological eradication were seen in 8/13 patients with documented bacteremia (36).

The effects of telithromycin and clarithromycin on Q-T interval were assessed in double-blind, randomized, placebo-controlled, crossover studies in 18 subjects given single and repeated oral doses of telithromycin (800 mg; once daily for 6 days) and clarithromycin (500 mg; twice daily for 6 days), and in 16 subjects given single oral doses of telithromycin of 800-2400 mg. The effects were tested at various heart rates. Neither telithromycin, even at high doses, nor clarithromycin was associated with significant prolongation of the duration of ventricular repolarization in subjects with normal heart rate (37).

Results from a randomized, double-blind, parallel-group, multicenter trial conducted in 404 patients with mild or moderate community-acquired pneumoniae showed that telithromycin (800 mg once daily for 10 days) was as safe and effective as amoxicillin (1000 mg t.i.d. for 10 days). Treatments were generally well tolerated. Clinical cure (94.6 and 90.1%, respectively) and eradication (87.5 and 86.7%, respectively) rates were comparable for the telithromycin and amoxicillin groups. *S. pneumoniae* was the most common pathogen in both treatment groups. Of the patients with pneumococcal bacteremia, 10/10 and 7/9 in the telithromycin and amoxicillin groups, respectively, had clinical cures (38).

Results from a randomized, double-blind, multicenter trial conducted in 336 patients with acute maxillary sinusitis showed similar efficacy for oral telithromycin (800 mg once daily) given for 5 or 10 days. Comparable clinical cure rates were obtained for both the 5- and 10-day regimens (91.1 and 91% for the per protocol population and 82.6 and 87.5% for the modified intent-to-treat population). Eradication rates for *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* and *S. aureus* for the 5- and 10-day regimens were 93.3 and 89.3%, 100 and 100%, 85.7 and 75% and 100 and 100%, respectively. Both treatment regimens were well tolerated (39).

Results from a randomized, double-blind, multicenter trial conducted in 325 patients with a history of chronic bronchitis and chronic obstructive pulmonary disease showed that oral telithromycin (800 mg once daily for 5 followed by placebo for 5 days) was as safe and effective as amoxicillin/clavulanic acid (500/125 mg t.i.d. for 10 days). Clinical cure rates were slightly higher in the telithromycin group as compared to amoxicillin/clavulanic acid (86.1 *vs.* 82.1% in the per protocol and 81.3 *vs.* 78.1% in the intent-to-treat populations). Satisfactory bacteriological outcomes were seen in 69.2 and 70% of the patients in the telithromycin and amoxicillin/clavulanic acid groups, respectively, and the overall bacterial eradication rates were 76.2 and 81.3%, respectively. Treatment-related adverse events were mild to moderate, with incidence rates of 23.8 and 36.9% for the telithromycin and amoxicillin/clavulanic acid groups, respectively (40).

The efficacy of telithromycin (800 mg once daily) was examined in phase IIIa trials conducted in a total of 4142 patients with community-acquired respiratory tract infections caused by *S. pneumoniae* with reduced susceptibility to penicillin or macrolides. The efficacy of telithromycin was compared to other microbials. Telithromycin cure rates for patients with community-acquired pneumonia, acute exacerbations of chronic bronchitis (AECB), sinusitis and tonsillopharyngitis were 91.8, 88, 82 and 93.6%, respectively. Bacteriological outcome rates for telithromycin against AECB and sinusitis were 80.4 and 91.8%, respectively. Rates for clinical cure (70 *vs.* 93%) and bacteriological eradication (80 *vs.* 93%) for comparator-treated patients with penicillin- and/or erythromycin-resistant pneumococcal infections were lower than those obtained for telithromycin-treated patients (41).

A randomized study conducted in 396 patients with group A beta-hemolytic streptococcus tonsillopharyngitis showed that telithromycin (800 mg once daily for 5 days followed by placebo for 5 days) provided faster symptom relief than penicillin V (50 mg t.i.d. for 10 days). Both treatments were well tolerated and similar safety profiles were obtained for the 2 agents. The clinical cure rates for telithromycin and penicillin were 85.9 and 85.8%, respectively, and the bacteriological outcome rates were 79.7 and 79.3%, respectively. During treatment in the modified intent-to-treated population, telithromycin resulted in significantly greater improvement in the total symptom score from baseline indicating faster resolution of symptoms; symptom scores for the 2 agents were similar at the end of treatment (42).

The Committee for Proprietary Medicinal Products (CPMP) has issued a positive opinion recommending marketing approval for telithromycin for the treatment of community-acquired respiratory tract infections, including penicillin- and/or erythromycin-resistant *S. pneumoniae*. Specifically, the CPMP has recommended telithromycin (800 mg orally once daily) for the treatment of patients aged 18 years and older with community-acquired pneumonia (CAP), acute exacerbation of chronic bronchitis (AECB), acute sinusitis and tonsillitis/pharyngitis caused by group A beta-hemolytic streptococci, as an alternative when beta-lactam antibiotics are not appropriate (43).

Aventis has received an approvable letter from the FDA for telithromycin (Ketek®) tablets (800 mg orally once daily) for the treatment of CAP, ABECB and acute bacterial sinusitis (ABS). At the same time, the company received a nonapprovable letter for for tonsillitis/pharyngitis (44).

