Drugs of the Future 2001, 26(2): 175-211

CCC: 0377-8282/2001

Information Update

Volume 1-25, Number 2

Estimated developmental phase for this month's updated products:

Preclinical

LY-294002 (oncolytic; Lilly)
Tenilsetam (treatment of diabetic retinopathy; Aventis Pharma)

Phase I

KRN-7000 (immunostimulant, oncolytic; Kirin Brewery)
Luteolin (antiinflammatory; Inst. Materia Med., Chin. Acad. Med. Sci.)
Recombinant methioninase (oncolytic; AntiCancer)

Phase II

Antineoplaston A10 (oncolytic; Burzynski Res. Inst.)
Brasofensine sulfate (antiparkinsonian, dopamine reuptake inhibitor; NeuroSearch)
EO9 (oncolytic; EORTC)
Fampridine (treatment of multiple sclerosis, treatment of spinal cord injury; Acorda, Elan)
KT-6149 (antineoplastic antibiotic; Kyowa Hakko)
Lometrexol (oncolytic; Lilly, Tularik)
LU-135252 (treatment of restenosis, antihypertensive, treatment of heart failure, endothelin ET_A antagonist; Aventis Pharma, Knoll)
Prinomastat (oncolytic, matrix metalloproteinase inhibitor; Agouron)
Sitaxsentan sodium (treatment of heart failure, treatment of pulmonary hypertension, antihypertensive, endothelin ET_A antagonist; Icos-Texoc Biotechnol., LG Chem)
Tipranavir (anti-HIV, HIV protease inhibitor; Pharmacia, Boehringer Ingelheim)

Phase III

Fedotozine tartrate (prokinetic, κ-opioid agonist; Jouveinal, Pfizer)
Leminoprazole (antiulcer, H^+/K^+-ATPase inhibitor; Nippon Chemiphar, Kyorin) (*discontinued*)
OPB-2045 (antibacterial; Otsuka)
SCH-56592 (antifungal; Schering-Plough)
Tomoxetine hydrochloride (treatment of ADHD; Lilly, Chugai)
Viozan® (treatment of COPD; AstraZeneca)

Preregistered

Pamicogrel (platelet antiaggregatory; Kanebo, Torii)
Ziconotide (analgesic; Elan, Draxis Health)

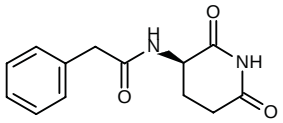
Launched/Year

Clopidogrel hydrogensulfate (platelet antiaggregatory; Sanofi-Synthélabo, Bristol-Myers Squibb, Daiichi Pharm.)/1998
Colforsin dapropate hydrochloride (treatment of heart failure, antiasthmatic, adenylate cyclase activator; Nippon Kayaku)/1999
Efavirenz (anti-HIV, reverse transcriptase inhibitor; DuPont Pharm.)/1998
Glatiramer acetate (treatment of multiple sclerosis; Teva, Aventis Pharma, AutoImmune)/1996
Levetiracetam (antiepileptic; UCB)/2000
Modafinil (antinarcoleptic, treatment of sleep apnea, treatment of ADHD; Lafon, Cephalon)/1994
Moxifloxacin hydrochloride (quinolone antibacterial; Bayer, Vita, Esteve)/1999
Olanzapine (antipsychotic; Lilly, Gador)/1990
Omeprazole (gastric antisecretory; AstraZeneca)/1988
Perospirone hydrochloride (antipsychotic; Sumitomo, Welfide)/2001
Propentofylline (cognition enhancer; Aventis Pharma)/1988
Sildenafil citrate (treatment of erectile dysfunction, treatment of female sexual dysfunction; Pfizer, Bagó)/1998
Taltirelin (treatment of neurodegenerative diseases, TRH analog)/2000

Antineoplaston A10

Oncolytic

EN: 090476



$C_{13}H_{14}N_2O_3$ **Burzynski Res. Inst. (US)**

A study showed that breast cancer patients displayed significantly higher neutrophil apoptosis levels which were negatively correlated to urinary antineoplaston A10 (A10) levels. *In vitro* studies examining the direct effect of A10 (10 ng/ml) on neutrophil apoptosis in cellular suspensions taken from breast cancer patients revealed that the agent significantly inhibited neutrophil apoptosis. It was concluded that A10 may be a potential adjuvant therapy for breast cancer patients (1).

A study involving 31 breast cancer patients and 17 normal women demonstrated that patients with breast cancer had significantly lower urinary A10 levels. Results suggest the existence of an inverse correlation between urinary A10 and breast cancer and measurement of A10 levels may be a predictive test for women at risk (2).

1. Badria, F., Mabed, M., El-Awadi, M., Abou-Zeid, L., Al-Nashar, E., Hawas, S. *Immune modulatory potentials of antineoplaston A-10 in breast cancer patients.* Cancer Lett 2000, 157(1): 57.

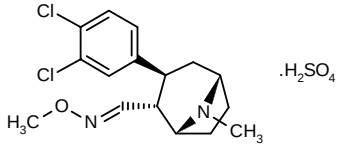
2. Badria, F., Mabed, M., Khafagy, W., Abou-Zeid, L. *Potential utility of antineoplaston A-10 levels in breast cancer.* Cancer Lett 2000, 155(1): 67.

Original monograph - Drugs Fut 1985, 10: 103.

Brasofensine Sulfate

Antiparkinsonian
Dopamine Reuptake Inhibitor

EN: 224675



$C_{16}H_{20}Cl_2N_2O.H_2O_4S$ **NeuroSearch**

A study in 8 Parkinson's disease patients receiving stable doses of levodopa/carbidopa investigated the effects of single escalating doses of brasofensine (0.5, 1, 2 and 4 mg) according to a double-blind, randomized, placebo-controlled design. Peak plasma levels and AUC of brasofensine were dose-dependent, C_{max} increasing from 0.35 ng/ml on 0.5 mg to 3.27 ng/ml on 4 mg, and AUC increasing from 8.54 ng·h/ml on 0.5 mg to 130.69 ng·h/ml on 4 mg. Brasofensine was generally well tolerated over this dose range, with mild headache, upper respiratory infection, vomiting, phlebitis and hypertension as the most frequent adverse events. No improvement was detected in the UPDRS motor subscale scores upon addition of brasofensine (1).

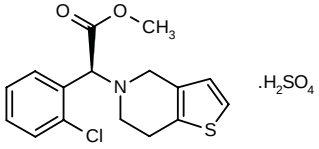
1. Cutler, N.R., Salazar, D.E., Sramek, J.J. *Assessments of BMS-204756 (brasofensine) co-administered with levodopa/carbidopa to Parkinson's disease patients.* 7th World Conf Clin Pharmacol Ther (July 15-20, Florence) 2000, Abst 711.

Original monograph - Drugs Fut 1999, 24: 128.

Clopidogrel Hydrogensulfate
Plavix®
Iscover®

Platelet Antiaggregatory

EN: 142672



$C_{16}H_{16}ClNO_2S.H_2O_4S$ **Sanofi-Synthélabo; Bristol-Myers Squibb; Daiichi Pharm.**

The safety of a standard treatment after coronary stenting, ticlopidine, has been compared to treatment with clopidogrel, also an ADP receptor antagonist. During the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS), 1020 patients with stents were randomized to one of three groups for 28 days of treatment. In the clopidogrel loading-dose group, patients received a loading dose of clopidogrel 300 mg and aspirin 325 mg on day 1 and then clopidogrel 75 mg/day and aspirin 325 mg/day thereafter. A second group received clopidogrel 75 mg/day and aspirin 325 mg/day with no loading dose. The ticlopidine group received that drug twice daily at 250 mg plus aspirin 325 mg/day. The primary endpoint was the incidence of major peripheral or bleeding complications, neutropenia, thrombocytopenia or early discontinuation of the study drug due to noncardiac adverse events. The primary endpoint was met by 9.1% and 4.6% of patients in the ticlopidine and combined clopidogrel groups, respectively. The major adverse cardiac events rates were low and similar among groups. Overall, clopidogrel plus aspirin demonstrated superior safety to ticlopidine plus aspirin. The clopidogrel loading dose was also well tolerated and did not increase the risk of bleeding. Secondary endpoint data indicated that the study drugs are similarly efficacious (1).

Clinical characteristics, the interval between clopidogrel treatment and the onset of disease, the response to treatment, outcomes and laboratory findings were determined in 11 patients in whom thrombotic thrombocytopenic purpura developed during or soon after treatment with clopidogrel. The 11 patients, 6 of whom were women, ranged in age from 35-70 years. Six patients received clopidogrel for coronary artery disease,

including 3 patients who received the drug after the placement of a coronary artery stent. Concomitant medications included the cholesterol-lowering drugs atorvastatin and simvastatin in 5 patients, long-term treatment with atenolol in 3 patients and long-term ciclosporin treatment in 1 patient. All but 1 of the patients developed thrombotic thrombocytopenic purpura within 3-14 days of receiving clopidogrel. The syndrome was characterized by the occurrence of thrombocytopenia, microangiopathic hemolytic anemia, neurological changes and renal dysfunction. All patients underwent plasma exchange after diagnosis of adverse effects. Although 10 of 11 patients had a response to plasma exchange, 2 required 20 or more exchanges before clinical improvement occurred, and 2 had relapses while not receiving clopidogrel. One patient died despite undergoing plasma exchange soon after diagnosis (2).

1. Bertrand, M.E., Rupprecht, H.-J., Urban, P., Gershlick, A.H. *Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting. The clopidogrel aspirin stent International cooperative study (CLASSICS).* Circulation 2000, 102(6): 624.

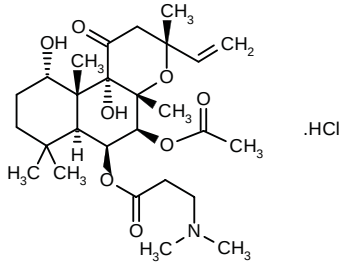
2. Bennett, C.L., Connors, J.M., Carwille, J.M. et al. *Thrombotic thrombocytopenic purpura associated with clopidogrel.* New Engl J Med 2000, 342(24): 1773.

Original monograph - Drugs Fut 1993, 18: 107.

Colforsin Dapropate Hydrochloride

Adehl® *Treatment of Heart Failure*
Antiasthmatic

EN: 133606 *Adenylate Cyclase Activator*



.HCl

$C_{27}H_{43}NO_8$.HCl **Nippon Kayaku**

Results from a study using a rat orthotopic lung transplantation model showed that NKH-477 (1, 2 or 3 mg/kg/day days 0-10) alone or in combination with ciclosporin (1 or 2 mg/kg i.p. days 0-6) inhibited acute rejection. The respective doses of NKH-477 alone significantly increased mean allograft survival time to 5.7 ± 0.2, 8.2 ± 0.3 and 9.5 ± 0.6 days as compared to 4.3 ± 0.2 days observed in untreated controls; 1 and 2 mg ciclosporin alone increased mean survival time to 6.8 ± 0.5 and 12.4 ± 1.4 days, respectively. Combination treatment (with 1 mg/kg NKH-477) enhanced mean survival to 10.2 ± 0.4 days (with 1 mg/kg ciclosporin) and 14.4 ± 0.6 (2 mg/kg ciclosporin) days. Average rejection scores from histological examination of allografts were significantly lower in animals treated with NKH-477 as compared to untreated controls (1).

1. Nakashima, S., Morikawa, M., Komatsu, K., Abe, T. *NKH477, a forskolin derivative, inhibits acute rejection in rat recipient on orthotopic lung allografts.* J Heart Lung Transplant 2000, 19(1): Abst 29.

Original monograph - Drugs Fut 1993, 18: 134.

Additional References

Hara, S. et al. *Effects of NKH477 on endothelin-1-induced renal responses in anaesthetized dogs.* Clin Exp Pharmacol Physiol 2000, 27(7): 513.

Iwatsubo, K. et al. *NKH477, a new inotropic reagent that directly stimulates adenylyl cyclase, does not cause the β-adrenergic receptor downregulation: Demonstration using a newly developed whole cell binding assay.* J Am Coll Cardiol 2001, 37(2, Suppl. A): 272A.

Kariyazono, H. et al. *Anti-platelet effects of colforsin dapropate in vitro.* 7th World Conf Clin Pharmacol Ther (July 15-20, Florence) 2000, Abst 629.

Suenaga, E. et al. *Remarkable effect of colforsin dapropate hydrochloride administration in two cases of heart failure after open heart surgery.* J New Rem Clin 2000, 49(9): 101.

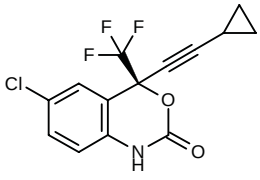
Yousif, M.H.M., Thulesius, O. *A pharmacological study of bronchodilator properties of NKH477, forskolin, and β-agonists on guinea pig and ovine isolated bronchioles.* Drug Dev Res 2000, 51(3): 169.

Yousif, M.H.M., Thulesius, O. *NKH477: A novel bronchodilator produces potentiation and tachyphylaxis reversal to salbutamol in isolated guinea pig trachea.* Drug Dev Res 1999, 48(4): 154.

Efavirenz

Sustiva® *Anti-HIV*
Stocrin® *Reverse Transcriptase Inhibitor*

EN: 207217



$C_{14}H_9ClF_3NO_2$ **DuPont Pharm.**

The efficacy of salvage therapy including efavirenz (600 mg/day) and adefovir dipivoxil (120 mg/day) combined with other antiretroviral agents was evaluated in 33 highly treatment-experienced (nucleoside- and nonnucleoside reverse transcriptase inhibitor [NRTI and NNRTI]) HIV-positive patients in a retrospective clinical cohort study. At 12 and 24 weeks, 30 and 24% of the patients, respectively, had an HIV viral load of < 500 copies/ml.

Failure was associated with prior NNRTI but not NRTI treatment and a history of any NNRTI mutations (1).

The FDA has granted full approval to efavirenz (Sustiva™) for use in combination with other anti-HIV agents, based on duration of response – the new FDA standard for anti-HIV agents – measured using Kaplan-Meier/time to treatment failure (TTF) analysis. DuPont is the first antiretroviral manufacturer to receive full approval based on this method of analysis, as well as the first to include data analyzed using the ultrasensitive assay (< 50 copies/ml) in their product labeling. The approval was based on studies involving a total of 1266 protease inhibitor (PI)-, NNRTI- and 3TC-naive patients with HIV infection. This randomized, open-label study demonstrated that patients taking efavirenz)/AZT/3TC experienced greater duration of response through 110 weeks of treatment than patients taking combinations of indinavir/AZT/3TC. In one of the studies, NRTI-experienced patients taking efavirenz plus 2 NRTIs achieved better virological suppression than patients taking nelfinavir plus 2 NRTIs after 48 weeks of treatment. In January 2000, the U.S. Department of Health and Human Services named efavirenz as the only NNRTI to be a "strongly recommended" antiretroviral agent for use in first-line combination treatment of individuals with HIV infection (2).

DuPont Pharmaceuticals has initiated an expanded access program that will allow HIV-infected children and adolescents 3-16 years of age to take an oral liquid formulation of efavirenz in combination regimens for the treatment of HIV. The Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection published in January 2000 recommend the use of efavirenz as first-line therapy in combination with 2 NRTIs. In addition, results from the Pediatric AIDS Clinical Trials Group Study demonstrated that combination treatment with efavirenz in capsule form was effective in maintaining viral load suppression through 48 weeks in 75.5% of the 57 children participating in the study. The type and frequency of adverse effects with efavirenz capsules were generally similar to those seen in adults, with a higher incidence of rash reported in children. The expanded access program will include treatment-experienced patients who are failing or intolerant of their current antiretroviral therapy regimen. In this open-label program, participants will initiate efavirenz liquid therapy along with at least 1 or more NRTIs and/or protease inhibitors with which they have no prior experience (3).

1. Shulman, N.S., Zolopa, A.R., Passaro, D.J. et al. *Efavirenz- and adefovir dipivoxil-based salvage therapy in highly treatment-experienced patients: Clinical and genotypic predictors of virologic response.* J Acquir Immune Defic Syndr Hum Retrovirol 2000, 23(3): 221.

2. *Sustiva granted traditional FDA approval based on duration of treatment response.* DailyDrugNews.com (Daily Essentials) Feb 15, 2000.

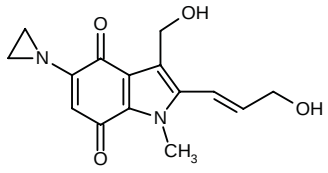
3. *DuPont expands access to liquid Sustiva in children.* DailyDrugNews.com (Daily Essentials) May 2, 2000.

Original monograph - Drugs Fut 1998, 23: 133.

EO9
Neoquin®

Oncolytic

EN: 141378



$C_{15}H_{16}N_2O_4$ **EORTC**

The newly formed anticancer subsidiary of NeoTherapeutics, NeoOncoRx, has signed a letter of intent to acquire the anticancer compound EO9 and numerous analogs from The Netherlands-based NDDO Research Foundation. EO9 and analogs originated from research carried out at the University of Amsterdam and much of the preclinical and clinical development has been performed in collaboration with EORTC research groups and clinical centers in Europe. NeoOncoRx will also receive the patent and worldwide rights for EO9 and its analogs and has chosen the name Neoquin® for EO9. These compounds form a family of bioreductive alkylating indolequinones, a novel class of anticancer agents. Preclinical studies have demonstrated preferential toxicity for EO9 against solid tumors, *i.e.*, colon, melanoma, brain, renal and non-small cell lung cancers. Animal studies have shown additional antitumor efficacy against stomach, ovarian and breast tumors. Moreover, the compound appears to lack bone marrow toxicity, which has been confirmed in clinical studies. NeoOncoRx plans to initiate a phase II trial of EO9 in bladder cancer in the U.K. during the first quarter of 2001 (1).

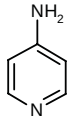
1. *NeoOncoRx to acquire worldwide rights to novel class of anticancer agents.* DailyDrugNews.com (Daily Essentials) Jan 5, 2001.

Original monograph - Drugs Fut 1996, 21: 143.

Fampridine
4-Aminopyridine
Neurelan®

Treatment of Multiple Sclerosis
Treatment of Spinal Cord Injury

EN: 182600



$C_5H_6N_2$ **Acorda; Elan**

The discriminative stimulus effects of 4-aminopyridine (4-AP) were examined and compared to pyridine, 3-AP,

2-AP, 2,3-diaminopyridine (2,3-DIAP), 2,6-DIAP, 3,4-DIAP and 4-dimethylaminopyridine (4-DMAP) in rats subjected to a standard 2-level food reinforced drug discrimination procedure. Results revealed an interaction between benzodiazepines and K^+ channels. 4-AP dose-dependently increased the percentage of responses on the 4-AP-associated lever. In addition, 3-AP, 2-AP and 2,3-DIAP dose-dependently increased responses and fully substituted for 4-AP. 2,6-DIAP and 3,4-DIAP dose-dependently increased responses but only partially substituted for 4-AP; 4-DMAP and pyridine did not substitute for 4-AP. Comparisons were also made with indirect dopamine, norepinephrine, serotonin and acetylcholine agonists and gamma-aminobutyric acid A (GABA-A) agonists and antagonists. Tomoxetin but not nisoxetin or imipramine dose-dependently increased responses and partially substituted for 4-AP. In contrast, chlordiazepoxide and diazepam dose-dependently attenuated discriminative stimulus effects of 4-AP. Results suggest that 4-AP can be trained as a discriminative stimulus and these effects are mediated via suppression of voltage-dependent K^+ channels (1).

The plasma concentrations of i.v. 4-AP and its effects on cardiac ion channels were reported in a study conducted in dogs. Plasma levels of the agent increased during maintenance infusion but did not exceed 250 μmol/l. Although the maximum plasma concentration of 4-AP obtained *in vivo* had no effect on ventricular transient outward current (I_{to}) and only slight effects on atrial I_{to} in isolated myocytes *in vitro*, a potent inhibitory effect on the ultrarapid delayed rectifier ($I_{Kur.d}$) was seen in treated atrial cells. *In vitro* results were corroborated *in vivo* where doses of 25 and 50 μmol/l 4-AP were found to significantly increase the atrial refractory period without affecting the ventricular refractory period (2).

An open-label trial in 25 spinal cord injury patients with chronic incomplete injuries reported the absorption characteristics of sustained release 4-AP. The mean C_{max}, t_{max} and AUC_{0-12} values were 27.7 ± 6.2 ng/ml, 3.4 ± 1.4 h and 210.5 ± 49.5 ng/ml.h, respectively. $AUCt_{max}$ for tetraplegics (51.25 ± 20.36) was significantly less than in paraplegics (76.02 ± 33.28). In addition, a difference in the initial rate and extent of absorption over 12 h was observed between tetraplegics (0.60 ± 0.23) and paraplegics (0.39 ± 0.14) and linear correlations between level of injury and $C_{max}/AUCt_{max}$ were observed. No difference in total 4-AP bioavailability was observed between the subgroups (3).

Data from an open clinical trial of 4-AP in 15 patients with relapsing-remitting multiple sclerosis were presented. In this trial, the drug was given for 1 month at a dose of 10 mg i.m. b.i.d. and patients were examined for physical disability by the Kurtzke Expanded Disability Status Scale (EDSS), as well as by a battery of neuropsychological assessments. One-month treatment with 4-AP led to significant improvement in cognitive function (memory, praxis and executive functions) and in disability scores, especially in terms of motor, sensory and visual functions. It was suggested that the functional improvement induced by 4-AP may be related to improvement in the conductance of demyelinated nerves, while the cognitive improvements may involve facilitation of cholinergic transmission in the CNS (4).

Acorda is beginning a late-stage, phase II clinical trial of a sustained-release oral tablet formulation of fampridine developed by the company's partner Elan. The company expects to begin the trial for chronic spinal cord injury in the first quarter of 2000. Fampridine is a nerve conduction-enhancing compound that is the first therapy to improve neurological function in people with chronic spinal cord injury. The trial, which will be a double-blind, randomized and placebo-controlled study, will enroll 90 patients with chronic spinal cord injury at 10 leading rehabilitation centers in the U.S. Fampridine is also in phase II clinical studies for the treatment of multiple sclerosis. Prior clinical studies have included over 130 subjects with chronic spinal cord injury and over 200 multiple sclerosis patients. Patients in these trials showed improvement in a variety of functions. Depending on the individual, these improvements have included enhanced bladder, bowel and sexual function, increased ease of movement and sensation, and reduced muscle spasticity, fatigue and chronic pain. Fampridine is not yet approved for any therapeutic use (5).

Acorda has initiated a phase II study of fampridine for the treatment of multiple sclerosis. The study will enroll 30 patients at several sites in the U.S. (6).

1. Brandsgaard, R., Barrett, J.E., Rosenzweig-Lipson, S. *Pharmacological characterization of the discriminative stimulus effects of the potassium channel blocker 4-aminopyridine in rats.* J Pharmacol Exp Ther 2000, 295(1): 382.

2. Nattel, S., Matthews, C., De Blasio, E., Han, W., Li, D., Yue, L. *Dose-dependence of 4-aminopyridine plasma concentrations and electrophysiological effects in dogs. Potential relevance to ionic mechanisms in vivo.* Circulation 2000, 101(10): 1179.

3. Segal, J.L., Hayes, K.C., Brunnemann, S.R., Hsieh, J.T.C., Potter, P.J., Pathak, M.S., Tierney, D.S., Mason, D. *Absorption characteristics of sustained-release 4-aminopyridine (Fampridine SR) in patients with chronic spinal cord injury.* J Clin Pharmacol 2000, 40(4): 402.

4. Dobreva, D., Nikolova, G., Georgiev, D., Kmestska, K., Petrova, T., Traykov, L. *Therapeutic efficacy of 4-aminopyridine in multiple sclerosis.* 7th World Conf Clin Pharmacol Ther (July 15-20, Florence) 2000, Abst 717.

5. *Acorda to commence phase II clinical trial of lead product for spinal cord injury.* DailyDrugNews.com (Daily Essentials) Feb 16, 2000.

6. *Fampridine-SR enters phase II trials for MS.* DailyDrugNews.com (Daily Essentials) Nov 29, 2000.

Original monograph - Drugs Fut 1995, 20: 142.

Additional References

Medina Ceja, L. et al. *Action of 4-aminopyridine on extracellular amino acids in hippocampus and entorhinal cortex: A dual microdialysis and electroencehalographic study in awake rats.* Brain Res Bull 2000, 53(3): 255.

Mei, Y.A. et al. *4-Aminopyridine, a specific blocker of K^+ channels, inhibited inward Na^+ current in rat cerebellar granule cells.* Brain Res 2000, 873(1): 46.

Miyashita, T. et al. *4-Aminopyridine inhibits the occurrence of ventricular fibrillation but not ventricular tachycardia in the reperfused, isolated rat heart.* Jpn Circ J - Engl Ed 2000, 64(8): 602.

Petkova-Kirova, P. et al. *4-Aminopyridine affects rat arterial smooth muscle BK (Ca) currents by changing intracellular pH.* Br J Pharmacol 2000, 131(8): 1643.

Peuler, J. et al. *4-Aminopyridine blocks the relaxant effect of metformin on adrenergic contractions in arterial smooth muscle.* J Hypertens 2000, 18(Suppl. 4): Abst P32.02.

Pollock, N.S. et al. *4-AP negates trophic effects of FGF-2 on retinal ganglion cells in vitro.* Soc Neurosci Abst 2000, 26(Part 1): Abst 217.3.

Quan, L., Sobey, C.G. *Selective effects of subarachnoid hemorrhage on cerebral vascular responses to 4-aminopyridine in rats.* Stroke 2000, 31(10): 2460.

Sabbah, S., Scriba, G.K.E. *Development and validation of a capillary electrophoresis assay for the determination of 3,4-diaminopyridine and 4-aminopyridine including related substances.* J Chromatogr 2001, 907(1-2): 321.

Smith, K.J. et al. *Effects of 4-aminopyridine on demyelinated axons, synapses and muscle tension.* Brain 2000, 123(Part 1): 171.

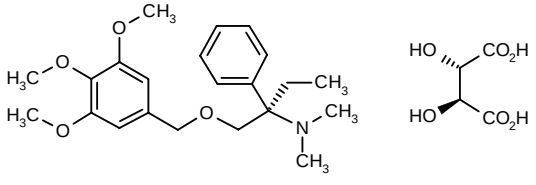
Traub, R.D. et al. *Model of synaptic and nonsynaptic contributions to giant IPSPS and ectopic spikes induced by 4-aminopyridine in the hippocampus in vitro.* Soc Neurosci Abst 2000, 26(Part 1): Abst 274.10.

Yang, C.R. et al. *Group I mGluR antagonists prevent, but AMPA antagonists block, 4AP-induced seizure in rat congulate cortical neurons in vitro.* Soc Neurosci Abst 2000, 26(Part 1): Abst 274.5.

Fedotozine Tartrate

Prokinetic
κ-Opioid Agonist

EN: 163822



$C_{22}H_{31}NO_4.C_4H_6O_6$ **Jouveinal; Pfizer**

A study using conscious rats examined the effects of fedotozine on acetic acid (AA; 0.6%, 10 ml/kg i.p.)-induced Fos expression. AA was shown to induce Fos expression (assessed 60 min after AA injection) in the thoraco-lumbar spinal cord (laminae IV, VII and X) and many brain structures including the nucleus tractus solitarius and paraventricular nucleus (PVN) of the hypothalamus. Pretreatment with capsaicin (14 days before AA injection) blocked Fos expression in all structures while pretreatment with fedotozine (20 min before AA injection) significantly decreased AA-induced abdominal cramps and Fos expression in the spinal cord and PVN; nor-binaltorphimine reversed the effects of fedotozine pretreatment (1).

1. Bonaz, B., Riviere, P.J.M., Sinniger, V., Pascaud, X., Junien, J.L., Fournet, J., Feuerstein, C. *Fedotozine, a κ-opioid agonist, prevents spinal and supra-spinal Fos expression induced by a noxious visceral stimulus in the rat.* Neurogastroenterol Motil 2000, 12(2): 135.

Original monograph - Drugs Fut 1992, 17: 101.

Additional Reference

De Schryver, A.M.P., Samsom, M. *New developments in the treatment of irritable bowel syndrome.* Scand J Gastroenterol 2000, 35(Suppl. 232): 38.

Glatiramer Acetate
Copolymer-1
Copaxone®

Treatment of Multiple Sclerosis

EN: 199999

Teva; Aventis Pharma; AutoImmune

The largest clinical study (CORAL) ever conducted in patients with multiple sclerosis will evaluate the efficacy of an oral tablet formulation of glatiramer acetate in patients with the relapsing-remitting form of the disease. The phase III CORAL study will last 56 weeks and aims to recruit 1300 participants in 18 countries. Patients in the randomized, double-blind, placebo-controlled study will receive a daily dose of 50 mg glatiramer acetate, 5 mg glatiramer acetate or a matching placebo (1).

Copaxone® (glatiramer acetate for injection) has been launched in the U.K., the product's first major European market, for reducing the frequency of relapses in relapsing-remitting multiple sclerosis. Recently published results of a 6-year follow-up trial with glatiramer acetate demonstrated a sustained clinical benefit and safety profile. The drug will be jointly marketed in the U.K. by Teva and Aventis (2).

1. *Global CORAL study will evaluate oral Copaxone in relapsing-remitting MS.* DailyDrugNews.com (Daily Essentials) April 28, 2000.

2. *Copaxone launched in the U.K.* DailyDrugNews.com (Daily Essentials) Dec 7, 2000.

Original monograph - Drugs Fut 1995, 20: 139.

Additional References

Dabbert, D. et al. *Glatiramer acetate (copolymer-1)-specific, human T cell lines: Cytokine profile and suppression of T cell lines reactive against myelin basic protein.* Neurosci Lett 2000, 289(3): 205.

Ge, Y. et al. *Glatiramer acetate (Copaxone) treatment in relapsing-remitting MS: Quantitative MR assessment.* Neurology 2000, 54(4): 813.

Gran, B. et al. *Mechanisms of immunomodulation by glatiramer acetate.* Neurology 2000, 55(11): 1704.

Johnson, K.P. et al. *Sustained clinical benefits of glatiramer acetate in relapsing multiple sclerosis patients observed for 6 years.* Multiple Scler 2000, 6(4): 255.

Kipnis, J. et al. *T cell immunity to copolymer 1 confers neuroprotection on the damaged optic nerve: Possible therapy for optic neuropathies.* Proc Natl Acad Sci USA 2000, 97(13): 7446.

La Mantia, L. et al. *Meta-analysis of clinical trials with copolymer 1 in multiple slcerosis.* Eur Neurol 2000, 43(4): 189.

Liu, C., Blumhardt, L.D. *Benefits of glatiramer acetate on disability in relapsing-remitting multiple sclerosis - An analysis by area under disability/time curves.* J Neurol Sci 2000, 181(1-2): 33.

Neuhaus, O. et al. *Multiple sclerosis: Comparison of copolymer-1-reactive T-cell lines from treated and untreated subjects reveals cytokine shift from T helper 1 to T helper 2 cells.* Proc Natl Acad Sci USA 2000, 97(13): 7452.

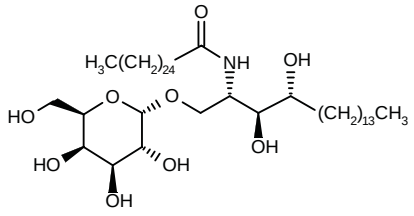
Schmied, M. et al. *Subcutaneous administration of glatiramer acetate induces antigen specific CD4 T cell tolerance.* Neurology 2000, 54(7, Suppl.3): Abst S23.004.

Windhagen, A. et al. *Glatiramer acetate (GLAT)-induced immune activation in patients with multiple sclerosis.* Neurology 2000, 54(7, Suppl.3): Abst P04.028.

KRN-7000

Immunostimulant
Oncolytic

EN: 222499



$C_{50}H_{99}NO_9$ **Kirin Brewery**

Results from an *in vitro* study using human natural killer (NK) T cells derived from peripheral blood mononuclear cells expressing the human Vα24+Vβ11+ T cell antigen receptor showed that the antitumor effects of KRN-7000 may occur via granule-mediated cell killing following activation of NK T cells. Dose-dependent stimulation of expansion was observed with KRN-7000 alone and synergistic stimulation was seen when the agent was combined with IL-15, IL-7 and IL-2. KRN-7000-expanded Vα24+Vβ11+ T cells were found to contain granzyme B-positive and perforin-positive granules which increased with addition of IL-15 but not IL-7 and IL-2 (1).

An *in vitro* study showed that α-glycosylceramides enhanced the antitumor activity of hepatic lymphocytes isolated from cancer patients against K562 and Colo201 tumor cell lines. Although proliferation of Vα24 NKT cells increased with α-glycosylceramide treatment, the effector cells responsible for the cytotoxicity were identified as CD3- CD56+ NK cells (2).

A study examined the antitumor activity of KRN-7000 (100 μg/kg i.v. on days 1, 5 and 9) as compared to IL-12 (1 μg/mouse i.p. days 1, 3, 5, 7 and 9) in mice with melanoma (B16) hepatic metastasis. KRN-7000 inhibited liver tumor growth and cured a high percentage of mice in a manner similar to IL-12. Immunohistological analysis showed that KRN-700 induced a significant infiltration of invasion of NK1.1+, CD8+ and F4/80+ cells into tumor nodules and liver-associated macrophages displayed strong lytic action against tumor cells (3).

The effects of treatment with KRN-7000 in a spontaneous hepatic metastasis model in mice transplanted with sarcoma M5076 were examined. Mice were transplanted with M5076 tumors followed by tumor excision on day 7 and treatment with KRN-7000 (100 mcg/kg i.v. on days 7, 11 and 15). The treatment was found to prolong survival in these animals, with increases in natural killer T-cell counts in the liver and in the production of interferon gamma and IL-12. The beneficial effects of KRN-7000 were abrogated by administration of an IL-12-neutralizing antibody. KRN-7000 thus appears to have potential for preventing hepatic metastasis following surgical removal of tumors (4).

A phase I study examined the efficacy and pharmacokinetics of KRN-7000 (50-2400 μg/m^2 weekly 5-min i.v. infusion for 3 weeks followed by 1-week rest) in 21 patients with solid tumors. No serious drug-related toxicities were observed. One patient developed a high fever within 4 h of infusion which was reduced within 24 h with paracetamol. Two patients developed facial edema that could be drug-related. Linear pharmacokinetics were obtained with no accumulation or saturation observed; the $t_{1/2}$ value was 36 h. Two patients exhibited slight increases in interferon-gamma and IL-4 with the first dose level; IL-12 and GM-CSF increased in several patients at all doses. Two patients given the highest dose showed increased NK activity and the majority of the patients showed NKT cell disappearance from peripheral blood 24 h after KRN-7000 administration. Accrual continues with 4800 μg/m^2 during a 30-min infusion (5).

1. Nishi, N., Van der Vliet, H.J.J., Koezuka, Y., Von Blomberg, B.M.E., Scheper, R.J., Pinedo, H.M., Giaccone, G. *Synergistic effect of KRN7000 with interleukin-15,-7, and -2 on the expansion of human Vα24+Vβ11+ T cells in vitro.* Hum Immunol 2000, 61(4): 357.

2. Ishihara, S., Nieda, M., Osada, T., Kitayama, J., Yabe, T., Kikuchi, A., Koezuka, Y., Polcelli, S.A., Tadokoro, K., Nagawa, H., Juji, T. *α-Glycosylceramides enhance the antitumor cytotoxicity of hepatic lymphocytes obtained from cancer patients, by activating CD3-CD56+ NK cells in vitro.* Proc Jpn Soc Immunol 2000, 30: Abst 1-E-234-P.

3. Nakagawa, R., Serizawa, I., Motoki, K., Sato, M., Ueno, H., Iijima, R., Nakamura, H., Shimosaka, A., Koezuka, Y. *Antitumor activity of α-galactosylceramide, KRN7000, in mice with the melanoma B16 hepatic metastasis and immunohistological study of tumor infiltrating cells.* Oncol Res 2000, 12(2): 51.

4. Fuji, N. et al. *Characterization of the antitumor effects of α-galactosylceramide (KRN 7000) in a marine model of spontaneous hepatic metastasis.* Nihon Gan Chiryo Gakkai-shi 2000, 35(2): Abst P-784.

5. Giaccone, G., Punt, C., Ando, Y. et al. *KRN7000, an NKT cell enhancer, in patients with solid tumors - A phase I study of the EORTC BTDG.* Proc Am Soc Clin Oncol 2000, 19: Abst 1871.

Original monograph - Drugs Fut 1996, 21: 152.

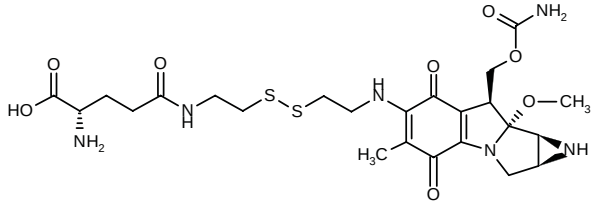
Additional Reference

Nicol, A. et al. *Human invariant Vα 24(+) natural killer T cells activated by α-galactosylceramide (KRN7000) have cytotoxic antitumour activity through mechanisms distinct from T cells and natural killer cells.* Immunology 2000, 99(2): 229.

KT-6149
KW-2149

Antineoplastic Antibiotic

EN: 142017



$C_{24}H_{34}N_6O_8S_2$ **Kyowa Hakko**

A recent report described a novel gradient high performance liquid chromatography method involving sample clean-up by solid-phase extraction on C-18 columns and separation on a YMC ODS-AQ column for simultaneously determining plasma KW-2149 and its 2 major metabolites (M-16 and M-18). The limits of quantitation were 10 ng/ml for KW-2149 and M-16 and 15 ng/ml for M-18, with recoveries of greater than 92% achieved. %CV values (intraday precision) ranged from 1.4-6.5% while intraday accuracy ranged from 94-107%. Interassay precision and accuracy values tended to be increased but were adequate (1).

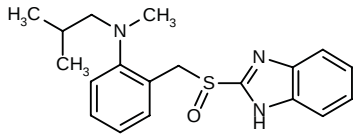
1. Zhang, Z.D., Guetens, G., DeBoeck, G., Van Cauwenberghe, K., Maes, R.A.A., Ardiet, C., Van Oosterom, A.T., Highley, M., de Brujin, E.A., Tjaden, U.R. *Simultaneous determination of the peptide-mitomycin KW-2149 and its metabolites in plasma by high-performance liquid chromatography.* J Chromatogr B - Biomed Sci Appl 2000, 739(2): 281.

Original monograph - Drugs Fut 1989, 14: 127.

Leminoprazole
Leminon®

Antiulcer
H^+/K^+-ATPase Inhibitor

EN: 175342



$C_{19}H_{23}N_3OS$ **Nippon Chemiphar; Kyorin**

Nippon Chemiphar has decided to withdraw the company's application for approval of leminoprazole tablets (Leminon 80®) (1).

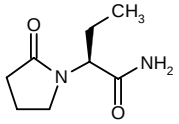
1. *Nippon Chemiphar withdraws Leminon 80 application for approval in Japan.* DailyDrugNews.com (Daily Essentials) Dec 15, 1999.

Original monograph - Drugs Fut 1996, 21: 155.

Levetiracetam
Keppra®

Antiepileptic

EN: 113936



$C_8H_{14}N_2O_2$ **UCB**

The pharmacokinetics of levetiracetam and its (*R*)-enantiomer (REV) were examined in dogs following i.v. administration. Although there were no significant differences observed in clearance (0.090 ± 0.020 l/h·kg) or volume of distribution (0.45 ± 0.13 and 0.51 ± 0.11 l/kg, respectively) for levetiracetam and REV, half-life (3.6 ± 0.8 *vs.* 4.3 ± 0.8 h, respectively), mean residence time (5 ± 1.2 *vs.* 6 ± 1.1 h, respectively), renal clearance (0.77 ± 0.21 *vs.* 1.10 ± 0.3 l/h, respectively) and the fraction excreted unchanged (50 ± 5 *vs.* 71 ± 10%, respectively) for the two compounds were significantly different. Renal clearance was less than the glomerular filtration rate, possibly indicating that tubular reabsorption is responsible for the enantioselectivity seen in renal clearance. No chiral inversion of levetiracetam to REV or *vice versa* was observed (1).

A placebo-controlled, randomized study in 246 patients with refractory partial onset seizures showed that levetiracetam (1000 or 3000 mg) as an add-on therapy improved scores on the 31-item Quality of Life in Epilepsy questionnaire. Significant differences were seen in total scores and in seizure worry, overall quality of life and cognitive functioning domains. Responders (≥ 50% reduction

in partial seizure onset) displayed improvements in all areas except medication effect as compared to nonresponders. Responders on 3000 mg showed clinically noticeable improvement (10% changes from baseline to follow-up) in all areas except emotional well-being; clinically noticeable improvement in the 1000 mg responders group occurred in 5/9 areas as compared to 2/9 areas in the placebo group (2).

A multicenter, randomized, double-blind, placebo-controlled, responder-selected study in 286 patients with refractory partial seizures showed the efficacy and tolerability of switching from levetiracetam as an add-on (1500 mg b.i.d. p.o. for 12 weeks) in responders to a monotherapy (12 weeks of downtitration and 12 weeks of 1500 mg b.i.d.). Of the 181 patients who received levetiracetam, 36 completed the study as compared to only 10 of the 105 on placebo. Responder rates during the add-on phase were significantly higher (42.1%) in levetiracetam-treated patients as compared to placebo (16.7%). The median percent reduction in partial seizure frequency as compared to baseline was 73.8% in the levetiracetam monotherapy group, with 18.4% of the patients seizure-free throughout treatment (3).

Pooled results from 3 double-blind, placebo-controlled trials conducted in a total of 904 patients with partial seizures showed the efficacy of levetiracetam (1000, 2000 or 3000 mg). The response rates (≥ 50% reduction in partial seizure frequency) increased with levetiracetam dose and were 27.7, 31.6 and 41.3%, respectively, as compared to 12.6% for placebo. At the end of the studies, significantly more levetiracetam-treated patients were seizure-free as compared to placebo (6.3 *vs.* 0.4%). The safety of levetiracetam was evaluated from the results of these 3 trials plus another trial involving patients with both partial and primarily generalized seizures; a total of 1023 patients were included. Significantly higher incidence of adverse events was observed in the levetiracetam group as compared to placebo. Adverse events included asthenia (14.1% *vs.* 9.7% in placebo), somnolence (14.9% *vs.* 9.7%), dizziness (9.2% *vs.* 4.3%) and infection (13.2% *vs.* 7.4%). No significant difference was observed in the rate of patients discontinuing due to adverse events or requiring dose reductions between the levetiracetam (15%) and placebo (11.6%) groups (4).

A dose-escalation, placebo-controlled study in 29 patients with refractory epilepsy showed the efficacy and tolerability of levetiracetam. Patients were treated consecutively with the following: placebo for 4 weeks, 1000 and 2000 mg/day levetiracetam for 2 weeks, and 3000 and 4000 mg/day levetiracetam for 4 weeks. Twenty-seven patients completed all periods. Median seizure frequency was markedly lower in all levetiracetam dose groups (1, 1.5, 1 and 0.75 seizures/week for 1000, 2000, 3000 and 4000 mg/day, respectively, *vs.* 2.06 seizure/week in placebo), with 22-33% (*vs.* 14% in placebo) of the patients seizure-free during treatment periods. The agent was well tolerated. Somnolence and asthenia were the most common adverse effects which increased with increasing doses of the agent (5).

Levetiracetam was shown to be effective and well tolerated as an add-on in a randomized, 24-week double-blind, placebo-controlled (2000 or 4000 mg/day p.o.) trial with a 24-week open-label phase (4000 mg/day) in 119 patients with refractory epilepsy. Somnolence and asthenia were seen more often in the levetiracetam groups (particularly the 4000 mg group) and were the most common reasons for discontinuation. Higher responder rates were achieved in the levetiracetam groups (48.1 and 28.6%, respectively) as compared to placebo (16.1%), with a significant difference observed between the 4000 mg and placebo groups. The overall responder rate in the open-label phase was 43%. Responder rates were not changed after switching from 2000 to 4000 mg levetiracetam, suggesting similar effects with both doses; switching from placebo to 4000 mg levetiracetam increased responder rates from 16.7% to 44% (6).

Levetiracetam demonstrated tolerability and significantly reduced seizure frequency in a multicenter clinical trial of patients with more than a 2-year history of refractory partial seizure epilepsy. Patients with a minimum of 12 seizures per 12 weeks entered a 12-week single-blind placebo baseline period and were then randomized to placebo, levetiracetam 1000 mg/day or levetiracetam 3000 mg/day. The baseline period was followed by a 4-week, double-blind upward titration period and 14 weeks of fixed-dose treatment. Previously established regimens of 1 or 2 antiepileptic drugs were continued during the study. Compared with placebo, the levetiracetam groups experienced 30.1% and 26.1% reductions in weekly partial seizure frequency for the 3000 mg and 1000 mg groups, respectively. The drug acted rapidly, with declines in weekly seizure frequency seen in the levetiracetam groups during the first 2 weeks of the titration period. A reduction of at least 50% in partial seizure frequency was experienced by 33%, 39.8% and 10.8% of subjects in the levetiracetam 1000 mg, levetiracetam 3000 mg and placebo groups, respectively. Treatment-emergent adverse events (≥ 10%) with incidences higher than placebo were asthenia, dizziness, flu syndrome, headache, infection, somnolence and rhinitis. At the study's end, only 2 of 268 patients chose to discontinue levetiracetam, the rest opting to enter a 1-year, open-label follow-up program (7).