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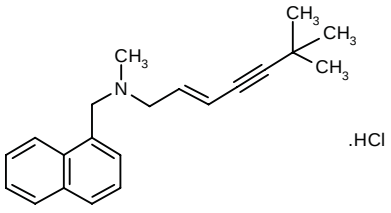

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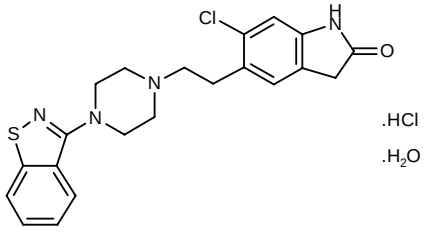


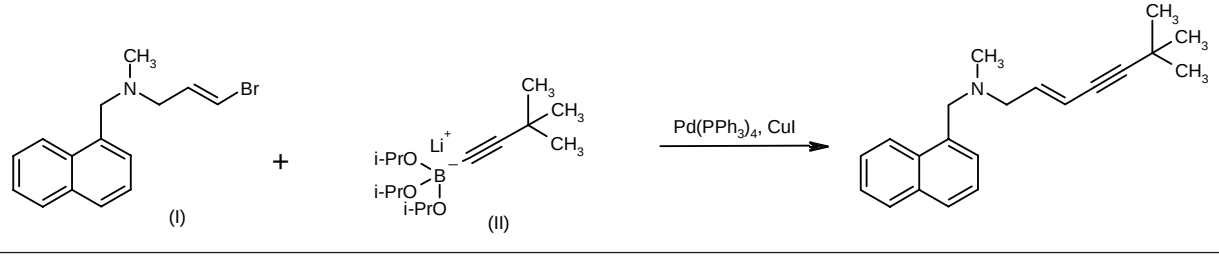
$C_{21}H_{21}ClN_4OS.HCl.H_2O$ **Pfizer**

Pharmaceutical formulations comprising ziprasidone free base or its hydrochloride in form of crystalline particles with a maximum size of 85 μm are reported to exhibit good solubility properties at physiologic pH and are indicated for the treatment of psychosis such as schizophrenia (1).

A multicenter, randomized, open-label, 7-day trial involving 132 hospitalized patients with acute psychotic agitation related to DSM-III-R diagnoses compared the efficacy and tolerability of ziprasidone (5-20 mg i.m. every 4-6 h for up to 3 days followed by 80-200 mg/day p.o. to day 7) with haloperidol (2.5-10 i.m. every 4-6 h for up to 3 days followed by 10-80 mg/day p.o. to day 7). Ziprasidone treatment was well tolerated and effective. Both ziprasidone and haloperidol significantly improved Brief Psychiatric Rating Scale (BPRS) totals and BPRS agitation items as well as Clinical Global Impressions Severity scales. Further reductions in these scores were observed after oral dosing with the agents. A reduction in the need for anticholinergic medication was associated with both i.m. and p.o. ziprasidone treatment as compared to haloperidol and movement disorder scales improved with ziprasidone in contrast to the deterioration in scores seen with haloperidol. Other adverse events were infrequent with both treatments (2).

Ziprasidone hydrochloride is a structurally novel antipsychotic agent whose profile of activity indicates

Scheme 4: Synthesis of Terbinafine



efficacy in the treatment of negative and affective symptoms of schizophrenia together with a low liability for extrapyramidal side effects. Subgroup analysis of 115 hospitalized patients with acute episodes of schizoaffective disorder from 2 multicenter, double-blind, randomized, placebo-controlled, parallel-group trials evaluating treatment with oral ziprasidone 40 mg/day, 80 mg/day, 120 mg/day or 160 mg/day or placebo for 4-6 weeks was recently reported. Compared to baseline, ziprasidone treatment was associated with significant and dose-dependent improvement in all primary efficacy variables (Brief Psychiatric Rating Scale [BPRS] total, BPRS Core and Clinical Global Impressions Severity scale [CGI-S] scores) and the BRPS Manic score. The highest dose of ziprasidone produced significantly greater improvement on all these scales compared to placebo, and the dose of 120 mg/day produced significantly greater improvement in the mean CGI-S scores. Improvement in the BPRS Depressive item and Montgomery-Asberg Depression Rating Scale (MADRS) total score on ziprasidone did not reach statistical significance compared to placebo. Ziprasidone was generally well tolerated and no clear relationship between adverse events and drug treatment emerged from these studies. Most adverse events were mild in severity, the most common being pain and headache. Moreover, a very low incidence of dystonia, akathisia, extrapyramidal symptoms, hypertonia, tachycardia, orthostatic hypotension, dry mouth, diarrhea, dysmenorrhea and erectile dysfunction was recorded. The results from these two studies thus indicate that ziprasidone is safe and effective in the treatment of both affective and psychotic symptoms of schizoaffective disorder (3).

According to a company spokesperson, both the oral and intramuscular formulations of ziprasidone hydrochloride (Zeldox®) were launched in Sweden, the product's first market, in mid-September. The capsule formulation (20 mg, 40 mg, 60 mg and 80 mg) was first approved in Sweden in 1998, whereas the i.m. formulation (20 mg/ml) was just approved in August of this year (4).

The FDA has approved ziprasidone hydrochloride for the treatment of schizophrenia. In placebo-controlled, short-term (4- and 6-week) clinical trials, ziprasidone at doses of 20-100 mg twice daily was statistically superior to placebo for the treatment of positive and negative symptoms in patients with acute exacerbations of schizophrenia and schizoaffective disorder. In a 1-year placebo-controlled study in chronic, stable inpatients, ziprasidone was shown to be effective in delaying the time to and rate of relapse. Ziprasidone will be launched in the U.S. as 20-, 40-, 60- and 80-mg capsules. Discussions between the company and the FDA regarding potential tradenames for ziprasidone are currently ongoing (5).

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