The Swiss Health Authority has approved levetiracetam (Keppra® as a new treatment option for epilepsy. Clinical trials have shown that it significantly reduces the frequency of partial seizures when added to current therapy (8).

Levetiracetam (Keppra®) was introduced in the U.S. in April 2000 as adjunctive therapy in the treatment of partial-onset seizures in adults. The mechanism of the antiepileptic activity of levetiracetam has not been established, although it appears not to involve interactions with known mechanisms involved in inhibitory and excitatory neurotransmission. The drug is supplied as tablets of 250 mg, 500 mg and 750 mg and is usually given initially as 500 mg twice daily up to a maximum recommended daily dose of 3000 mg (9).

The European Medicines Evaluation Agency has approved levetiracetam (Keppra®), which will be sold progressively in the different countries of the E.U. as of November 2000 (10).

1. Isoherranen, N., Yagen, B., Roeder, M., Soback, S., Schuring, V., Bialer, M. *Stereoselective pharmacokinetic analysis of levetiracetam and its enantiomer in dogs.* 5th Eilat Conf New Antiepileptic Drugs (June 25-29, Eilat) 2000, 69.

2. Cramer, J.A., Arrigo, C., Van Hammee, G., Gauer, L.J., Cereghino, J.J. *Effect of levetiracetam on epilepsy-related quality of life.* Epilepsia 2000, 41(7): 868.

3. Ben Menachem, E., Falter, T. *Efficacy and tolerability of levetiracetam 3000 mg/d in patients with refractory partial seizures: A multicenter, double-blind, responder-selected study evaluating monotherapy.* Epilepsia 2000, 41(10): 1276.

4. Betts, T. *Levetiracetam (LEV) in partial seizures: Pooled data from 3 double-blind placebo controlled studies.* Int J Neuropsychopharmacol 2000, 3(Suppl. 1): Abst P.06.03.

5. Grant, R., Shorvon, S.D. *Efficacy and tolerability of 1000-4000 mg per day of levetiracetam as add-on therapy in patients with refractory epilepsy.* Epilepsy Res 2000, 42(2-3): 89.

6. Betts, T., Waegemans, T., Crawford, P. *A multicentre, double-blind, randomized, parallel group study to evaluate the tolerability and efficacy of two oral doses of levetiracetam, 2000 mg daily and 4000 mg daily, without titration in patients with refractory epilepsy.* Seizure 2000, 9(2): 80.

7. Cereghino, J.J., Biton, V., Abou-Khalil, B., Dreifuss, F., Gauer, L.J., Leppik, G.I. *Levetiracetam for partial seizures - Results of a double-blind, randomized clinical trial.* Neurology 2000, 55(2): 236.

8. *Keppra receives Swiss approval for treatment of epilepsy.* DailyDrugNews.com (Daily Essentials) April 12, 2000.

9. *First market launch for novel antiepileptic drug Keppra.* DailyDrugNews.com (Daily Essentials) May 19, 2000.

10. *Keppra receives E.U. approval for treatment of epilepsy.* DailyDrugNews.com (Daily Essentials) Oct 3, 2000.

Original monograph - Drugs Fut 1994, 19: 111.

Additional References

French, J.A. et al. *Rapid onset of action of levetiracetam in refractory epileptic patients.* Neurology 2000, 54(7, Suppl.3): Abst S16.001.

French, J.A. *Levetiracetam.* 5th Eilat Conf New Antiepileptic Drugs (June 25-29, Eilat) 2000, 41.

Krakow, K. et al. *Long-term efficacy and tolerability of levetiracetam (LEV) in refractory epilepsy.* Neurology 2000, 54(7, Suppl.3): Abst S16.002.

Krauss, G.L. et al. *Suppression of posthypoxic and postencephalitic myoclonus with levetiracetam.* Neurology 2001, 56(3): 411.

Leppik, I. et al. *Seizure-free days gained with levetiracetam in refractory epileptic patients.* Neurology 2000, 54(7, Suppl.3): Abst P04.116.

Loscher, W. et al. *Anticonvulsant efficacy of gabapentin and levetiracetam in phenytoin-resistant kindled rats.* Epilepsy Res 2000, 40(1): 63.

Loscher, W., Richter, A. *Piracetam and levetiracetam, two pyrrolidone derivatives, exert antidystonic activity in a hamster model of paroxysmal dystonia.* Eur J Pharmacol 2000, 391(3): 251.

Margineanu, D.G., Klitgaard, H. *Inhibition of neuronal hypersynchrony in vitro differentiates levetiracetam from classical antiepileptic drugs.* Pharmacol Res 2000, 42(4): 281.

Niespodziany, I. et al. *Levetiracetam had no effects on the low-voltage-activated (T-type) Ca^{2+} current in rat CA1 hippocampal neurons.* Neurology 2000, 54(7, Suppl.3): Abst P04.117.

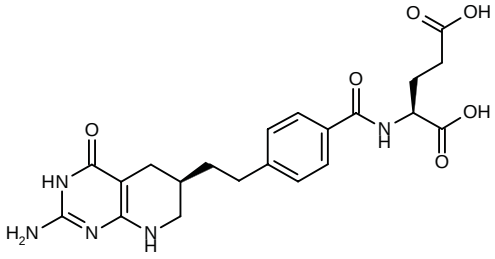
Patsalos, P.N. *Pharmacokinetic profile of leviracetam: Toward ideal characteristics.* Pharmacol Ther 2000, 85: 77.

Shorvon, S.D. et al. *Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures.* Epilepsia 2000, 41(9): 1179.

Lometrexol

Oncolytic

EN: 166355



$C_{21}H_{25}N_5O_6$ **Lilly; Tularik**

Tularik has initiated phase II efficacy and phase I combination studies at major cancer centers worldwide for its anticancer compound lometrexol. Phase II studies will be conducted in cancer centers in the U.S., the U.K. and Australia. These studies will include patients with soft tissue sarcoma, melanoma, breast cancer, non-small cell lung cancer, and head and neck cancer. Lometrexol is being evaluated in phase I combination studies with temozolomide, doxorubicin, carboplatin, gemcitabine and paclitaxel at cancer centers in the U.S., the U.K. and The Netherlands. Tularik is developing this compound under license from Lilly (1).

1. *Tularik initiates phase II studies of T-64 for treatment of solid tumors.* DailyDrugNews.com (Daily Essentials) July 19, 2000.

Original monograph - Drugs Fut 1993, 18: 121.

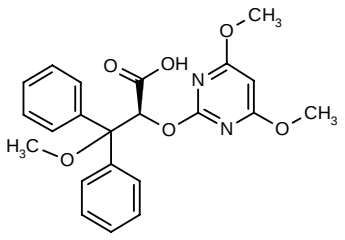
Additional Reference

Roberts, J.D. et al. *Weekly lometrexol with daily oral folic acid is appropriate for phase II evaluation.* Cancer Chemother Pharmacol 2000, 45(2): 103.

LU-135252
HMR-4005
Darusentan

Treatment of Restenosis
Antihypertensive
Treatment of Heart Failure
Endothelin ET_A Antagonist

EN: 231818



$C_{22}H_{22}N_2O_6$

Aventis Pharma; Knoll

A study using rats with chronic heart failure following myocardial infarction showed the efficacy of LU-135252 (30 mg/kg/day) in restoring renal function. LU-135252 treatment prevented decreases in creatinine clearance and increased urinary excretion of endothelin, while fractional sodium and protein excretion and plasma endothelin levels were unaffected. Results suggest that the agent may be a potential treatment for renal insufficiency in chronic heart failure patients (1).

LU-135252 (0.5, 1 and 5 mg/kg/day i.v. via osmotic pump for 4 days) was shown to dose-dependently improve kidney function in a rat model of acute ischemic renal failure (clamping of both renal arteries for 40 min). Treatment did not alter creatinine clearance. Only the highest dose was effective in significantly ameliorating the increase in serum creatinine and decreasing fractional sodium excretion on days 1 and 2 (2).

LU-420627 (50 mg/kg/day for 3 weeks) was shown to be more effective than LU-135252 in a rat model of monocrotaline (60 mg/kg)-induced pulmonary hypertension and right ventricular hypertrophy. Blocking both ET_A and ET_B receptors resulted in better improvements in this model. Significantly increased survival at 5 weeks was observed in the group receiving LU-420627 (67%) as compared to controls (38%) and animals treated with LU-135252 (56%). Both agents significantly improved pulmonary hypertension with right systolic pressures of 72 ± 3 and 67 ± 3 mmHg obtained for the LU-135252 and LU-420627 groups, respectively, as compared to 87 ± 1 mmHg seen in controls. Although LU-135252 had no effect on right ventricular hypertrophy, LU-420627 significantly reduced it to 54 ± 3% (*vs.* 71-72% in controls and LU-135252-treated animals). Both agents significantly improved pulmonary resistive properties (*e.g.*, flow rate and pulmonary pressure) (3).

An *in vivo* study in rats with myocardial infarction and overt congestive heart failure showed that 6-week treatment with LU-135252 (50 mg/kg/day starting 6 months after myocardial infarction) ameliorated heart failure indices and increased nitric oxide (NO) metabolite content in the right but not left ventricle. Treatment with the agent prevented the decrease in systolic blood pressure, attenuated the increase in body weight and decreased the right ventricular weight/total heart weight ratio seen in untreated animals. In addition, nitrate levels in the right ventricular myocardium were significantly increased (3.7 ± 1 *vs.* 1.5 ± 0.2 μmol/mg protein). [^{125}I]-ET_1 clearance was not altered by treatment. It was concluded that chronic blockade of the ET_A receptor in infarcted hearts selectively affects the L-arginine/NO pathway (4).

A study using rats with liquorrhice (gycyrrhetinic acid 302 ± 21 mg/kg/day for 21 days in drinking water)-induced hypertension showed the efficacy of LU-135252 (45.2 ± 6.5 mg/kg/day on days 8-12) treatment in normalizing blood pressure and improving endothelial function. LU-135252 treatment significantly decreased systolic blood pressure (SBP) during treatment (189 ± 8 *vs.* 146 ± 7 mmHg). Experiments using isolated aortic rings from treated animals showed that treatment significantly improved acetylcholine-induced endothelium-dependent relaxation (5).

Results from a study using a rat model of chronic allograft rejection showed that the efficacy of LU-135252 (30 mg/kg i.v. bolus) in this model was not due to improvements in renal hemodynamics but possibly via antiinflammatory and immune responses (6).

Results from a study using a porcine model of acute lung injury (ALI; surfactant depletion via repetitive lung lavages) showed that LU-135252 (3 mg/kg inhaled over 1 h) significantly improved arterial oxygenation and maintained stable pulmonary artery pressure without systemic vasodilation. LU-135252 treatment decreased intrapulmonary right-left shunting (58 ± 8 to 27 ± 12 and 24 ± 9% at 3 and 6 h post-ALI, respectively) and increased PaO_2 (55 ± 12 to 257 ± 148 and 270 ± 136 mmHg at 3 and 6 h post-ALI, respectively). Cardiac output was also significantly decreased (by 31 ± 11%) and systemic vascular resistance significantly increased (by 60 ± 29%) in treated animals (7).

A study using rats with experimental chronic heart failure 12 weeks after myocardial infarction showed the efficacy of LU-135252 (30 mg/kg/day p.o. starting day 7 postsurgery) in improving pulmonary vasoreactivity. Pulmonary arterial pressure was normalized with LU-135252 treatment (9 ± 0.3 *vs.* 12.6 ± 0.5 and 8.9 ± 0.2 mmHg in untreated and sham animals, respectively) and treatment also significantly suppressed the irreversible increase in pulmonary pressure seen in untreated animals following injection of ET-1 (10 nM) into the pulmonary artery (8).

A study using subtotally nephrectomized rats examined the effects of LU-135252 on flow and mesenteric arterial remodeling. The agent prevented renal failure-induced increases in the intimal and media thickness of low flow arteries. The increase in proliferating cell nuclear antigen seen in high flow mesenteric artery media was also suppressed by treatment with the agent (9).

An *in vivo* study in dogs subjected to 90 min of LAD occlusion and 180 min of reperfusion showed the protective effects of LU-135252 (5 mg/kg i.v. bolus 5 min before

LAD reopening) as assessed using myocardial contrast echocardiography. At 180 min of reperfusion, microvascular flow (89 ± 4% *vs.* 70 ± 7.4% of baseline) and myocardial thickness (108.9 ± 7.4% *vs.* 138.6 ± 9.9% of baseline) were significantly decreased and increased, respectively, in control animals as compared to LU-135252-treated animals (10).

Chronic heart failure (CHF) is associated with impaired endothelium-dependent vasodilatation and increased basal vascular tone, partly due to elevated plasma ET-1 levels. A study therefore evaluated the effects of LU-135252 on endothelial function in CHF patients. Twenty-one patients with CHF were randomized to receive LU-135252 (30 or 300 mg/day) or placebo for 3 weeks and assessed for baseline and end-of-treatment flow-mediated vasodilatation (FMD), as a measure of the ability of blood vessels to dilate, thereby increasing blood flow, using high-resolution ultrasound. All CHF patients showed impaired FMD at study entry compared to 11 control patients. This parameter significantly improved in all 14 LU-135252-treated patients compared to baseline, but not in placebo-treated patients. However, subgroup analysis demonstrated a significant increase in FMD compared to baseline only in patients receiving the lower dose of LU-135252. The lack of a significant effect on impaired FMD in those given the higher dose of LU-135252 was suggested to be due to the significant increase seen in brachial artery diameter in this group. The big ET-1 plasma levels were elevated in the CHF patients compared to controls, but LU-135252 had no significant effect. Although preliminary and limited to assessing the effect on blood flow, this study indicates potential for selective ET_A receptor antagonists in improving endothelium-dependent vasodilatation in CHF (11).

Results from a multicenter study conducted in 95 patients with congestive heart failure (NYHA II-III; ejection fraction < 35%) showed that single-dose LU-135252 (1, 10, 30, 100 or 300 mg p.o.) was well tolerated and dose-dependently improved hemodynamics. Significant and dose-dependent increases in cardiac index and decreases in mean arterial pressure, right arterial pressure, MPAP, PCWP and systemic and pulmonary vascular resistance were observed with treatment; heart rate and plasma catecholamines were not altered. Although 1 mg had no effect on plasma ET-1 at 2 h postdosing, significant increases of 23, 29, 56 and 101% were seen with the respective remaining doses (12).

The hemodynamic and neurohumoral effects of LU-135252 have been examined and compared to placebo in a multicenter, placebo-controlled trial in 31 patients with severe heart failure randomized to receive LU-135252 at doses of 30, 100 or 300 mg or placebo, in addition to standard ACE inhibitors, for 3 weeks. Beneficial hemodynamic effects included a significant increase in cardiac index and significant decreases in mean pulmonary artery pressure, heart rate and mean arterial blood pressure after 3 weeks of treatment with LU-135252, and neurohumoral benefits, including a significant decrease in plasma BNP levels, were also described (13).

Results from a multicenter, double-blind, placebo-controlled study conducted in 179 patients with congestive heart failure (NYHA III; ejection fraction < 35%; cardiac index < 2.8 ml/min/m^2; PCWP > 12 mmHg) on standard medication showed that a single oral dose of LU-135252 (1, 10, 30, 100 or 300 mg) was well tolerated and dose-dependently improved hemodynamics (14).

Darusentan is the proposed international nonproprietary nane for LU-135252 (15).

1. Bauersachs, J., Braun, C., Fraccarollo, D., Widder, J., Ertl, G., Schilling, L., Kirchengast, M., Rohmeiss, P. *Improvement of renal dysfunction in rats with chronic heart failure after myocardial infarction by treatment with the endothelin A receptor antagonist, LU 135252.* J Hypertens 2000, 18(10): 1507.

2. Knoll, T., Birck, R., Braun, C., Kirchengast, M., van der Woude, F., Rohmeiss, P., Junemann, K.-P. *Dose-dependent effect of the endothelin receptor A antagonist LU 135252 in a rat model of acute ischaemic renal failure.* J Hypertens 2000, 18(Suppl. 4): Abst P34.28.

3. Jasmin, J.-F., Dupuis, J. *Superiority of mixed $ET_{A/B}$ over specific ET_A antagonist in treatment of pulmonary hypertension and right ventricular hypertrophy in the monocrotaline rat model.* J Am Coll Cardiol 2000, 35(2, Suppl. A): 323A.

4. Barton, M., Vetter, D., d'Uscio, L.V., Brandes, R.P., Lattmann, T., Lyuzkanov, G., Lüscher, T.F., Shaw, S. *Endothelin ET_A receptor blockade ameliorates heart failure indices and increases NO metabolite content in right but not left ventricle in long-term survivors of myocardial infarction.* Eur Heart J 2000, 21(Suppl.): Abst 2624.

5. Quaschning, T., Ruschitzka, F.T., Lunt, C.M.B., Niggli, B., Shaw, S., Lüscher, T.F. *Endothelin receptor antagonism normalizes blood pressure and restores endothelial function in liquorrhice-induced hypertension.* Eur Heart J 2000, 21(Suppl.): Abst P607.

6. Knoll, T., Oltersdorf, J., Braun, C., Kirchengast, M., van der Woude, F., Rohmeiss, P., Jynemann, K.-P. *Influence of selective endothelin-A-receptor blockade on renal hemodynamics in a rat model of chronic allograft rejection.* J Hypertens 2000, 18(Suppl. 4): Abst P34.29.

7. Kaisers, U., Busch, T., Wolf, S., Lohbrunner, H., Wilkens, K., Hocher, B., Boemke, W. *Inhaled endothelin A antagonist improves arterial oxygenation in experimental acute lung injury.* Intensive Care Med 2000, 26(9): 1334.

8. Bauersachs, J., Hu, K., Ertl, G., Koch, T.H., Hagebeuker, A., Konrad, C., Schmeck, J. *Pulmonary vasoreactivity in rats with heart failure following myocardial infarction: Effect of long-term oral therapy with the selective endothelin-A receptor antagonist LU 135252.* Eur Heart J 2000, 21(Suppl.): Abst 3252.

9. Miltenberger-Miltényi, G., Simonaviciene, A., Koch, A., Ritz, E., Amann, K. *Flow and arterial remodeling in renal failure? Effect of endothelin receptor blockade.* 37th Congr Eur Renal Assoc - Eur Dialysis Transpl Assoc (Sept 17-20, Nice) 2000, 170.

10. Galiuto, L., De Maria, A.N., del Balzo, U., May-Newman, K., Flaim, S.F., Wolf, P.L., Kirchengast, M., Iliceto, S. *Ischemia-reperfusion injury at the microvascular level. Treatment by endothelin A-selective antagonist and evaluation by myocardial contrast echocardiography.* Circulation 2000, 102(25): 3111.

11. Berger, R., Hülsmann, M., Stanek, B., Frey, B., Heher, S., Pacher, R., Neunteufl, T. *Effects of endothelin A receptor block-*

ade on endothelial function in patients with chronic heart failure. Circulation 2001, 103(7): 981.

12. Noll, G., Spieker, L.E., Pacher, R., Mitrovic, V., Schulze, M., Schalcher, C., Kiowski, W., Luscher, T.F. *Acute haemodynamic effects of selective ET_A receptor blockade in patients with congestive heart failure.* Eur Heart J 2000, 21(Suppl.): Abst 708.

13. Bergler-Klein, J., Pacher, R., Berger, R., Bojic, A., Boltzmann, L., Stanek, B. *Neurohumoral and hemodynamic effects fo the selective endothelin antagonist LU 135252 in advanced heart failure.* Circulation 2000, 102(18, Suppl.): Abst 2871.

14. Ruschitzka, F., Noll, G., Mitrovic, V., Pacher, R., Corti, R., Kiowski, W., Enseleit, F., Lüscher, T.F. *Clinical and haemodynamic effects of chronic selective ET_A receptor blockade in congestive heart failure (HEAT, Heart Failure ET_A Receptor Blockade Trial).* Eur Heart J 2000, 21(Suppl.): Abst 705.

15. *Proposed international nonproprietary names (Prop. INN): List 82.* WHO Drug Inf 1999, 13(4): 270.

Original monograph - Drugs Fut 1999, 24: 141.

Additional References

Jansen, R. et al. *Structural similarity and its suprises: Endothelin receptor antagonists - Process research and development report.* Org Process Res Dev 2001, 5(1): 16.

Kiss, O. et al. *Endothelin-A-receptor antagonist LU 135.252 inhibits the formation of ventricular arrhythmias caused by intrapericardial infusion of endothelin-1.* J Cardiovasc Pharmacol 2000, 36(5, Suppl. 1): S317.

Merkely, B. et al. *The selective endothelin-A-receptor antagonist LU 135.252 inhibits the direct arrhythmogenic action of endothelin-1.* J Cardiovasc Pharmacol 2000, 36(5, Suppl. 1): S314.

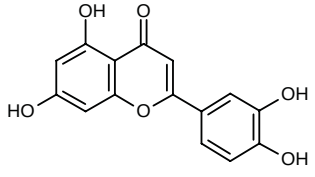
Quaschning, T. et al. *ET_A receptor antagonism prevents vascular dysfunction and hypertension induced by 11beta-hydroxysteroid dehydrogenase inhibition: Role of nitric oxide and endothelin.* Circulation 2000, 102(18, Suppl.): Abst 816.

Szabó, T. et al. *LU 135252 the selective endothelin A-receptor antagonist inhibits the direct arrhythmogenic action of endothelin-1.* J Heart Failure 2000, 6(1): Abst 441.

Luteolin

Antiinflammatory

EN: 244028



$C_{15}H_{10}O_6$ **Inst. Materia Med.; Chin. Acad. Med. Sci.**

A study examined the efficacy of luteolin (200 ppm in diet for) against azoxymethane (15 mg/kg s.c. once/week for 3 weeks)-induced colon carcinogenesis in rats. At 40 weeks, luteolin tended to decrease tumor development in the large intestine. Tumor development rates in the large intestine were 52-57% as compared to 61% in untreated animals (1).

1. Matsunaga, K., Yoshimi, N., Yamada, Y., Shimizu, M., Kuno, T., Katayama, M., Hirose, Y., Mori, H. *Effect of luteolin on azoxymethane-induced colon carcinogenesis in rats.* Jpn J Cancer Res 2000, 91(Suppl.): Abst 3889.

Original monograph - Drugs Fut 2000, 25: 146.

Additional References

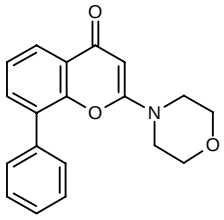
Chan, E.C.H. et al. *Relaxation to flavones and flavonols in rat isolated thoracic aorta: Mechanism of action and structure-activity relationships.* J Cardiovasc Pharmacol 2000, 35(2): 326.

Lee, M.-T. et al. *Molecular mechanism of growth inhibition and apoptosis induced by luteolin and quercetin, in MiaPaCa2 cells expression EGF receptors.* Proc Amer Assoc Cancer Res 2000, 41: Abst 2583.

LY-294002

Oncolytic

EN: 209179



$C_{19}H_{17}NO_3$ **Lilly**

The ability of LY-294002 to dephosphorylate proapoptotic proteins and thereby promote apoptosis in myeloid leukemia cells has been examined. The results showed that incubation of cytokine-dependent MO7E cells with LY-294002 inhibited AKT kinase activity, dephosphorylated AKT and BAD and induced apoptosis. Inhibition of cell growth and clonogenicity was seen in primary AML cells following culture with LY-294002, and it acted synergistically with all-*trans*-retinoic acid (ATRA) to induce apoptosis in these cells, whereas normal bone marrow progenitor cells were not affected. Thus, it appears that LY-294002 is able to selectively promote apoptosis in leukemia cells (1).

An *in vitro* study reported the synergistic effects of LY-294002 pretreatment (1 mcg/ml for 30 min) followed by doxorubicin (8-1000 ng/ml for 48 h) in MDA-MB-231 breast cancer cells. Synergy was observed with the doxorubicin doses of 8 and 10 ng/ml. Growth inhibition was 45% with doxorubicin alone as compared to 61 and 72% when 8 and 10 ng/ml of the agent, respectively, were combined with LY-294002. LY-294002 alone resulted in 43% growth inhibition. Combination treatment resulted in enhanced arrest in the G_2 phase; no DNA fragmentation was observed (2).

1. Zhao, S., Konopleva, M., Xie, Z., Hu, W., Estrov, Z., Milella, M., Mills, G. *Inhibition of PI3K by LY294002 promotes apoptosis and dephosphorylates BAD in myeloid leukemias.* Blood 2000, 96(11, Part 1): Abst 416.

2. McCarragher, L.S.M., Al-Sakkaf, , K.A., Brown, B.L., Dobson, P.R.M. *Synergestic effects between LY294002, a specific PI-3 kinase inhibitor and doxorubicin in MDA-MB-231 breast cancer cells.* Br J Cancer 2000, 83(Suppl. 1): Abst P154.

Original monograph - Drugs Fut 1995, 20: 165.

Additional References

Bakin, A.V. et al. *Phosphatidylinositol-3 kinase is required for epithelial mesenchymal transition induced by TGF-β_1 in mammary epithelial cells.* Proc Amer Assoc Cancer Res 2000, 41: Abst 4538.

Clutton, P.M. et al. *Inhibition of platelet PI3-kinase leads to platelet disaggregation and enhanced release of platelet-derived nitric oxide.* FASEB J 2000, 14(4): Abst 332.4.

Guo, M. et al. *Suppression of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-mediated aryl hydrocarbon receptor transformation and CYP1A1 induction by the phosphatidylinositol 3-kinase inhibitor 2-(4-morpholinyl)-8-phenyl-4H-1-benzopyran-4-one (LY294002).* Biochem Pharmacol 2000, 60(5): 635.

Hartman, A.D. et al. *PI3-kinase regulation of ADH-stimulated sodium absorption.* FASEB J 2000, 14(4): Abst 102.3.

Hu, L.M. et al. *In vivo and in vitro ovarian carcinoma growth inhibition by a phosphatidylinositol 3-kinase inhibitor (LY294002).* Clin Cancer Res 2000, 6(3): 880.

Kang, I. et al. *Activation of AMP-activated protein kinase enhances oxidative stress-induced apoptosis in neuro-2B neuroblastoma cells.* Soc Neurosci Abst 2000, 26(Part 1): Abst 286.14.

Mitsuuchi, Y. et al. *The phosphatidylinositol 3-kinase (PI3K)/AKT signal transduction pathway plays a critical role in the expression of the cyclin-dependent kinase inhibitor P21 WAF1/CIP1/SDI1.* Proc Amer Assoc Cancer Res 2000, 41: Abst 1988.

Nishida, W. *Signal transduction and transcriptional regulation mechanisms involved in differentiation of smooth muscle cells.* J Jpn Atheroscler Soc 2000, 28(Suppl.): 92.

Orike, N. et al. *Neurotrophin-independent survival and cell death in adult sympathetic neurons: The role of PI3-kinase.* Soc Neurosci Abst 2000, 26(Part 1): Abst 320.6.

Paunescu, T.G. et al. *Role of LY294002 inhibitable PI3-kinase in cAMP activation of PKA and Na^+ transport in A6 epithelia.* FASEB J 2000, 14(4): Abst 102.4.

te Poele, R. et al. *The use of expression profiling to identify genes regulated by the PI3K inhibitor LY294002.* Clin Cancer Res 2000, 6(Suppl.): Abst 411.

Wong, W.S.F. et al. *Inhibitors of the tyrosine kinase signaling cascade attenuated antigen challenge of guinea pig airways.* FASEB J 2000, 14(8): Abst 272.

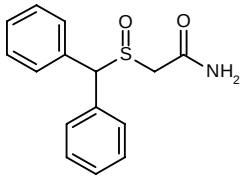
Yorek, M.A. et al. *Wortmannin and LY294002 inhibit myo-inositol accumulation by cultured bovine aorta endothelial cells and murine 3T3-L1 adipocytes.* Biochim Biophys Acta - Mol Cell Res 2000, 1497(3): 328.

Yusta, B. et al. *The glucagon-like peptide-2 receptor mediates direct inhibition of cellular apoptosis via a cAMP-dependent protein kinase-independent pathway.* J Biol Chem 2000, 275(45): 35345.

Modafinil
Modasomil®
Provigil®

Antinarcoleptic
Treatment of Sleep Apnea
Treatment of ADHD

EN: 129674



$C_{15}H_{15}NO_2S$ **Lafon; Cephalon**

A double-blind, placebo-controlled clinical trial comparing the safety and efficacy of 100-mg and 400-mg doses of modafinil to placebo in 113 adults with attention deficit hyperactivity disorder (ADHD) showed that modafinil, as compared to placebo, had no benefit in reducing the symptoms of ADHD, as measured by the DSM-IV ADHD Rating Scale. Modafinil was generally well tolerated (1).

The safety and efficacy of modafinil in narcolepsy has been demonstrated in a 9-week, multicenter clinical trial of 271 patients. In this trial and another 2-week placebo-controlled trial in 240 patients, symptoms of drug dependency and withdrawal were not observed. Patients in the 9-week trial were administered either 200 or 400 mg of modafinil or placebo daily and attempted to stay awake while sitting in a darkened room. Those given modafinil were able to stay awake longer and showed significant improvement in measures of excessive daytime sleepiness (EDS) and in patient and clinician assessments. Nighttime sleep was not affected by modafinil treatment. In the following examination of treatment discontinuance, modafinil patients did not experience withdrawal symptoms and returned to their EDS baseline levels. Headache was observed in modafinil-treated patients, but not significantly more than in those administered placebo. These trials indicate that modafinil is an effective alternative to stimulant therapies, which can affect heart rate and may become addictive (2).

A double-blind, randomized, placebo-controlled, crossover trial in 22 adults meeting DSM-IV criteria for ADHD compared modafinil, dextroamphetamine and placebo. The study included three 2-week treatment periods separated by 4-day washout periods; the optimal doses of active drugs were selected over 4-7 days and maintained for the remainder of the treatment period. The mean optimal doses of modafinil and dextroamphetamine were 206.8 and 21.8 mg/day, respectively. Both active treatments were associated with significant improvement compared to placebo in ADHD symptoms on the DMS-IV ADHD scale; a nonsignificant trend for less severe symptoms was seen on modafinil compared to dextroamphetamine. A nonsignificant trend for improvement in

  CCC: 0377-8282/2001

cognitive test scores was also seen on active drugs, but no effect was seen on mood. Treatments were well tolerated and no significant differences were seen among groups in the frequency of adverse events. These preliminary results will require confirmation in larger trials, but suggest that modafinil has potential as a safe and effective alternative to stimulants in adult ADHD (3).

A drug used to treat symptoms of narcolepsy has now been shown to be useful in controlling fatigue in patients with multiple sclerosis (MS). In this trial, 72 MS patients received a single daily dose of placebo for the first 2 weeks, 200 mg/day modafinil during the third and fourth weeks, 400 mg/day modafinil during the fifth and sixth weeks, and placebo during the last 3 weeks. Efficacy was assessed by patients using the Fatigue Severity Scale (FSS), a visual analogue global fatigue scale and the Modified Fatigue Impact Scale (MFIS). According to interim analysis of 43 patients, the lower dose of modafinil significantly improved fatigue on all 3 assessment scales, whereas the higher dose was not significantly different from placebo. Adverse events included headache (21, 19 and 5% on placebo, 200 mg and 400 mg modafinil, respectively), nervousness (5, 14 and 3% on placebo, 200 mg and 400 mg, respectively) and asthenia (14, 12 and 10% on placebo, 200 mg and 400 mg, respectively), none of which were serious (4).

Cephalon has launched modafinil in Switzerland for the treatment of narcolepsy. Modafinil is marketed by Cephalon in the U.S., the U.K., Ireland and Italy under the brand name Provigil® and in Austria and Switzerland under the brand name Modasomil®. In addition, Cephalon also has exclusive marketing rights to Provigil(R) in Japan, Latin America, South Korea and Taiwan (5).

1. *Clinical trial results disappointing for Provigil as treatment for adult ADHD.* DailyDrugNews.com (Daily Essentials) Aug 2, 2000.

2. *Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy.* Neurology 2000, 54(5): 1166.

3. Taylor, F.B., Russo, J. *Efficacy of modafinil compared to dextroamphetamine for the treatment of attention deficit hyperactivity disorder in adults.* J Child Adolesc Psychopharmacol 2000, 10(4): 311.

4. Rammohan, K.W., Rosenberg, J.H., Pollak, C.P., Lynn, D.J., Blumenfeld, A., Nagaraja, H.N. *Modafinil - Efficacy and safety for the treatment of fatigue in patients with multiple sclerosis.* Neurology 2000, 54(7, Suppl. 3): Abst S11.004.

5. *Modafinil launched in Switzerland for treatment of narcolepsy.* DailyDrugNews.com (Daily Essentials) Sept 25, 2000.

Original monograph - Drugs Fut 1990, 15: 130.

Additional References

Bogan, R.K. et al. *Modafinil as adjunct therapy for the treatment of excessive daytime sleepiness in obstructive sleep apnea.* Chest 2000, 118(4, Suppl.): 145S.

Feldman, N. et al. *Effect of modafinil on nightime sleep and quality of life in patients with sleep apnea and residual daytime sleepiness despite effective NCPAP therapy.* Chest 2000, 118(4, Suppl.): 146S.

Kaufman, K.R. et al. *Modafinil monotherapy in depression.* Int J Neuropsychopharmacol 2000, 3(Suppl. 1): Abst P.03.229.

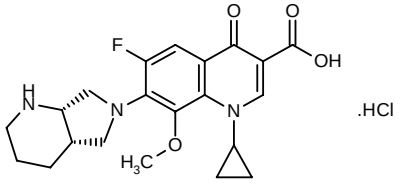
Menza, M.A. et al. *Modafinil augmentation of antidepressant treatment in depression.* J Clin Psychiatry 2000, 61(5): 378.

Moxifloxacin Hydrochloride

Avelox®
Avalox®
Actira®
Octegra®
Proflox®

Quinolone Antibacterial

EN: 240775



$C_{21}H_{24}FN_3O_4.HCl$ **Bayer; Vita; Esteve**

An *in vitro* study compared the efficacy of moxifloxacin with sparfloxacin and levofloxacin against nonefflux (ATCC 49619 and 2136) and efflux-positive (49619E) resistant strains of *Streptococcus pneumoniae*. The MIC values against the 3 strains, respectively, were (μg/ml): 0.19, 0.09 and 0.25 for moxifloxacin; 0.38, 0.19 and 0.5 for sparfloxacin; and 0.75, 0.5 and 1.5 for levofloxacin. The AUC kill curve (AUKC) values against nonefflux strains were 17.1 ± 0.1, 18.6 ± 0.4 and 18.4 ± 0.4 for moxifloxacin, sparfloxacin and levofloxacin, respectively. The AUKC values for the efflux-positive resistant strain were 82, 279 and 1600% greater for the respective agents than values obtained for the nonefflux strain 49619. The antimicrobial effect (AME) of moxifloxacin was significantly greater than sparfloxacin and levofloxacin while the AMEs for the latter two agents were similar (1).

An *in vitro* study examined the killing efficacy of moxifloxacin (1.3 and 2.7 mg/l) against *Streptococcus pyogenes* group A strains including erythromycin-susceptible SA P1800, erythromycin-resistant (MLSB inducible) SA 197, erythromycin-resistant (by efflux mechanism) SA 138 and erythromycin-resistant (MLSB constitutive) SA 176. The MIC values for all strains were between 0.125 and 0.25 mg/l and AUC values for the 2 doses were 18 and 36 mg·h/l, respectively. No regrowth was seen with the higher dose and cfu counts were below detection at 12 h. However, regrowth of SA 197 and SA 176 was seen with the lower dose (2).

An *in vitro* study showed the efficacy of moxifloxacin, clinafloxacin, trovafloxacin and levofloxacin against 6 clinical isolates of *Legionella pneumophila* serogroup 1

obtained from bronchoalveolar lavage. Clinafloxacin and trovafloxacin (MIC = 0.004 μg/ml) were the most active followed by levofloxacin and moxifloxacin (MIC = 0.015-0.03 μg/ml). Moxifloxacin and levofloxacin (0.015 μg/ml), trovafloxacin (0.004 μg/ml) and clinafloxacin (0.002 μg/ml) all significantly decreased intracellular bacterial counts in the Mono Mac 6 infection model; the agents were active at concentrations 4 times lower than *in vitro* MICs (3).

An *in vitro* study examined the synergy between moxifloxacin and ceftriaxone or vancomycin against clinical isolates of penicillin-susceptible (PenS) or penicillin-resistant (PenR) *S. pneumoniae*. MIC values for moxifloxacin and vancomycin against 20 PenS and 20 PenR strains were 0.06-0.25 and 0.25-1 μg/ml, respectively; MIC values for ceftriaxone against PenS and PenR strains were 0.03-0.0125 and 1 μg/ml, respectively. Moxifloxacin + ceftriaxone and moxifloxacin + vancomycin showed synergistic or additive effects against 9 and 5 PenS strains, respectively, and 15 and 3 PenR strains, respectively. Antagonism was not seen and indifference was observed against all the remaining strains (4).

An *in vitro* study examined the emergence of resistance mutations in a clinical strain of *S. pneumoniae* subcultured in increasing concentrations of moxifloxacin (MIC 0.125-128 μg/ml), gatifloxacin (0.25-128 μg/ml) or ciprofloxacin (1-256 μg/ml) for 23 days. Results showed that GyrA was the preferential target site of moxifloxacin and gatifloxacin and while gatifloxacin selected for substitutions in ParC and GyrA (also seen with ciprofloxacin), moxifloxacin targeted novel ParC substitutions (5).

An *in vitro* study compared the mutation prevention concentrations (MPCs) of moxifloxacin, gatifloxacin and levofloxacin against 111 clinical isolates of *S. pneumoniae*. Moxifloxacin was the most active agent and its activity was not significantly affected by penicillin-resistance. The MPC_{50}/MPC_{90} values for the 3 agents were 0.5/2, 1/4 and 4/16 μg/ml, respectively (6).

An *in vitro* study using human monocytic (THP-1) and alveolar epithelial (A549) cell lines showed that the uptake and intracellular activity of moxifloxacin (20 μg/ml) was superior to ciprofloxacin (20 μg/ml). While the intracellular to extracellular drug concentration ratio for moxifloxacin was only slightly higher than ciprofloxacin (6.3 ± 0.9 *vs.* 4.5 ± 0.7) in THP-1 cells, it was significantly higher (36.9 ± 9.8 *vs.* 5.8 ± 0.5) in A549 cells. Moxifloxacin suppressed intracellular multiplication of *L. pneumophila* in both cell lines at a concentration of 0.008 μg/ml. Ciprofloxacin suppressed multiplication at concentrations of 0.16 and 0.064 μg/ml in THP-1 and A549 cells, respectively (7).

An *in vitro* study using J774 macrophages examined the cellular accumulation of moxifloxacin and ciprofloxacin and the effects of glucose, Mg^{2+} and fetal serum on accumulation. Moxifloxacin accumulated more than ciprofloxacin. Accumulation of ciprofloxacin was similar to moxifloxacin in the presence of probenecid (PRB) indicating that the low accumulation of ciprofloxacin was due to more efficient efflux by the PRB-inhibitable transporter. Glucose decreased ciprofloxacin accumulation, an effect inhibited by PRB. Moxifloxacin accumulation was unchanged in the presence of PRB or glucose. Both Mg^{2+} and fetal serum decreased ciprofloxacin and moxifloxacin accumulation, possibly due to their ability to bind these agents extracellularly (8).

The *in vitro* activity of moxifloxacin was compared with gatifloxacin, ciprofloxacin and levofloxacin against 379 Gram-negative strains isolated from cancer patients. Moxifloxacin activity was similar to gatifloxacin and ciprofloxacin but superior to levofloxacin against most strains. MIC_{90} values for moxifloxacin ranged from 0.06-8 μg/ml (9).

The efficacy of moxifloxacin (50 and 100 mg/kg t.i.d. i.p. for 4 days starting 8 h postinfection) was shown against *Staphylococcus aureus*-induced foreign body (s.c. implanted dialysis tubing bags) abscesses in rats. Peak blood concentrations of the agent 30 min following administration of the last 50 mg dose was 2.2 mg/l and decreased to 0.6 mg/l at 240 min postdosing. Intraabscess levels of the agent peaked (0.9 mg/l) at 120 min after the last dose and intraabscess bacterial counts were 3.69 and 3.82 $\log_{10}$ cfu at 240 min and immediately after the last dose, respectively. Peak blood and abscess concentrations following the 100 mg dose were 7.5 mg/l at 30 min and 2 mg/l at 120 min postdosing. Of the 13 animals treated with 100 mg, 6 had no abscesses and sterilized intraabscessal bacterial inoculum immediately following the last dose; all tubing bags were sterile at 240 min. The abscess AUC ratios were 0.45 and 0.29 for the 50 and 100 mg/kg doses at 240 min; peak blood to peak abscess fluid moxifloxacin level ratios were similar for both doses (10).

Pooled results from 2 open-label studies conducted in 16 patients with mild or moderate liver cirrhosis (Child Pugh A or B) and 18 healthy volunteers given single-dose moxifloxacin (400 mg) showed that no dose adjustments are required in these patients. AUC values for Child Pugh A patients were about 22% below those obtained for healthy subjects while values from Child Pugh B patients were 2% above. C_{max} values were similar for both groups of patients with liver impairment but lower than the value obtained in healthy subjects (3.13 *vs.* 1.36 mg/l). However, this value was still in the population range for healthy subjects. Oral clearance of the agent was not affected by liver disease. A greater than 5-fold increase in the M1 metabolite and increase in renal clearance was seen in individuals with moderate liver cirrhosis. Further accumulation of metabolites was not seen (11).

The safety of moxifloxacin was summarized following meta-analysis of 26 phase II and III studies conducted in more than 1.2 million patients. Results from 6178 patients treated with 400 mg revealed a low incidence of adverse events (26%) which was similar to treatment with comparators (23%). Common adverse events included nausea/diarrhea (14 *vs.* 10% for comparators) and dizziness (3 *vs.* 2% for comparators). Analysis of 2650 patients showed that prolongation of the QTc interval occurred in 2.8% of moxifloxacin-treated patients as compared to 2.2

and 3.7% for all comparators and clarithromycin, respectively. Of the > 1.2 million patients given moxifloxacin, only 379 adverse events were reported of which 15/22 of the cardiovascular events seen were considered serious; 1 case of cardioconverted torsade de pointes was seen in an 83-year-old female on concurrent medication and suffering from hypokalemia and other predisposing factors. No malignant ventricular tachyarrhythmias, cardiac-related mortalities, phototoxicity, arthritis/tendinitis, severe hepatic events or new toxicities were seen with moxifloxacin treatment (12).

The efficacy of moxifloxacin (400 mg once daily for 7 or 10 days) against penicillin-resistant (PenR) *S. pneumoniae*-induced acute sinusitis was shown in 2 open-label, uncontrolled studies involving a total of 805 patients. Treatment was well tolerated. Clinical resolution was seen in 80 and 85% of the patients treated for 7 and 10 days, respectively. Of the 15 patients from whom PenR *S. pneumoniae* was isolated, 14 had resolution and presumed bacterial eradication. Adverse events were reported in 25% of the patients of which only 0.7% were serious and 2% required discontinuation (13).

Analysis of pooled results from the global clinical safety database of moxifloxacin trials involving over 7500 patients showed that of the 228 moxifloxacin (400 mg once daily)-treated patients who also received QTc prolonging agents, no significant differences were seen in cardiovascular events (*i.e.*, tachycardia, palpitation, arrhythmias, ischemia, syncope, further QTc prolongation) as compared to groups receiving moxifloxacin alone, comparators alone (clarithromycin, cephalexin, cefuroxime and amoxicillin) or comparators + QTc prolonging drugs (14).

A randomized study conducted in 12 healthy males showed that itraconazole (200 mg b.i.d. for 9 days) had no effect on the pharmacokinetics of moxifloxacin (400 mg p.o. for 9 days alone or on day 7). Both treatments were well tolerated and it was concluded that dose adjustments were not required with combination treatment. Itraconazole had no effect on the sulpho-metabolite (M1) of moxifloxacin although a 30% decrease in AUC and a 54% increase in renal excretion was observed for its glucuronide metabolite (M2). Moxifloxacin only slightly affected the AUC values of itraconazole (5% increase) and its hydroxy metabolite (5% decrease) and C_{max} values were reduced by 14 and 18%, respectively (15).

Results from 11 placebo-controlled studies in 140 healthy male volunteers showed that single-dose (50-800 mg) and multiple-dose (100 mg b.i.d. to 600 mg once daily) moxifloxacin had no clinically significant effect on the QTc interval. Although a small prolongation of QTc was observed, subjects were asymptomatic. The mean prolongation of the interval following a 400 mg single dose was 6.9 ms as compared to 3.5 ms following placebo (16).

Moxifloxacin hydrochloride (Avelox®) has been approved for launch in Canada for community-acquired pneumonia, acute bacterial exacerbations of chronic bronchitis and acute bacterial sinusitis (17).

Bayer has submitted an NDA to the FDA seeking approval for the intravenous formulation of moxifloxacin hydrochloride for the treatment of common adult community-acquired respiratory tract infections. Among the indications for which approval is being sought are community-acquired pneumonia caused by *S. pneumoniae* (including PenR strains), *Haemophilus influenzae*, *Moraxella catarrhalis*, *S. aureus*, *Klebsiella pneumonia*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *L. pneumophila*. The intravenous dose of moxifloxacin recommended in the NDA is 400 mg, the same as the currently approved oral dose of the drug. Supporting the NDA submission were data from 2 multicenter studies involving more than 1100 patients hospitalized with CAP. One study involved 516 patients from 89 centers in the U.S. and 15 in Canada. The other study included 628 patients from 65 centers in Europe, Israel and South Africa. These studies compared the effect of i.v. moxifloxacin 400 mg to either fluoroquinolone or a β-lactam with or without a macrolide. In both studies, doctors initiated all patients on i.v. therapy, but then had the option to switch to oral therapy after 3 days. Additional studies with both i.v. and oral formulations of moxifloxacin are under way in the hospital setting for the treatment of patients with hospital-acquired pneumonia, intraabdominal infections or complicated skin infections (18).

Alcon has obtained an exclusive worldwide license from Bayer to develop, manufacture and market moxifloxacin-based drops to treat eye and ear infections. The license agreement between the two companies is subject to review under U.S. antitrust laws (19).

1. Madaras-Kelly, K.J., Daniels, C., Hegbloom, M., Nielson, C., Kurtz, T. *A pharmacodynamic characterization of Streptococcus pneumoniae (SP) fluoroquinolone (FQ) efflux (EFX) resistance utilizing moxifloxacin (M), sparfloxacin (S), and levofloxacin (L).* 40th Interscl Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst A-296.

2. Odenholt, I., Löwdin, E., Cars, O. *Pharmacodynamic studies of moxifloxacin in an in vitro kinetic model against Streptococcus pyogenes group A.* 40th Interscl Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst A-308.

3. Frank, U.K., Jonas, D., Engels, I., Friedhof, C., Spitmueller, B., Dettenkofer, M., Daschner, F.D. *Efficacy of moxifloxacin and other novel fluoroquinolones against intracellular L. pneumophila serogroup 1.* 40th Interscl Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst D-338.

4. Noviello, S., Esposito, S., Ianniello, F. *Assessment of in vitro synergy between moxifloxacin (MXF) and ceftriaxone (CRO) or vancomycin (VAN) against Streptococcus pneumoniae (SP).* 40th Interscl Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst E-529.

5. Kilburn, L., Downar, J., Tong, B., Salim, K.Y., Low, D.E., Bast, D.J., De Azavedo, J.C.S. *Moxifloxacin and gatifloxacin preferentially target GyrA in Streptococcus pneumoniae.* 40th Interscl Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst C-743.

6. Blondeau, J.M., Zhao, X., Drlica, K., Hansen, G. *Comparison of moxifloxacin, levofloxacin and gatifloxacin by the mutation prevention concentration (MPC) using clinical isolates of*

Streptococcus pneumoniae (SP). 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst E-2325.

7. Takemura, H., Yamamoto, H., Kunishima, H., Hara, T., Ikejima, H., Terakuba, S., Kanemitsu, K., Shimada, J. *Comparative uptake and intracellular activity of moxifloxacin and ciprofloxacin in human monocytic cell line THP-1 and alveolar epithelial cell line A549.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst E-2323.

8. Uwamahoro, M.J., Carryn, S., Michot, J.M., Mingeot-Lecrecq, M.P., Tulkens, P.M., Van Bambeke, F. *Modulation of the cellular accumulation of ciprofloxacin (CIP) and moxifloxacin (MOX) in J774 macrophages.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst A-2268.

9. Rolston, K.V.I., Leblanc, B.M., Balakrishnan, M., Ho, D.H. *In-vitro activity of moxifloxacin against Gram-negative isolates from cancer patients.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst E-2324.

10. Lev, A., Yoseph, G., Rubinstein, E. *The concentrations and activity of moxifloxacin (moxi) in S. aureus induced foreign body abscesses.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst A-305.

11. Stass, H., Kubitza, D., Wensing, G. *Pooled analysis of pharmacokinetics, safety and tolerability of single oral 400 mg moxifloxacin (MFX) doses in patients with mild and moderate liver cirrhosis (LC).* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst A-2269.

12. Kubin, R., Reiter, C. *Safety update of moxifloxacin: A current review of clinical trials and post-marketing observational studies.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst M-820.

13. Church, D., Painter, B.G., Herrington, J., Haverstock, D., Warner, J.H., Heyd, A. *Efficacy of moxifloxacin in the treatment of acute bacterial sinusitis caused by penicillin-resistant Streptococcus pneumoniae.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst N-833.

14. Hollister, A.S., Haverstock, D., Choudhri, S. *Moxifloxacin has a favorable cardiovascular safety profile in patients taking concomitant QTc prolonging drugs.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst M-818.

15. Stass, H., Schuhly, U., Delesen, H., Moller, J., Nagelschmitz, J. *Lack of influence of itraconazole (ITR) on moxifloxacin (MFX) pharmacokinetics in healthy male subjects.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst A-2270.

16. Kubitza, D., Delesen, H. *Influence of oral moxifloxacin on the QTc interval of healthy volunteers.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst M-611.

17. *Bayer's Avelox approved in Canada.* DailyDrugNews.com (Daily Essentials) Oct 25, 2000.

18. *Bayer seeks FDA approval for intravenous formulation of Avelox.* DailyDrugNews.com (Daily Essentials) Nov 8, 2000.

19. *Alcon to develop drop formulation of moxifloxacin.* DailyDrugNews.com (Daily Essentials) July 21, 2000.

Original monograph - Drugs Fut 1997, 22: 109.

Additional References

Akins, R.L. et al. *Pharmacodynamic (PD) comparison and activity of moxifloxacin (M), ciprofloxacin (C), gatifloxacin (Ga), gemifloxacin (Ge) and levofloxacin (L) against clinical isolates of Streptococcus pneumoniae (SP) and Staphylococcus aureus (SA).* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst A-303.

Allen, G.P. et al. *Evaluation of the mutant prevention concentration (MPC) in Staphylococcus aureus (SA) and Streptococcus pneumoniae (SP) - Effect of varying fluoroquinolone (FQ) dosage regimens on the development of resistance in an in vitro pharmacodynamic infection model (IVPM).* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst A-299.

Alvirez-Freites, E. et al. *Activity of moxifloxacin in the treatment of tuberculosis in a murine model.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst B-997.

Andrews, J.M., Wise, R. *Comparison of the Etest with a conventional agar dilution method in evaluating the in vitro activity of moxifloxacin.* J Antimicrob Chemother 2000, 45(2): 257.

Ball, P. *Moxifloxacin (Avelox): An 8-methoxyquinolone antibacterial with enhanced potency.* Int J Clin Pract 2000, 54(5): 329.

Betlejewska, K. et al. *Susceptibility to moxifloxacin and other antimicrobial agents of major pathogens responsible for community acquired infections of respiratory tract.* Clin Microbiol Infect 2000, 6(Suppl. 1): Abst WeP113.

Betriu, C. et al. *Comparative activity of moxifloxacin and trovafloxacin against erythromycin-susceptible and erythromycin-resistant Streptococcus pyogenes and Streptococcus agalactiae.* Rev Esp Quimioter 2000, 13(Suppl. 2): Abst M180.

Betriu, C. et al. *Comparative in vitro activities of linezolid, quinupristin-dalfopristin, moxifloxacin, and trovafloxacin against erythromycin-susceptible and -resisant streptococci.* Antimicrob Agents Chemother 2000, 44(7): 1838.

Beyer, R. et al. *A convenient assay for estimating the possible involvement of efflux of fluoroquinolones by Streptococcus pneumoniae and Staphylococcus aureus: Evidence for diminished moxifloxacin, sparfloxacin, and trovafloxacin efflux.* Antimicrob Agents Chemother 2000, 44(3): 798.

Black, J. et al. *In vitro activity of moxifloxacin and other oral agents against antibiotic resistant Streptococcus pneumoniae.* Clin Microbiol Infect 2000, 6(Suppl. 1): Abst WeP115.

Blondeau, J.M. et al. *Comparative in vitro activity of gatifloxacin, grepafloxacin, levofloxacin, moxifloxacin and trovafloxacin against 4151 Gram-negative and Gram-positive organisms.* Int J Antimicrob Agents 2000, 14(1): 45.

Bonapace, C.R. et al. *Differences in fluoroquinolone (FQ) pharmacodynamics (PD) against recent isolates of 20 different bacterial species.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst A-297.

Brown, D.F.J., Thomson, C.J. *Activity of moxifloxacin against isolates from patients with community-acquired lower respiratory tract infection in the UK.* Rev Esp Quimioter 2000, 13(Suppl. 2): Abst M175.

Cardenosa, O., Soto Hernandez, J.L. *In vitro activity of moxifloxacin (BAY 12-8039) against respiratory tract pathogens from six Latin-American countries.* Chemotherapy 2000, 46(6): 379.

Cosigny, S. et al. *Bactericidal activities of HMR 3647, moxifloxacin, and rifapentine against Mycobacterium leprae in mice.* Antimicrob Agents Chemother 2000, 44(10): 2919.

Craig, W.A., Andes, D.R. *Correlation of the magnitude of the AUC24/MIC for 6 fluoroquinolones against Streptococcus pneumoniae (SP) with survival and bactericidal activity in an animal*

model. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst A-289.

Démolis, J.-L. et al. *Effect of a single oral dose of moxifloxacin (400 mg and 800 mg) on ventricular repolarization in healthy subjects.* Clin Pharmacol Ther 2000, 68(6): 658.

Dorai-John, T. et al. *Sequential laboratory-generated mutations to moxifloxacin resistance in Streptococcus pneumoniae R6: The role of target alterations and permeability barriers.* Rev Esp Quimioter 2000, 13(Suppl. 2): Abst M174.

Dubreuil, L. et al. *Antianaerobic activity of moxifloxacin compared with those of ciprofloxacin, imipenem and metronidazole.* Clin Microbiol Infect 2000, 6(Suppl. 1): Abst WeP121.

Edlund, C. et al. *Comparative effects of moxifloxacin and clarithromycin on the normal intestinal microflora.* Scand J Infect Dis 2000, 32(1): 81.

Farinati, A.E. et al. *Decrease in susceptibility to moxifloxacin (MO) and gatifloxacin (GA) of S. pneumoniae (Sp) isolated from sinus aspirates during two periods.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst C-2107.

Firsov, A.A. et al. *Comparative pharmacodynamics of moxifloxacin and levofloxacin in an in vitro dynamic model: Prediction of the equivalent AUC/MIC breakpoints and equiefficient doses.* J Antimicrob Chemother 2000, 46(5): 725.

Firsov, A.A. et al. *Predictors of fluoroquinolone (FQ) antimicrobial effect (AME) in pharmacodynamic studies with in vitro dynamic models.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst A-302.

García Sánchez, J.E. et al. *Susceptibility of Helicobacter pylori to mupirocin, oxazolidinones, quinupristin/dalfopristin and new quinolones.* J Antimicrob Chemother 2000, 46(2): 283.

García-Rodriguez, J.A. et al. *Comparative in vitro activity of moxifloxacin against respiratory tract pathogens: Results of a Spanish multicenter study.* Rev Esp Quimioter 2000, 13(Suppl. 2): Abst M172.

García-Rodríguez, J.A., Gómez García, A.C. *The microbiology of moxifloxacin.* Drugs Today 2000, 36(4): 215.

Hardy, D. et al. *Comparative in vitro activities of ciprofloxacin, gemifloxacin, grepafloxacin, moxifloxacin, ofloxacin, sparfloxacin, trovafloxacin, and other antimicrobial agents against bloodstream isolates of Gram-positive cocci.* Antimicrob Agents Chemother 2000, 44(3): 802.

Johnson, A. et al. *Activity of moxifloxacin and other quinolones against pneumococci from geographically diverse UK hospitals, including strains resistant to penicillin, erythromycin, tetracycline and ciprofloxacin.* Rev Esp Quimioter 2000, 13(Suppl. 2): Abst M179.

Jonas, D. et al. *Efficacy of moxifloxacin, trovafloxacin, clinafloxacin and levofloxacin against intracellular Legionella pneumophila.* J Antimicrob Chemother 2001, 47(2): 147.

Jones, M.E. et al. *Benchmarking the in vitro activities of moxifloxacin and comparator agents against recent respiratory isolates from 377 medical centers throughout the United States.* Antimicrob Agents Chemother 2000, 44(10): 2645.

Kang, J. et al. *Interactions of a series of fluoroquinolone antibacterial drugs with the human cardiac K+ channel HERG.* Mol Pharmacol 2001, 59(1): 122.

Kawahara, S. et al. *In vitro antibacterial activity of moxifloxacin, a new quinolone for treating acid-fast bacteria.* J Jpn Assoc Infect Dis 2000, 74: Abst 184.

Kelley, T. et al. *Multi-site evaluation of moxifloxacin on the Sensititre dried susceptibility panel compared to NCCLS microdilution method.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst D-331.

Klossek, J.-M. *Moxifloxacin versus trovafloxacin in the treatment of acute sinusitis.* Rev Esp Quimioter 2000, 13(Suppl. 2): Abst M178.

Kowalsky, S. et al. *Moxifloxacin Susceptibility Program (MSP): Regional and national susceptibility of common respiratory tract pathogens.* 100th Gen Meet Am Soc Microbiol (May 21-25, Los Angeles) 2000, Abst A-3.

Kubin, R. et al. *Moxifloxacin - A safety update from 26 clinical studies.* Rev Esp Quimioter 2000, 13(Suppl. 2): Abst M171.

Lemoine, T. et al. *Determination of moxifloxacin (BAY 12-8039) in plasma and lung tissue by high-performance liquid chromatography with ultraviolet detection using a fully automated extraction method with a new polymeric cartridge.* J Chromatogr B - Biomed Sci Appl 2000, 742(2): 247.

Lode, H. et al. *Clinical results in the treatment of respiratory infections with moxifloxacin.* Drugs Today 2000, 36(4): 245.

Lopez, H. et al. *Multicentric study for in vitro evaluation of moxifloxacin and other antimicrobial agents against clinical bacterial isolates from Argentina.* Clin Microbiol Infect 2000, 6(Suppl. 1): Abst WeP134.

Lorenz, J. et al. *Correlation between clinical efficacy and patient assessment of a 5-day course of moxifloxacin therapy for acute exacerbations of chronic bronchitis.* Chest 2000, 118(4, Suppl.): 191S.

Lubasch, A. et al. *Comparative pharmacokinetics of ciprofloxacin, gatifloxacin, grepafloxacin, levofloxacin, trovafloxacin, and moxifloxacin after single oral administration in healthy volunteers.* Antimicrob Agents Chemother 2000, 44(10): 2600.

Lubenko, I. et al. *Comparative pharmacodynamics of moxifloxacin, grepafloxacin and trovafloxacin with Staphylococcus aureus in an in vitro dynamic model.* Rev Esp Quimioter 2000, 13(Suppl. 2): Abst M169.

Maggiolo, F. et al. *Effects of subinhibitory concentrations of moxifloxacin in an in-vitro dynamic model.* J Chemother 2000, 12(2): 129.

Moise, P.A. et al. *Pharmacokinetics and metabolism of moxifloxacin.* Drugs Today 2000, 36(4): 229.

Musafija, A. et al. *Trans-epithelial intestinal elimination of moxifloxacin in rabbits.* J Antimicrob Chemother 2000, 45(6): 803.

Naber, K.G. et al. *In vitro activity of gatifloxacin compared with gemifloxacin, moxifloxacin, trovafloxacin, ciprofloxacin and ofloxacin against uropathogens cultured from patients with complicated urinary tract infections.* Int J Antimicrob Agents 2000, 16(3): 239.

Nagai, K. et al. *In vitro selection of resistant (R) mutants in gemifloxacin (GEM), trovafloxacin (TRO), ciprofloxacin (CIP), gatifloxacin (GAT), moxifloxacin (MOX) to Streptococcus pneumoniae (Sp).* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst C-744.

Nightingale, C.H. *Moxifloxacin, a new antibiotic designed to treat community-acquired respiratory tract infections: A review of microbiologic and pharmacokinetic pharmacodynamic characteristics.* Pharmacotherapy 2000, 20(3): 245.

Nilsson, L.E., Hanberger, H. *A Nordic study of activity of moxifloxacin and other antimicrobial agents against the Bacteriodes fragilis group.* Clin Microbiol Infect 2000, 6(Suppl. 1): Abst WeP132.

Nilsson, L.E., Hanberger, H. *A Nordic study of activity of levofloxacin, moxifloxacin and other antimicrobial agents against staphylococci.* Clin Microbiol Infect 2000, 6(Suppl. 1): Abst WeP131.

Nilsson, L.E., Hanberger, H. *A Nordic study of activity of moxifloxacin, levofloxacin and other antimicrobial agents against respiratory pathogens.* Clin Microbiol Infect 2000, 6(Suppl. 1): Abst WeP129.

Ostergaard, C. et al. *Evaluation of moxifloxacin, a new 8-methoxyquinolone, for treatment of meningitis caused by a penicillin-resistant pneumococcus in rabbits.* Antimicrob Agents Chemother 1998, 42(7): 1706.

Owens, R.C. et al. *Pharmacodynamic (PD) comparison of new fluoroquinolones (FQ) against Streptococcus pneumoniae (SP) using Monte Carlo (MC) analysis.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst A-285.

Parish, L.C. et al. *Moxifloxacin versus cephalexin in the treatment of uncomplicated skin infections.* Int J Clin Pract 2000, 54(8): 497.

Patel, T. et al. *Efficacy and safety of ten day moxifloxacin 400 mg once daily in the treatment of patients with community-acquired pneumonia.* Respir Med 2000, 94(2): 97.

Patmore, L. et al. *Effects of sparfloxacin, grepafloxacin, moxifloxacin, and ciprofloxacin on cardiac action potential duration.* Eur J Pharmacol 2000, 406(3): 449.

Pestova, E. et al. *Intracellular targets of moxifloxacin: A comparison with other fluoroquinolones.* J Antimicrob Chemother 2000, 45(5): 583.

Petitpretz, P. et al. *Oral moxifloxacin vs high-dosage amoxicillin in the treatment of mild-to-moderate, community-acquired, suspected pneumococcal pneumonia in adults.* Chest 2001, 119(1): 185.

Piddock, L.J.V. et al. *Ability of moxifloxacin (MXF) and other fluoroquinolones to select resistant Staphylococcus aureus.* Clin Microbiol Infect 2000, 6(Suppl. 1): Abst WeP123.

Piddock, L.J.V. et al. *Molecular analysis of fluoroquinolone-resistant Streptococcus pneumoniae selected with moxifloxacin compared with ciprofloxacin.* Rev Esp Quimioter 2000, 13(Suppl. 2): Abst M170.

Rouse, M.S. et al. *In vitro emergence of resistance among methicillin-resistant Staphylococcus aureus to ciprofloxacin, levofloxacin, moxifloxacin, trovafloxacin or vancomycin.* Clin Microbiol Infect 2000, 6(Suppl. 1): Abst WeP119.

Saravolatz, L. et al. *In vitro activity and pharmacodynamics of moxifloxacin and five quinolones against S. pneumoniae.* Clin Microbiol Infect 2000, 6(Suppl. 1): Abst WeP117.

Schaberg, T. *Comparative effect of moxifloxacin and co-amoxiclav in the treatment of AECB.* Clin Microbiol Infect 2000, 6(Suppl. 1): Abst WeP236.

Schaumann, R. et al. *In vitro activities of fourteen antimicrobial agents against obligately anaerobic bacteria.* Int J Antimicrob Agents 2000, 16(3): 225.

Schmitz, F.-J. et al. *In vitro potency of moxifloxacin, clinafloxacin and sitafloxacin against 248 genetically defined clinical isolates of Staphylococcus aureus.* J Antimicrob Chemother 2000, 46(1): 109.

Seidel, D. et al. *Synthesis of carbon-14 labelled moxifloxacin hydrochloride.* J Label Compd Radiopharm 2000, 43(8): 795.

Sens, K. et al. *Activity of new quinolones, macrolide, and ketolide against 100 strains of Legionella species using broth dilution and intracellular susceptibility testing methods.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst E-2159.

Siegert, R. et al. *A comparison of the safety and efficacy of moxifloxacin (BAY 12-8039) and cefuroxime axetil in the treatment of acute bacterial sinusitis in adults.* Respir Med 2000, 94(4): 337.

Spiteri, M.A. et al. *In vitro effect of moxifloxacin on human respiratory ciliary kinetics.* Rev Esp Quimioter 2000, 13(Suppl. 2): Abst M176.

Steele-Moore, L. et al. *An in vitro evaluation of moxifloxacin against 200 clinical isolates of aerobic bacteria.* 100th Gen Meet Am Soc Microbiol (May 21-25, Los Angeles) 2000, Abst A-2.

Sunderland, J. et al. *In-vitro comparison of the phototoxic potential of ciprofloxacin, lomefloxacin and moxifloxacin on human corneal fibroblast cells.* Clin Microbiol Infect 2000, 6(Suppl. 1): Abst WeP116.

Trigo-Daporta, M. et al. *In vitro activity of older and newer fluoroquinolones against Streptococcus pneumoniae. Influence of mutations in DNA gyrase and topoisomerase IV.* Rev Esp Quimioter 2000, 13(Suppl. 2): Abst M146.

Trpeski, L. et al. *The comparative in vitro activities of the newer fluoroquinolones against Canadian Streptococcus pneumoniae: 1996-1999.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst E-2322.

Ullmann, U., Schubert, S. *Influence of several new fluoroquinolones on the intracellular bactericidal activity of PNG against S. aureus and K. pneumoniae.* Rev Esp Quimioter 2000, 13(Suppl. 2): Abst M153.

Weiss, K. et al. *Comparative activity of new quinolones against 326 clinical isolates of Stenotrophomonas maltophilia.* J Antimicrob Chemother 2000, 45(3): 363.

Wilhelm, C., Shah, P.M. *Bactericidal activity of moxifloxacin compared to that of penicillin G against penicillin-sensitive (S) and -resistant (R) Streptococcus pneumoniae.* Clin Microbiol Infect 2000, 6(Suppl. 1): Abst WeP127.

Xuan, D. et al. *Streptococcus pneumoniae response to repeated exposure of moxifloxacin or levofloxacin using a rabbit tissue cage model.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst A-286.

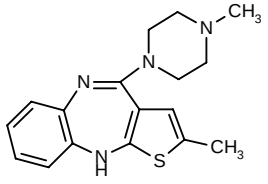
Yagüe Guirao, G. et al. *Activity of new fluorquinolones against Neisseria meningitidis clinical strains.* Rev Esp Quimioter 2000, 13(Suppl. 2): Abst M141.

Zhanel, G.G. et al. *Activity of free (unbound) fluoroquinolone serum concentrations versus multi-drug resistant Streptococcus pneumoniae using an in vitro pharmacodynamic model.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst A-292.

Olanzapine
Zyprexa®

Antipsychotic

EN: 177756



$C_{17}H_{20}N_4S$ **Lilly; Gador**

The use of a combination comprising an atypical antipsychotic and an H_2 antagonist has been claimed for the treatment or prevention of weight gain associated with the use of antipsychotics. Adjunctive therapy and oral administration are preferred. Combinations of olanzapine as antipsychotic and nizadipine as H_2 antagonist are specifically claimed (1).

A potential new therapeutic approach in resistant unremitting schizophrenia consists of combination of olanzapine, an atypical neuroleptic, and sulpiride, a selective dopamine D_2 receptor antagonist. The potential for enhanced clinical efficacy of this combination is suggested to be a product of the differential receptor affinity of the two compounds: olanzapine is a more potent 5-HT_2 than dopamine D_2 receptor antagonist, whereas sulpiride is a selective D_2 antagonist. A preliminary study in 6 patients with chronic schizophrenia demonstrated substantial and rapid clinical improvement following treatment with this combination, in the absence of serious adverse events. Further studies thus appear warranted (2).

The FDA has approved olanzapine (Zyprexa®) for the short-term treatment of acute manic episodes associated with bipolar disorder. The recommended starting dose is 10 mg or 15 mg, once daily at any time, without regard to meals (3).

Lilly has launched an orally disintegrating tablet formulation of olanzapine (Zyprexa® Zydis®) that dissolves in the patient's mouth on contact with saliva, in the U.S. Zyprexa® Zydis® is the first antipsychotic approved in this formulation and is now available in 5-mg and 10-mg tablets. The new formulation was approved in April 2000 as an orally disintegrating formulation for the management of the manifestations of psychotic disorders and acute manic episodes associated with bipolar I disorder. The new medication offers a new dimension in the pharmacological treatment of schizophrenia and bipolar mania. It will be especially useful to physicians who practice in hospitals of long-term care or home-care settings due to the special needs of patients in these facilities. Zyprexa® Zydis® typically takes 5-15 seconds to dissolve in the patient's mouth and will completely disintegrate in approximately 2 minutes, being absorbed in the gastrointestinal tract. Unlike liquid formulations, which may offer some of the same advantages in this patient population, Zyprexa® Zydis® does not need to be refrigerated, measured or mixed. The new formulation is unflavored and equivalent to Zyprexa® oral tablets with respect to safety, tolerability and efficacy. Zyprexa® Zydis® is manufactured by R.P. Scherer and is marketed by Lilly (4).

The FDA has approved olanzapine (Zyprexa®) for long-term schizophrenia therapy and maintenance of treatment response. The drug is the first of the newer generation of antipsychotics, known as "atypicals", to demonstrate long-term efficacy in clinical trials. In a placebo-controlled clinical trial, the drug demonstrated long-term safety and an efficacy so high that it warranted early termination of the trial to limit unnecessary patient exposure to placebo. Placebo-treated patients were almost 10 times as likely to relapse over a 6-month period compared to olanzapine-treated patients. The 6-month cumulative relapse rate for olanzapine was statistically superior to placebo (6% *vs.* 55%). The FDA's approval was based on results of a double-blind, placebo-controlled discontinuation study in 326 clinically stable outpatients with few or no symptoms for at least 6 weeks. They received olanzapine therapy for another 6 weeks followed by an 8-week observation period to confirm stability. Following the observation period, 224 patients were randomized to olanzapine (10-20 mg/day) and 102 patients were randomized to placebo. There were 177 patients with schizophrenia (79%) and 47 with schizoaffective disorder (21%) in the olanzapine group, and 89 patients with schizophrenia (87.3%) and 13 with schizoaffective disorder (12.7%) receiving placebo. Olanzapine-treated patients were significantly less likely to discontinue treatment as a result of either an adverse event or because of lack of efficacy. The olanzapine-treated group also improved on all quality-of-life measures, while those on placebo worsened. The drug was safe and generally well tolerated at doses of 10, 15 or 20 mg/day (5).

1. Todd, J.R. (Eli Lilly and Company). *Combination for treating weight gain associated with antipsychotic use comprising an atypical antipsychotic and an H_2 antagonist.* WO 0074784.

2. Raskin, S., Durst, R., Katz, G., Zislin, J. *Olanzapine and sulpiride: A preliminary study of combination/augmentation in patients with treatment-resistant schizophrenia.* J Clin Psychopharmacol 2000, 20(5): 500.

3. *Zyprexa approved in U.S. for bipolar-associated mania.* DailyDrugNews.com (Daily Essentials) March 21, 2000.

4. *New formulation of Zyprexa introduced for psychotic disorders and manic episodes.* DailyDrugNews.com (Daily Essentials) Sept 20, 2000.

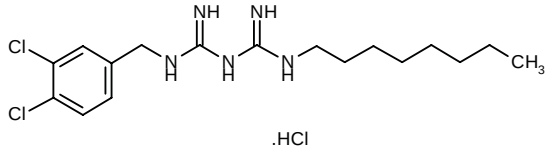
5. *Lilly's Zyprexa approved by FDA for extended schizophrenia indication.* DailyDrugNews.com (Daily Essentials) Nov 15, 2000.

Original monograph - Drugs Fut 1994, 19: 114.

OPB-2045
Olanexidine Hydrochloride

Antibacterial

EN: 248893



.HCl

$C_{17}H_{27}Cl_2N_5.HCl$ **Otsuka**

An *in vitro* study using dog liver microsomes characterized the oxidative cleavage of the octyl side chain of olanexidine. The agent was first transformed to the monohydroxylated metabolite 2-octanol (DM-215) which was then oxidized to *threo*-2,3-octandiol (DM-221) and *erythro*-2,3-octandiol (DM-222). These diols were then transformed to a ketol derivative and a C-C bond cleavage metabolite (DM-210). Biotransformation of these metabolites showed single-enzyme Michaelis-Menten kinetics. K_m and V_{max} values for DM-210 formation from oxidation of DM-221 were 2.42 μM and 26.6 pmol/min/mg, respectively, and from DM-222 were 2.48 μM and 30.2 pmol/min/mg, respectively. Quinidine inhibited these oxidative reactions, suggesting that CYP2D mediates C-C bond cleavage of the octyl side chain of olanexidine (1).

An *in vitro* study using transmission electron microscopy examined the bactericidal effects of OPB-2045 against methicillin-resistant *Staphylococcus aureus* (MRSA IID 1677). The MIC and minimum bactericidal concentration (MBC) values were 0.78 and 1.56 μg/ml, respectively. The morphology of cells was examined after incubating bacteria with 0.39 μg/ml (1/2 MIC), 0.78 μg/ml (1 MIC), 1.56 μg/ml (2 MIC), 3.13 μg/ml (4 MIC) and 7.8 μg/ml (10 MIC) for 30 s, 3 min, 30 min or 6 h. A similar degree of cell damage was observed after incubation for 30 min or 6 h with any of the OPB-2045 concentrations although the numbers of damaged MRSA cells increased with dose. Treatment with 1/2 MIC or 1 MIC resulted in a few leaking cells although no destroyed cells were detected. While no morphological changes were observed after incubation with 1 MIC or 2 MIC for 30 s, 3 min or 30 min, changes were observed after incubation for 6 h with these concentrations. No changes in MRSA cell numbers were seen in untreated controls or following incubation with 1/2 MIC but a pronounced decrease in the number of surviving MRSA cells was observed with the higher concentrations (2).

OPB-2045 distribution was examined in male, female and pregnant rats using whole body autoradiography following administration of a single s.c. dose of [^{14}C]-OPB-2045 and using microautoradiography following single percutaneous dosing with [^{14}C]-OPB-2045 and [^{14}C]-chlorhexidine. High levels of radioactivity were seen at the site of administration and in intestinal and bladder contents and the adrenals. Only slight levels were detected in the brain, blood, testes, seminal vesicles, ovaries and uterus; almost no radioactivity was detected in fetuses and amniotic fluid. Percutaneous administration of [^{14}C]-OPB-2045 revealed distribution predominantly in the corneal layer of the epidermis with only slight detection in hair and hair follicles. Percutaneous [^{14}C]-chlorhexidine dosing resulted in distribution from the corneal to the basal layers of the epidermis and in the sebaceous glands and hair with only slight detection in the hair follicles (3).

Olanexidine hydrochloride is the proposed international nonproprietary name for OPB-2045 (4).

1. Umehara, K., Kudo, S., Hirao, Y., Morita, S., Ohtani, T., Uchida, M., Miyamoto, G. *In vitro characterization of the oxidative cleavage of the octyl side chain of olanexidine, a novel antimicrobial agent, in dog liver microsomes.* Drug Metab Dispos 2000, 28(12): 1417.

2. Sakagami, Y. et al. *Electron-microscopic study of the bactericidal effect of OPB-2045, a new disinfectant produced from biguanide group compounds, against methicillin-resistant Staphylococcus aureus.* J Pharm Pharmacol 2000, 52(12): 1547.

3. Fujio, N., Furukawa, M., Miyamoto, G. *Distribution (autoradiography) of a new synthetic antibacterial agent OPB-2045 in rats.* Xenobiotic Metab Dispos 2000, 15(4): 309.

4. *Proposed international nonproprietary names (Prop INN): List 81.* WHO Drug Inform 1999, 13(2): 121.

Original monograph - Drugs Fut 1999, 24: 151.

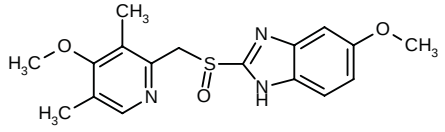
Additional Reference

Umehara, K. et al. *Oxidative cleavage of the octyl side chain of 1-(3,4-dichlorobenzyl)-5octylbiguanide (OPB-2045) in rat and dog liver preparations.* Drug Metab Dispos 2000, 28(8): 887.

Omeprazole
Losec®

Gastric Antisecretory

EN: 090859



$C_{17}H_{19}N_3O_3S$ **AstraZeneca**

Researchers from the Chinese University of Hong Kong assessed the effects of omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. After treatment with epinephrine injection followed by thermocoagulation to achieve hemostasis, 240 patients were randomly assigned to omeprazole or placebo. Treatment was administered as a bolus intravenous injection (80 mg), followed by an infusion (8 mg/h for 72 h), and finally by oral omeprazole (20 mg/day) for 8 weeks. Recurrent bleeding within 30 days after

endoscopy, the primary endpoint, was observed in 8 out of 120 patients in the omeprazole group and in 27 out of 120 patients in the placebo group. Most recurrent bleeding occurred during the first 3 days, while patients were receiving the infusion. In addition, in the omeprazole group, fewer patients underwent surgery or died within 30 days after endoscopy as compared to placebo. Therefore, high-dose infusion of omeprazole reduces the risk of recurrent bleeding after endoscopic treatment of bleeding peptic ulcers (1).

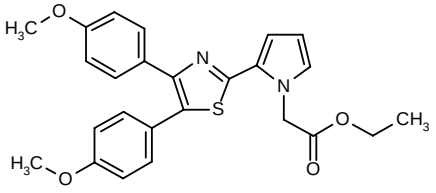
1. Lau, J.Y.W., Sung, J.J.Y., Lee, K.K.C. et al. *Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers.* New Engl J Med 2000, 343(5): 310.

Original monograph - Drugs Fut 1983, 8: 129.

Pamicogrel Paminate®

Platelet Antiaggregatory

EN: 118825



$C_{25}H_{24}N_2O_4S$ **Kanebo; Torii**

A study involving a total of 21 elderly (65 years or older) and nonelderly patients with chronic arterial occlusive disease (arteriosclerosis obliterans or thromboangiitis obliterans) examined the effects of KBT-3022 (5 mg once daily p.o. for 6 weeks) on platelet aggregation. Examination of platelets of 8 elderly and 9 nonelderly patients showed that the agent significantly inhibited arachidonic acid-induced platelet aggregation at week 2 as compared to baseline. Platelet aggregation induced by 5 and 10 μM and 2, 5 and 10 μM ADP was significantly inhibited in elderly and nonelderly patients, respectively. At week 6, collagen-induced platelet aggregation was also significantly inhibited. Plasma clearance rates were similar in both groups and > 80% of the patients showed recovery to 80% of baseline values 7 days after the final dose. This indicates a reversibility of the effects KBT-3022 (1).

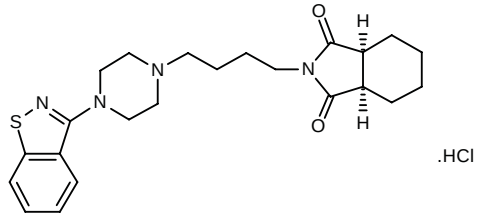
1. Tanemoto, K. et al. *Clinical study of KBT-3022: Platelet aggregation effects and pharmacokinetics in elderly (≥ 65 years of age) and nonelderly paients with chronic arterial occlusion.* Curr Ther Res 2000, 61(12): 891.

Original monograph - Drugs Fut 1991, 16: 105.

Perospirone Hydrochloride Lullan®

Antipsychotic

EN: 161247



$C_{23}H_{30}N_4O_2S.HCl$ **Sumitomo; Welfide**

A report reviewing the pharmacological properties of perospirone concluded that the agent acts as both a 5-HT_2 and D_2 receptor antagonist, indicating broader clinical efficacy and a lower risk for extrapyramidal side effects as compared to haloperidol as a treatment for schizophrenia. Results from a double-blind study conducted in schizophrenic patients showed that the agent was significantly better than haloperidol in positive symptom improvement and resulted in lower extrapyramidal scores (1).

A new fine granule formulation of perospirone hydrochloride has been assessed in an open multicenter trial in 42 patients with schizophrenia. The patients received perospirone fine granules at doses of 8-48 mg/day for 8 weeks and were rated for efficacy on the Global Improvement Rate, Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Symptom Scale (PANSS). According to the Glocal Improvement Rate scale, at the end of treatment, moderate to marked improvement and slight to marked improvement was obtained in 49% and 66% of patients, respectively. Mean total BPRS scores were significantly lower from the second week through to the end of the study compared to baseline, and the total PANSS scores also decreased significantly. Improvement in hallucinations, anxiety and emotional withdrawal was seen. Side effects were reported by 62% of patients, extrapyramidal symptoms by 45% and laboratory abnormalities were detected in 27% of patients. It was concluded that the optimal dose range for the fine granules is 12-48 mg/day, similar to the effective range for the tablet formulation (2).

Perospirone hydrochloride hydrate, developed at Sumitomo, has been launched in Japan as Lullan®. The product is copromoted by Sumitomo and the Welfide subsidiary Yoshitomi as tablets of 4 and 8 mg (3).

1. Ohno, Y. *Pharmacological characteristics of perospirone hydrochloride, a novel antipsychotic agent.* Folia Pharmacol Jpn 2000, 116(4): 231.

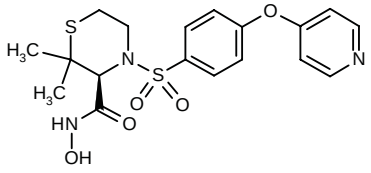
2. Matsubara, R., Hirabayashi, Y., Narita, H., Ikeda, T., Miyano, S., Yamashita, I. *Clinical evaluation of perospirone hydrochloride (SM-9018) in fine granule form for the treatment of schizophrenic patients.* Int J Neuropsychopharmacol 2000, 3(Suppl. 1): Abst P.01.172.

3. *Japanese introduction announced for new atypical antipsychotic.* DailyDrugNews.com (Daily Essentials) Feb 23, 2001.

Original monograph - Drugs Fut 1991, 16: 122.

Prinomastat *Oncolytic*
AG-3340 *Matrix Metalloproteinase Inhibitor*

EN: 231137



$C_{18}H_{21}N_3O_5S_2$ **Agouron**

Results from a study using SCID-NOD mice implanted s.c. with U87 human glioma xenografts showed that AG-3340 (100 mg/kg i.p. o.d.) inhibited xenograft growth, cellular invasion, angiogenesis and increased survival. These effects were enhanced when AG-3340 was combined with radiotherapy (7.5 Gy) (1).

A study using rabbits with surgically induced posterior penetrating eye trauma in one eye demonstrated the efficacy of prinomastat (0.5 mg intravitreally for 6 weeks starting 1 week posttrauma) in inhibiting posttraumatic proliferative vitreoretinopathy (PVR). Eyes treated with prinomastat showed significantly lower scores when measuring the degree of PVR as compared to control eyes (3.58 *vs.* 5.75), and significantly fewer prinomastat-treated eyes displayed tractional retinal detachment (3 *vs.* 9 eyes) (2).

The effects of prinomastat in two *in vivo* breast cancer xenograft models were investigated. Prinomastat has demonstrated broad-spectrum antitumor activity in rodents and is in clinical evaluation for lung, esophageal and prostate cancer. The first model employed human breast cancer MDA-MB-231 cells inoculated into the mammary fat pad of nude mice, treated with prinomastat 25 or 50 mg/kg twice daily p.o. starting when tumors were palpable. Significant and dose-dependent suppression of primary tumor growth was seen, with 59% and 70% reductions, respectively, on day 60 at doses of 25 and 50 mg/kg. Another model involving intracardiac inoculation of tumor cells mimics bone metastasis in breast cancer. Treatment with prinomastat 50 mg/kg twice daily p.o. starting 48 h before tumor cell inoculation delayed osteolytic bone damage. At these doses, the drug was well tolerated (3).

Pfizer has decided to halt two phase III trials of prinomastat in combination with standard chemotherapy in patients with advanced hormone-refractory prostate cancer and advanced (stage IV) non-small cell lung cancer. This decision was based on the failure to meet the primary efficacy objectives and was not related to safety concerns. Pfizer will continue to study prinomastat in a second ongoing trial in patients with stage IIIB non-small cell lung cancer. In addition, the company intends to test the product in earlier stage disease and other tumor types. Four phase II trials are now under way and two additional phase II trials will begin shortly (4).

1. Shi, Z., Raithatha, S., Spencer, D. et al. *Enhanced effectiveness of a novel MMP inhibitor, prinomastat (AG3340) with radiotherapy (RT) in a glioma model.* Proc Amer Assoc Cancer Res 2000, 41: Abst 2071.

2. Ozerdem, U., Mach-Hofacre, B., Keefe, K., Pham, T., Soules, K., Appelt, K., Freeman, W.R. *The effect of prinomastat (AG3340), a synthetic inhibitor of matrix metalloproteinases, on posttraumatic proliferative vitreoretinopathy.* Ophthalmic Res 2001, 33(1): 20.

3. Waltham, M., Tester, A., Ruangpanit, N., Bills, M., Shalinsky, D.R., Thompson, E.W. *Prinomastat inhibits primary tumor growth and retards osteolytic disease in xenograft models of breast cancer metastasis.* 23rd Annu San Antonio Breast Cancer Symp (Dec 6-9, San Antonio) 2000, Abst 359.

4. *Pfizer discontinues phase III trials of prinomastat in advanced cancers.* DailyDrugNews.com (Daily Essentials) Aug 7, 2000.

Original monograph - Drugs Fut 2000, 25: 150.

Additional References

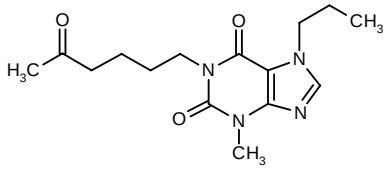
Chong, W.K.M. *Matrix metalloproteinases (MMP) inhibitors as possible cancer therapeutics: Molecular modelling, SAR and synthesis.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst.

Hortobagyi, G.N. *Integration of new drugs in the management of advanced breast cancer.* 10th Int Congr Anti-Cancer Treat (Jan 31-Feb 3, Paris) 2000, Abst EL034.

Morton, T.L. et al. *In vitro transport of the model compounds, nelfinavir mesylate, prinomastat, and mannitol, across bovine brain microcapillary endothelial cells: Temperature dependence studies.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 2102.

Propentofylline *Cognition Enhancer*

EN: 090664



$C_{15}H_{22}N_4O_3$ **Aventis Pharma**

Aventis has decided to discontinue development of propentofylline as a potential treatment for Alzheimer's disease. This decision was based on the disappointing outcome of a recently completed 72-week, placebo-controlled phase IIIb study. In this study, patients receiving

  CCC: 0377-8282/2001

long-term treatment with propentofylline did not show significant benefits over patients receiving placebo (1).

1. *Aventis discontinues development of propentofylline.* DailyDrugNews.com (Daily Essentials) March 6, 2000.

Original monograph - Drugs Fut 1982, 7: 119.

Recombinant Methioninase rMETase ONCase®

Oncolytic

EN: 219531

AntiCancer

A study examining the survival of nude mice with human colon cancer (AC3488) liver metastasis examined the efficacy of liver resection (3 days after implantation) combined with 1 of 2 schedules of combination 5-FU + recombinant methinoninase (rMETase). In schedule A, rMETase (100 units b.i.d. i.p.) was given 24 h before resection and for 9 days after 5-FU treatment (20 mg/kg i.p. 2 h before and 4 days after resection); in schedule B, rMETase (100 units b.i.d.) was given first for 9 days after resection followed by 4 days of 5-FU (20 mg/kg) treatment. After 40 days, 90% of the animals treated with schedule B survived as compared to 40% on schedule A, 50% treated with 5-FU alone, 100% treated with rMETase alone and 100% treated only with liver resection (1).

Results from a study in athymic mice with Daoy medulloblastoma and D-54 glioblastoma multiforme xenografts showed that tumor growth was delayed (20 and 12 days, respectively) by reducing plasma methionine (under 5 μM for up to 12 days) by treatment with a diet deficient in methionine, homocysteine and choline and i.p. injection of rMETase (1500 units/kg every 8 h) + homocysteine (20 mg/kg every 8 h). Mild toxicity seen with treatment included weight loss in 6% of the animals. Depletion of plasma methionine resulted in mitotic and cell cycle arrest, apoptosis and necrosis although tumor eradication was not observed. Plasma methionine returned to normal values and tumors resumed growth when rMETase treatment was stopped after 12 days. In addition, the efficacy of BCNU (25 mg/msq administered after 12-days of methionine depletion) was enhanced against both Daoy and D-54 xenografts with 5/6 and 3/6, respectively, eradicated and regression observed in the remaining animals; both Daoy and D-54 were resistant to BCNU alone (2).

The efficacy of combination liver resection (3 days after tumor implantation) and sequential rMETase and 5-FU treatment were demonstrated in a study using nude mice with a human AC3488 metastatic colon tumor implanted into the left lobe of the liver. All animals were first treated with rMETase (100 units b.i.d. i.p.) and 5-FU (20 mg/kg i.p.) 24 and 2 h, respectively, before resection. After resection, animals received one of the following schedules: A: 5-FU (20 mg/kg) for 4 days followed by rMETase (200 units/day) for 9 days; B: rMETase (100 units b.i.d.) for 9 days followed by 5-FU (20 mg/kg) for 4 days. At 55 days after implantation, 80, 20 and 50% of the animals were alive in groups treated with schedule B, schedule A and 5-FU alone, respectively; untreated animals and all animals treated only with resection or rMETase alone died (3).

1. Rashidi, B., An, Z., Sun, F.-X., Han, Q., Moossa, A.R., Hoffman, R.M. *Intra-hepatectomy methioninase and 5-FU treatment prevents human colon cancer liver metastasis recurrence in nude mice.* 10th Int Congr Anti-Cancer Treat (Jan 31-Feb 3, Paris) 2000, Abst S6-10.

2. Kokkinakis, D.M., Tan, Y., Zung, X., Hoffman, R.M. *Recombinant methioninase and BCNU in combination eradicate BCNU-resistant human CNS tumors in athymic mice.* 10th Int Congr Anti-Cancer Treat (Jan 31-Feb 3, Paris) 2000, Abst S11-06.

3. Rashidi, B., An, Z., Sun, F., Machover, D., Moosa, A.R., Hoffman, R.M. *Methioninase and 5-FU intra-hepatectomy combination therapy prevents human colon cancer liver metastasis recurrence in nude mice.* Proc Am Soc Clin Oncol 2000, 19: Abst 1068.

Original monograph - Drugs Fut 1997, 22: 130.

Additional References

Kuh, H.-J. et al. *Dose ratio-dependent synergistic interaction between oxaliplatin and 5-FU in human gastric cancer cells.* Proc Amer Assoc Cancer Res 2000, 41: Abst 1534.

Machover, D. et al. *Cytotoxic synergism of methioninase in combination with 5-fluorouracil and folinic acid.* Proc Amer Assoc Cancer Res 2000, 41: Abst 1535.

Miki, K. et al. *Methioninase gene therapy of human cancer cells is synergistic with recombinant methioninase treatment.* Proc Amer Assoc Cancer Res 2000, 41: Abst 4262.

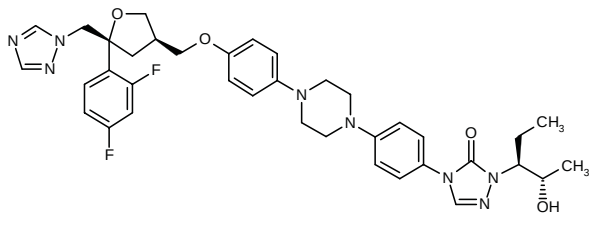
Sun, F. et al. *Mechanisms of radiation sensitization by recombinant methioninase (RMETASE).* Proc Amer Assoc Cancer Res 2000, 41: Abst 1867.

Xu, M. et al. *Methioninase as a tumor-selective apoptosis inducer.* Proc Amer Assoc Cancer Res 2000, 41: Abst 4919.

SCH-56592 Posaconazole

Antifungal

EN: 226562



$C_{37}H_{42}F_2N_8O_4$

Schering-Plough

The *in vitro* activity of SCH-56592 was compared to fluconazole, itraconazole and ketoconazole against 257 clinical yeast isolates including 220 isolates of 12 species of *Candida*, 15 isolates of *Cryptococcus neoformans*, 15 isolates of *Saccharomyces cerevisiae* and 7 isolates of *Rhodotorula rubra*. SCH-56592 ($MIC_{50/90}$ = 0.06/2 μg/ml) was more active than fluconazole ($MIC_{50/90}$ = 1/64 μg/ml) and slightly more active than itraconazole ($MIC_{50/90}$ = 0.25/2 μg/ml) and ketoconazole ($MIC_{50/90}$ = 0.125/4 μg/ml) (1).

The *in vitro* activities of posaconazole were compared to itraconazole, voriconazole and amphotericin B against clinical *Aspergillus* isolates (284 *A. fumigatus*, 66 *A. niger*, 31 *A. flavus* and 43 *Aspergillus* spp.) and laboratory selected *A. fumigatus* isolates resistant to amphotericin B (15), itraconazole (25) and voriconazole (12). Significantly lower geometric mean MICs were obtained for posaconazole for *A. fumigatus* (0.17 ± 0.11 mg/l) and non-*A. fumigatus* (0.16 ± 0.28 mg/l) isolates as compared to the other agents and the MICs for posaconazole increased only 2- to 3-fold against itraconazole- and voriconazole-resistant isolates. The fungicidal activity of posaconazole was time- and dose-dependent with minimum fungicidal concentrations (MFCs) of 4.45 ± 2.7 and 4.14 ± 3.3. mg/l obtained against *A. fumigatus* and non-*A. fumigatus* isolates, respectively (2).

Researchers have used mice with depleted CD4 and CD8 cell counts to mimic the immunosuppression seen in AIDS patients in order to test posaconazole in the treatment of histoplasmosis under this condition. Immunosuppressed mice were infected with *Histoplasma capsulatum* before treatment. Posaconazole 1 and 0.1 mg/kg by gavage was found to be highly effective in treating disseminated histoplasmosis, with equivalent efficacy to amphotericin B 2 mg/kg i.p. or itraconazole 75 mg/kg orally in preventing death. All mice treated with these compounds at these doses survived to day 29 of the study. Posaconazole at doses of 1 mg/kg and higher also reduced fungal burden and sterilized lung and spleen tissues in 70% of the mice; similar results were obtained with itraconazole 75 mg/kg. The authors concluded that, overall, posaconazole was as effective as amphotericin B and more effective than itraconazole in intratracheally induced histoplasmosis in immunosuppressed mice (3).

The efficacy of SCH-56592 was shown *in vivo* in immunocompetent and immunosuppressed (cyclophosphamide) mice infected with several strains of *Trypanosoma cruzi* parasites including strains susceptible (CL), partially resistant (Y) or highly resistant (Colombiana, SC-28, VL-190) to nifurtimox and benznidazole; all strains were resistant to antifungal azoles. SCH-56592 (20 mg/kg/day p.o. for 20 days starting on day 4 postinfection) protected immunocompetent animals against death (80-90%) in a manner similar or superior to benznidazole (100 mg/kg/day); 90-100% of the surviving animals infected with CL or Y strains and 50% of those infected with the Colombiana strain were cured with SCH-56592 treatment. SCH-56592 (20 mg/kg/day) and benznidazole (100 mg/kg/day) both attenuated the significant decrease in the mean survival time seen in immunosuppressed animals. Overall cure rate in these animals was higher for SCH-56592 as compared to benznidazole and similar results were obtained when animals were treated with 43 doses. Increased survival was also observed in animals with chronic disease treated with SCH-56592 (for 20 days starting on day 120 postinfection), where cures were seen in 50-60% of surviving animals regardless of strain; no cures were seen with benznidazole treatment (4).

A study using a neutropenic rabbit model of invasive pulmonary aspergillosis (*A. fumigatus*) and assessing fungal burden and the serum galactomannan index (GMI) showed the antifungal efficacy of posaconazole (2, 6 or 20 mg/kg for 12 days starting 24 h after endotracheal inoculation). Posaconazole treatment was compared to itraconazole. Rabbits treated with posaconazole displayed significant decreases in GMI. GMI negative animals were observed in the 6 and 20 mg/kg dose groups at day 6 which correlated with low pulmonary fungal burden. All control animals were GMI positive. In contrast to animals treated with 20 mg/kg itraconazole who were GMI negative, animals treated with 2 and 6 mg/kg itraconazole remained GMI positive and showed progression of infection and increases in tissue fungal burden (5).

SCH-56592 was shown to be more effective than itraconazole and as effective as amphotericin B in an immunosuppressed rabbit model of invasive aspergillosis. Treatment with SCH-56592 increased survival and significantly decreased tissue *Aspergillus* spp. counts (6).

The pharmacokinetics of posaconazole (2, 4 and 6 mg/kg p.o. once daily or b.i.d. for 12 days starting 24 h after endotracheal inoculation) were reported from a study using a neutropenic rabbit model of invasive pulmonary aspergillosis. The pharmacokinetics obtained showed linear disposition and fit a 2-compartment model. Plasma and lung C_{max} values ranged from 0.18 ± 0.05 to 1.09 ± 0.15 μg/ml and 0.30 ± 0.08 to 2.16 ± 0.28 μg/g, respectively; mean plasma elimination $t_{1/2}$ was 7-10 h.

The pharmacokinetics of i.v. and oral SCH-56592 (hydroxypropyl-β-cyclodextrin [HPβCD] solution or 0.4% methylcellulose [MC] suspension) was examined in mice, rats, rabbits, dogs and cynomolgus monkeys. Oral bioavailability was shown in all species with higher availability observed with the HPβCD solution (52-100%) as compared to the MC suspension (14-48%) in mice (100 *vs.* 47%), rats (66 *vs.* 48%) and dogs (72 *vs.* 37%); the MC suspension resulted in better bioavailability in rabbits with a terminal half-life of 9 h. The terminal half-life of the agent following i.v. administration was 7, 15 and 23 h in mice, dogs and monkeys, respectively. Serum concentrations of the agent following oral dosing in mice, rats and dogs were dose-related and food reduced serum levels 4-fold in dogs. Accumulation was observed following multiple dosing (40 mg/kg for 8 days) in dogs. Concentrations above the MIC values reported for most organisms were seen 24 h following single oral doses of 20 mg/kg in mice, rats and rabbits and 10 mg/kg in dogs and monkeys (8).

The population pharmacokinetics of posaconazole (50-400 mg/day p.o. for 14 days with food; 400 mg b.i.d. only on day 1) were reported from results of a phase II study in HIV-positive patients with oropharyngeal candidiasis. It was concluded that the pharmacokinetics of the agent follow a 1-compartment model with first-order absorption and elimination. Mean clearance was 31.3 l/h with an interpatient variability of 72%. No covariants were found to affect the pharmacokinetics of the agent, indicating that it may be used in a broad patient population (9).

The effects of liver dysfunction on the pharmacokinetics of single-dose posaconazole (200 mg p.o.) were examined in an open-label, parallel-group, multicenter phase I study in 16 subjects with either normal liver function or mild, moderate or severe hepatic dysfunction. Patients with moderate to severe liver dysfunction tended to have decreased C_{max} (414 and 347 ng/ml, respectively, *vs.* 508 ng/ml) and increased t_{max} (14 and 19.3 h, respectively, *vs.* 8 h) and $t_{1/2}$ (35.3 and 46.1 h, respectively, *vs.* 22.1 h) values as compared to normal subjects, suggesting delayed absorption and prolonged elimination. However, dose modifications were not recommended in these types of patients (10).

A multicenter, randomized, double-blind phase II study conducted in 485 HIV-positive patients with oropharyngeal candidiasis showed that posaconazole (50, 100, 200 or 400 mg p.o.) was as safe and effective as fluconazole (100 mg p.o.). Both treatments were well tolerated. Clinical success rates were 85, 87, 77 and 87% for the respective posaconazole doses as compared to 87% in the fluconazole-treated group. Mycological eradication rates were 36, 37, 35 and 40% for posaconazole, respectively, compared to 50% in the fluconazole group. Adverse events were mild and similar in all treatment groups with the exception of nausea which was seen in 17 and 5-9% of patients treated with fluconazole and posaconazole, respectively (11).

Preliminary results from a multicenter, noncomparator, open trial in 51 patients (47% leukemia and 14% HIV-positive) refractory or intolerant to standard therapy showed the safety and efficacy of oral posaconazole (200 mg q.i.d. for inpatients and 400 mg b.i.d. for outpatients for 2-24 weeks) in treating invasive fungal infections. Treatment was well tolerated and clinical responses for patients with aspergillosis (25 cases), candidiasis (7), fusariosis (5) and other infections (14) were 53, 75, 75 and 70%, respectively, at week 4, and 85, 67, 50 and 50%, respectively, at week 8. Common drug-related adverse events were diarrhea (7.8%), asthenia (3.9%), flatulence (3.9%) and eye pain (3.9%) (12).

The safety and tolerability of posaconazole (400 mg/day for 6 months) were shown in a multicenter trial conducted in 20 patients with chronic pulmonary or nonmeningeal disseminated coccidioidomycosis (soft tissue and/or skeletal). Fifteen subjects completed 23 weeks or more of treatment with 1 patient dying due to rheumatoid lung disease and 4 others switched to fluconazole or itraconazole. The median scores using the Mycoses Study Group system at 16 weeks was reduced to 40% of baseline (11 patients were below 50%). Scores were reduced to 22% of baseline at 24 weeks. The 10 adverse events reported were concluded to be probably or possibly related to treatment (13).

Posaconazole is the proposed international nonproprietary name for SCH-56592 (14).

1. Barchiesi, F., Arzeni, D., Fothergill, A.W., Di Francesco, L.F., Caselli, F., Rinaldi, M.G., Scalise, G. *In vitro activities of the new antifungal triazole SCH 56592 against common and emerging yeast pathogens.* Antimicrob Agents Chemother 2000, 44(1): 226.

2. Manavathu, E.K., Cutright, J.L., Loebenberg, D., Chandrasekar, P.H. *A comparative study of the in vitro susceptibilities of clinical and laboratory-selected resistant isolates of Aspergillus spp. to amphotericin B, itraconazole, voriconazole and posaconazole (SCH 56592).* J Antimicrob Chemother 2000, 46(2): 229.

3. Connolly, P. et al. *Comparison of a new triazole, posaconazole, with itraconazole and amphotericin B for treatment of histoplasmosis following pulmonary challenge in immunocompromised mice.* Antimicrob Agents Chemother 2000, 44(10): 2604.

4. Molina, J., Martins-Filho, O., Brener, Z., Romanha, A.J., Loebenberg, D., Urbina, J.A. *Activities of the triazole derivative SCH 56592 (posaconazole) against drug-resistant strains of the protozoan parasite Trypanosoma (Schizotrypanum) cruzi in immunocompetent and immunosuppressed murine hosts.* Antimicrob Agents Chemother 2000, 44(1): 150.

5. Petraitiene, R., Petraitis, V., Sein, T., Groll, A., Schaufele, R.L., Bacher, J., Walsh, T.J. *Correlation between serum galactomannan concentrations and antifungal efficacy of posaconazole (SCH 56592) in treatment and prevention of invasive pulmonary aspergillosis in persistently neutropenic rabbits.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst J-1346.

6. Kirkpatrick, W.R., McAtee, R.K., Fothergill, A.W., Loebenberg, D., Rinaldi, M.G., Patterson, T.F. *Efficacy of SCH 56592 in a rabbit model of invasive aspergillosis.* Antimicrob Agents Chemother 2000, 44(3): 780.

7. Groll, A.R., Mickiene, D., Petraitiene, R., Petraitis, V., Sein, T., Roach, J., Roth, K., Piscitelli, S.C., Walsh, T.J. *Pharmacokinetics and pharmacodynamics of posaconazole (SCH 56592) in a neutropenic animal model of invasive pulmonary aspergillosis.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst J-1675.

8. Nomeir, A.A., Kumari, P., Hilbert, M.J. et al. *Pharmacokinetics of SCH 56592, a new azole broad-spectrum antifungal agent, in mice, rats, rabbits, dogs, and cynomolgus monkeys.* Antimicrob Agents Chemother 2000, 44(3): 727.

9. Jen, J., Courtney, R., Chung, C., Keung, A., Laughlin, M., Batra, V.K., Gontz, H., Lim, J., Clement, R., Haijan, G. *Population pharmacokinetic analysis of posaconazole (SCH 56592) in HIV-positive patients with oropharyngeal candidiasis.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 2329.

10. Courtney, R.D., Laughlin, M., Gontz, H., Lim, J., Clement, R., Keung, A., Salfi, M., Batra, V.K. *Single-dose pharmacokinetics of posaconazole in subjects with various degrees of chronic liver*

disease. Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 3495.

11. Vazquez, J.A., Northlan, R., Miller, S., Dickinson, G., Wright, G. *Posaconazole compared to fluconazole for oral candidiasis in HIV-positive patients.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst J-1107.

12. Hachem, R.Y., Raad, L.I., Afif, C.M., Negroni, R., Graybill, J., Hadley, S., Kamtarjian, H., Adams, S., Mukwaya, G. *An open, non-comparative multicenter study to evaluate efficacy and safety of posaconazole (SCH 56592) in the treatment of invasive fungal infections (IFI) refractory (R) to or intolerant (I) to standard therapy (ST).* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst J-1109.

13. Catanzaro, A., Cloud, G., Stevens, D., Levine, B., Williams, P., Johnson, R., Sanchez, R., Perez, L., Rendon, A., Mireles, L., Lutz, J., Holloway, M., Blum, D., Murphy, M. *Safety and tolerance of posaconazole (SCH 56592) in patients with nonmeningeal disseminated coccidioidomycosis.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst J-1417.

14. *Proposed international nonproprietary names (Prop. INN): List 82.* WHO Drug Inf 1999, 13(4): 284.

Original monograph - Drugs Fut 1996, 21: 160.

Additional References

Al-Abdely, H.M. et al. *SCH 56592, amphotericin B, or itraconazole therapy of experimental murine cerebral phaeohyphomycosis due to Ramichloridium obovoideum ("Ramichloridium mackenziei").* Antimicrob Agents Chemother 2000, 44(5): 1159.

Cacciapuoti, A. et al. *In vitro and in vivo activities of SCH 56592 (posaconazole), a new triazole antifungal agent, against Aspergillus and Candida.* Antimicrob Agents Chemother 2000, 44(8): 2017.

Dupont, B. *Recent advances in the treatment of esophageal candidiasis.* Rev Iberoam Micol 2000, 17(3): Abst L-24.

Espinel-Ingroff, A. *Germinated and nongerminated conidial suspensions for testing of susceptibilities of Aspergillus spp. to amphotericin B, itraconazole, posaconazole, ravuconazole, and voriconazole.* Antimicrob Agents Chemother 2001, 45(2): 605.

González, G.M. et al. *In vitro activities of approved and investigational antifungal agents against 44 clinical isolates of basidiomycetous fungi.* Antimicrob Agents Chemother 2001, 45(2): 633.

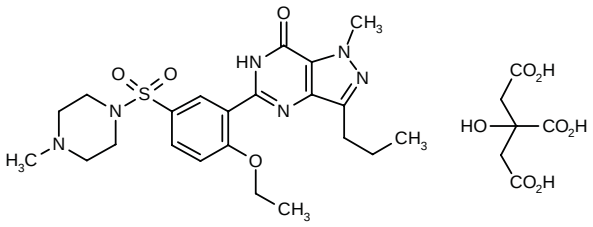
Kim, H. et al. *Chiral high-performance liquid chromatographic analysis of antifungal SCH 56592 and evaluation of its chiral inversion in animals and humans.* Chirality 2000, 12(7): 590.

Nieto, L. et al. *Posaconazole equivalent to fluconazole in the treatment of oropharyngeal candidiasis.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst J-1108.

Odds, E.C. *Have we seen the best of the triazole anti-fungals?* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst G-639.

Sildenafil Citrate *Treatment of Erectile Dysfunction*
Viagra® *Treatment of Female Sexual Dysfunction*

EN: 184491



$C_{22}H_{30}N_6O_4S.C_6H_8O_7$ **Pfizer; Bagó**

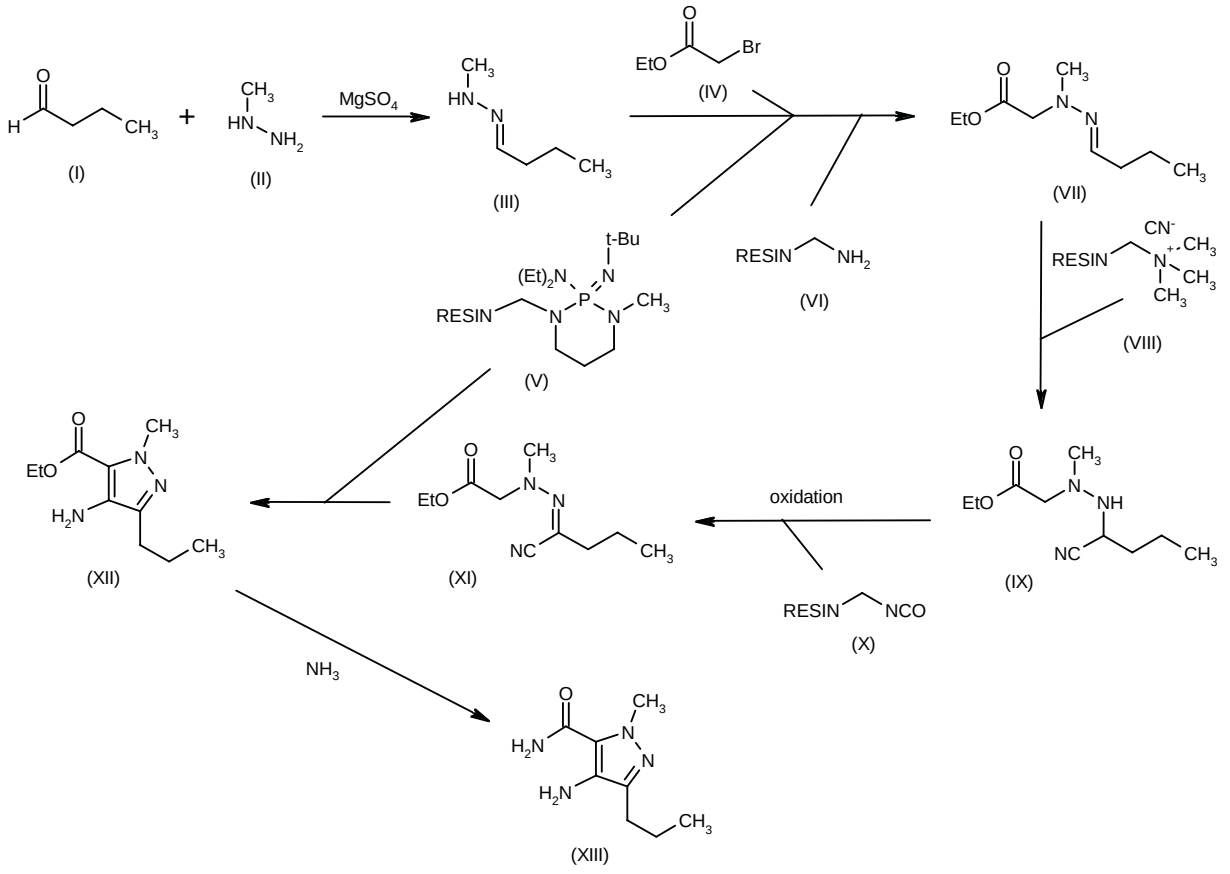
A synthesis of sildenafil using polymer-supported reagents has been reported:

1) Synthesis of the aminopyrazole intermediate (XIII): The reaction of butanal (I) with methylhydrazine (II) in dichloromethane in the presence of $MgSO_4$ gives the corresponding hydrazide (III), which is alkylated with ethyl bromoacetate (IV) by means of the polymer-supported base 2-(*tert*-butylimino)-2-(diethylamino)-1,3-dimethylperhydro-1,3,2-diazaphosphorine (PS-BEMP) (V) and polymer-supported methylamine (VI) to yield the hydrazino ester (VII). Treatment of compound (VII) with an ion exchange tetramethylammonium cyanide resin (VIII) in refluxing ethanol containing a catalytic amount of AcOH affords the adduct (IX), which is dehydrogenated with Pd/C/cyclopentene or MnO_2 and treated with a polymer-supported ethyl isocyanate resin (X) in order to eliminate the unreacted product, providing the hydrazone (XI). Cyclization of (XI) by means of PS-BEMP (V) in ethanol gives 4-amino-1-methyl-3-propyl-1*H*-pyrazole-5-carboxylic acid ethyl ester (XII), which is finally treated with ammonia in methanol to afford the desired pyrazolecarboxamide intermediate (XIII) (1). Scheme 1.

2) Synthesis of sildenafil: Reaction of 5-(chlorosulfonyl)-2-hydroxybenzoic acid (XIV) with 1-methylpiperazine (XV) by means of DIEA gives the sulfonamide (XVI), which is treated with diethyl sulfate, yielding 2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)benzoic acid (XVII). The activation of (XVII) with a polymer-supported 1-hydroxybenzotriazole (HOBt) variant (XVIII) and bromotris(pyrrolidino)phosphonium (PyBrOP) as catalyst affords the activated ester (XIX), which is condensed with the aminopyrazole intermediate (XIII), and treated with the methyl isocyanate resin (X) in order to eliminate the excess of aminopyrazole (XIII), to provide the diamide (XX). Finally, the cyclization and dehydration to sildenafil are performed by microwave irradiation of an ethanolic solution of compound (XX) containing a catalytic amount of NaOEt (1). Scheme 2.

Johns Hopkins University researchers have identified the mechanism producing gastroparesis in diabetic mice, and have found that it can be reversed with sildenafil or insulin. In nonobese diabetic mice, in streptozotocin-diabetic mice and in knockout mice lacking the gene that

Scheme 1: Synthesis of Intermediate (XIII) of Sildenafil



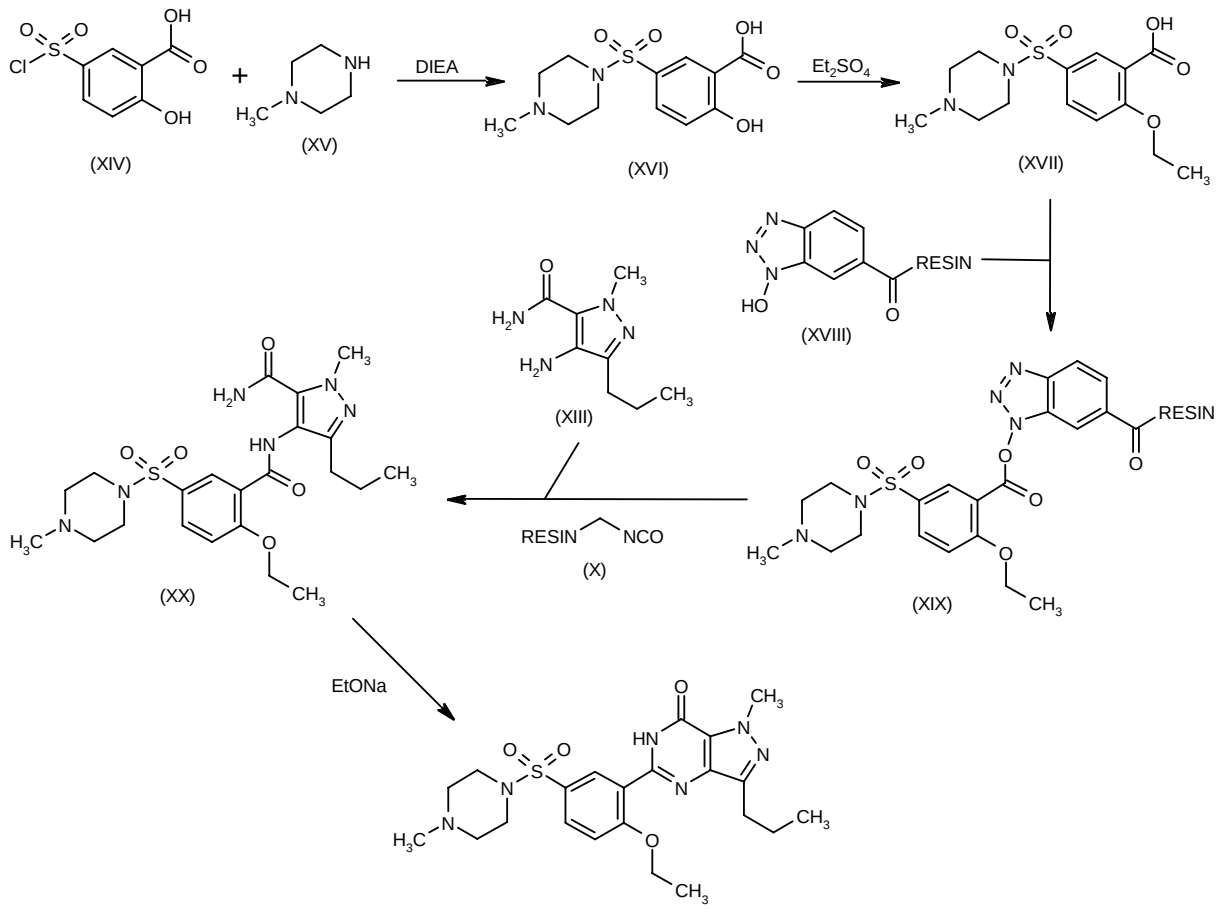
produces nitric oxide, nitric oxide production was at zero or significantly lower levels than that in normal mice. All of the mice also exhibited the symptoms of gastroparesis, establishing the link between the condition and nitric oxide production. After administration of insulin, nitric oxide expression and pyloric muscle function were restored to normal. Sildenafil treatment was also found to restore normal gastric emptying. Sildenafil treatment for gastroparesis may be especially beneficial in diabetic patients due to the drug's rapid onset of action and because it might alleviate some of the symptoms not affected by insulin (2).

A pilot clinical study was performed in hysterectomized women with the aim of determining the relationship between hysterectomy and sexual complaints, as well as the impact of sildenafil citrate. The study included 24 women, 22 with a history of hysterectomy and 2 with a hysterectomy/oophorectomy, the latter on HRT. At baseline and following 6 weeks of sildenafil, the subjects filled out the Brief Index of Sexual Function for Women (BISF-Q) questionnaire. Sildenafil treatment was associated with significant decreases in the symptoms of low sensation (22% *vs.* 100% at baseline), inability to reach orgasm (18% *vs.* 100%) and pain or discomfort (33% *vs.* 68%), as well as a decrease in lubrication difficulties (3).

A randomized, double-blind, placebo-controlled, parallel-group, flexible-dose study conducted in 229 patients showed the safety and efficacy of sildenafil (25-100 mg for 12 weeks) as a treatment for erectile dysfunction in men with type 2 diabetes. A significant improvement was seen in the number of intercourse attempts that were successful in patients treated with sildenafil as compared to placebo (14.4-58.8 *vs.* 13.2-14.4%). Adverse events were mild and moderate, with headache (20%) and flushing (15%) the most common in patients treated with the agent; only 2 patients discontinued from this group for adverse events (4).

Analysis of subgroups (152 men with type 1 diabetes, 822 men with type 2 diabetes and 1693 nondiabetics) from 11 randomized, double-blind, placebo-controlled studies showed the efficacy of sildenafil (25-100 mg for 3-6 months) in patients with type 1 diabetes. Efficacy was assessed from a global efficacy question (did treatment improve your erections?) and 2 International Index of Erectile Dysfunction questions regarding the ability to achieve and maintain erections. Significant and similar

Scheme 2: Synthesis of Sildenafil



improvements in erectile function were observed in men with type 1 and type 2 diabetes. Responses rates in diabetic patients were less than those observed in nondiabetic patients (5).

Results from the first prospective study of sildenafil citrate conducted in patients with left ventricular dysfunction (LVD) have been presented. Sildenafil was administered to 19 patients who met the International Index of Erectile Function (IIEF) criteria for erectile dysfunction and 13 excluded patients served as controls. The two groups were similar with respect to age, percent left ventricular ejection fraction (LVEF), NYHA class, ischemic etiology and medical regimen. In addition, no significant differences in headaches, flushing, chest pain, dyspnea, palpitations or nausea/vomiting were observed between groups. These results suggest that sildenafil may be safe and effective for the treatment of erectile dysfunction in patients with heart failure (6).

In a University of Pennsylvania trial in 14 men with severe coronary artery disease, administration of 100 mg oral sildenafil produced no negative cardiovascular events. In this study, all of the patients had severe stenosis of at least one coronary artery and were scheduled to undergo percutaneous coronary revascularization. Blood pressure and blood flow were measured in patients during cardiac catheterization, both prior to sildenafil administration and 1 h after drug intake. Sildenafil had no effect on pulmonary capillary wedge pressure, right atrial pressure, heart rate or cardiac output, although small decreases (< 10%) in systemic arterial and pulmonary arterial pressures were seen. Administration of the drug did not result in significant changes in average peak coronary flow velocity, coronary artery diameter, volumetric coronary blood flow or coronary vascular resistance. A small beneficial effect on coronary blood flow reserve was noted. The authors conclude that oral sildenafil is safe for patients with stable coronary artery disease who are not taking medications containing nitrates (7).

1. Baxendale, I.R., Ley, S.V. *Polymer-supported reagents for multi-step organic synthesis: Application to the synthesis of sildenafil.* Bioorg Med Chem Lett 2000, 10(17): 1983.

2. Watkins, C.C. et al. *Insulin restores neuronal nitric oxide synthase expression and function that is lost in diabetic gastropathy.* J Clin Invest 2000, 106(3): 373.

3. Berman, L.A., Berman, J.R., Padwa, R., Goldstein, I. *Hysterectomy and sexual dysfunction: Effects of sildenafil in a clinical setting.* J Urol 2000, 163(4, Suppl.): Abst 857.

4. Boulton, A.J.M., Ziegler, D., Sweeney, M. *The first study of sildenafil for erectile dysfunction in men with type 2 diabetes mellitus.* Diabetes 2000, 49(Suppl. 1): Abst 143-OR.

5. Blode, L., Koreman, S.G., Siegel, R.L., Orazem, J. *Sildenafil citrate for treatment of erectile dysfunction is similarly effective in men with type 1 and type 2 diabetes mellitus.* Diabetes 2000, 49(Suppl. 1): Abst 354-P.

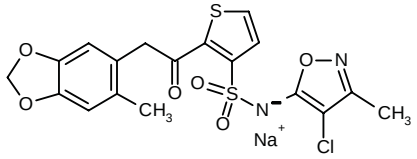
6. Hebert, K.A., Arcement, L.M., Ferguson, T.G. *Is sildenafil (Viagra®) safe and effective for the treatment of erectile dysfunction in patients with heart failure?* Circulation 2000, 102(18, Suppl.): Abst 2009.

7. Herrmann, H.C., Chang, G., Klugherz, B.D., Mahoney, P.D. *Hemodynamic effects of sildenafil in men with severe coronary artery disease.* New Engl J Med 2000, 342(22): 1622.

Original monograph - Drugs Fut 1997, 22: 138.

Sitaxsentan Sodium *Treatment of Heart Failure*
TBC-11251 *Treatment of Pulmonary Hypertension*
Antihypertensive

EN: 234463 *Endothelin ET_A Antagonist*



$C_{18}H_{14}ClN_2O_6S_2.Na$ **Icos-Texas Biotechnol.; LG Chem**

An open-label trial assessed 3 different doses of sitaxsentan (160, 320 and 480 mg) for 14 days in 30 patients with mild to moderate essential hypertension. Statistically significant reductions in sitting diastolic and systolic blood pressure were recorded at all dose levels, without an increase in heart rate. In fact, the heart rate was reduced by the two higher doses of sitaxsentan. Treatment was well tolerated, headache, edema and anemia being the most frequent adverse events in this trial (1).

An open-label clinical study was performed in patients with primary or secondary pulmonary arterial hypertension who received chronic sitaxsentan. Sitaxsentan was well tolerated during the 12-week trial, the most common adverse events being nasal congestion, abnormal coagulation parameters and flushing. Chronic treatment with the drug produced significant and sustained improvements in exercise capacity, assessed by the mean distance walked over 6 min, as well as significant improvements in mean pulmonary artery pressure and pulmonary vascular resistance (2).

A double-blind, placebo-controlled, multicenter trial was conducted to assess the hemodynamic effects of sitaxsentan sodium in 48 patients with chronic NYHA functional class III or IV heart failure treated with ACE inhibitors and diuretics. Participants had a baseline pulmonary capillary wedge pressure of ≥ 15 mmHg and a cardiac index of ≤ 2.5 l/min/m^2. Sitaxsentan was administered at 1.5, 3.0 or 6.0 mg/kg as an intravenous infusion over 15 min and hemodynamic responses were measured for 6 h. Sitaxsentan administration led to decreases in pulmonary artery systolic pressure, pulmonary vascular resistance, mean pulmonary artery pressure and right atrial pressure. However, the drug had no effect on heart rate, mean arterial pressure, pulmonary capillary wedge pressure, cardiac index or systemic vascular resistance. Sitaxsentan also decreased elevated plasma ET-1 levels. This product may therefore have application in the treatment of patients with pulmonary hypertension secondary to chronic heart failure (3).

Enrollment is now complete in the open-label phase II trial of oral sitaxsentan sodium in 20 patients with pulmonary hypertension. A phase IIb/III trial of sitaxsentan is also planned for the second half of 2000 (4).

1. Calhoun, D.A., Renfroe, K., Alper, A.B. *Oral sitaxsentan, an endothelin-A selective receptor antagonist, reduces systemic blood pressure in patients with mild-to-moderate primary hypertension.* Circulation 2000, 102(18, Suppl.): Abst 2029.

2. Barst, R.J., Rich, S., Horn, E.M., McLaughlin, V.V., Kerstein, D., Widlitz, A.C., McFarlin, J.D., Dixon, R.A. *Efficacy and safety of chronic treatment with the oral selective endothelin-A receptor blocker sitaxsentan in pulmonary arterial hypertension (PAH).* Circulation 2000, 102(18, Suppl.): Abst 2076.

3. Givertz, M.M., Colucci, W.S., Lejemtel, T.H. et al. *Acute endothelin A receptor blockade causes selective pulmonary vasodilation in patients with chronic heart failure.* Circulation 2000, 101(25): 2922.

4. *Texas Biotechnology reports progress during Q1 2000.* DailyDrugNews.com (Daily Essentials) May 18, 2000.

Original monograph - Drugs Fut 2000, 25: 159.

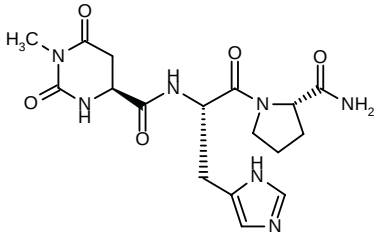
Additional Reference

Tilton, R.G. et al. *Attenuation of pulmonary vascular hypertension and cardiac hypertrophy with sitaxsentan sodium, an orally active ETA receptor antagonist.* Pulm Pharmacol Ther 2000, 13(2): 87.

Taltirelin
Ceredist®

Treatment of Neurodegenerative Diseases
TRH Analog

EN: 117740



$C_{17}H_{23}N_7O_5$ **Tanabe Seiyaku**

Taltirelin was launched for the first time on September 7, 2000 by Tanabe Seiyaku in Japan as Ceredist® tablets for the treatment of spinocerebellar degeneration. Spinocerebellar degeneration is a neurodegenerative disease of unknown origin, with symptoms such as ataxia due to degeneration of the cerebellum or spinal cord, and is designated a rare intractable disease by the Japanese Ministry of Health and Welfare. The only drug therapy available for the disease until now has been TRH by injection. Taltirelin is an orally bioavailable TRH derivative with a long duration of action and reduced hormonal effects compared to TRH (1).

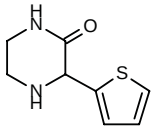
1. *First oral drug for rare neurodegenerative disease launched in Japan.* DailyDrugNews.com (Daily Essentials) Oct 2, 2000.

Original monograph - Drugs Fut 1991, 16: 127.

Tenilsetam

Treatment of Diabetic Retinopathy

EN: 117791



$C_8H_{10}N_2OS$ **Aventis Pharma**

Tenilsetam was shown in a preclinical model to prevent the development of early diabetic retinopathy. In male Wistar rats with streptozotocin-induced diabetes, treatment with tenilsetam (50 mg/kg for 9 months) was associated with complete inhibition of 3-deoxyglucosone-type advanced glycosylation endproducts (AGEs) and methylglyoxal-modified protein-type AGEs, and with partial reductions in anti-CML-type AGEs. Acellular capillaries were reduced by 70% among tenilsetam-treated rats, while pericyte loss was unaffected. These results demonstrate the ability of tenilsetam to inhibit AGEs and prevent the formation of diabetic retinopathy (1).

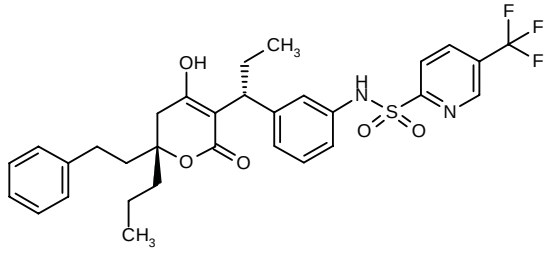
1. Lin, J., Alt, A., Lochnit, G., Bretzel, R.G., Hammes, H.-P. *Tenilsetam, a new AGE inhibitor, prevents early retinopathy experimental diabetes.* Diabetes 2000, 49(Suppl. 1): Abst 707-P.

Original monograph - Drugs Fut 1988, 13: 130.

Tipranavir

Anti-HIV
HIV Protease Inhibitor

EN: 240094



$C_{31}H_{33}F_32O_5S$ **Pharmacia; Boehringer Ingelheim**

An *in vitro* study characterized the genotypic resistance pattern for tipranavir using site-directed mutants mimicking HIV clinical isolates with > 4-fold resistance to the agent. Common genotypic patterns seen were a backbone including 10I, 20R, 36I, 71V and 84V with 82T and/or 90M. Viruses constructed with mutations only in the backbone were 2-fold resistant to the agent while those constructed with mutations in the backbone and 82T and/or 90M in addition to other secondary mutations, were 2.4-fold resistant to the agent. Passage of existing clinical isolates in increasing concentrations of tipranavir (up to 30 μM) resulted in a 13- to 30-fold increase in IC_{50} values and emergence of mutations in I47V, V82L, I85V and T91A. It was concluded that no combinations of known protease inhibitors would confer tipranavir resistance and resistance requires multiple and complex mutations (1).

The anti-HIV-1 activity of tipranavir was examined *in vitro* against patient isolates resistant to several protease inhibitors. IC_{50} and IC_{90} values were obtained using peripheral blood mononuclear cells with fixed amounts of virus. All isolates showed maximal resistance to indinavir, ritonavir and nelfinavir (IC_{50} = > 0.1 μM). Resistance mutations included L10I, K20R, L24I, M36I, N37D, G48V, I54V, L63P, I64V, A71V, V77I, V82A, I84V, L90M, I15V, E35D, R41K, D60E and A71T. The IC_{50} value for the agent against IIIB, 14aPre and N70 infections was 0.18 ± 0.02 μM and the IC_{90} value for all multidrug resistant isolates was 0.619 ± 0.055 μM. It was concluded that the agent may be effective in combination regimens in patients who failed other therapies containing protease inhibitors (2).

An *in vitro* study using recombinant viruses made from clinical isolates of protease inhibitor-treated HIV-1-infected patients showed the efficacy of tipranavir against isolates with reduced susceptibility to other protease inhibitors. Isolates containing resistance mutations at protease positions 10, 20, 36, 63, 71, 82 and 90 showed susceptibility to tipranavir and recombinant viruses with

24-fold reduced susceptibility to ritonavir were susceptible to tipranavir (3).

Tipranavir was shown to have similar activity against a wild-type HIV-1 isolate and an isolate derived from a patient heavily treated with protease inhibitors and carrying several mutations conferring protease inhibitor resistance, giving respective IC_{50} values of 0.224 μM and 0.268 μM (4).

Tipranavir is a selective, orally active HIV protease inhibitor with potent activity against laboratory strains and clinical isolates of HIV-1, including protease inhibitor-resistant strains, *in vitro*, giving a mean IC_{90} value of 0.16 μM. Due to the extensive protein binding of the compound, however, target plasma concentrations for antiviral activity in humans are estimated to be about 0.5-1.0 μM. Synergistic activity in combination with other antiretroviral agents was seen *in vitro* and tipranavir concentrations were found to be significantly increased by concomitant administration of ritonavir. Coadministration of tipranavir 300 and 1200 mg twice daily and ritonavir 200 mg twice daily for 2 weeks in treatment-naive patients was well tolerated and produced reductions in HIV RNA of 1.5-1.6 log_{10} copies/ml, with median trough tipranavir concentrations (21-67 μM) well above the target concentrations (5).

1. Kemp, S., Salim, M., Field, N., Dehertogh, P., Hertogs, K., Azijn, H., De Bethune, M.P. *Site-directed mutagenesis and in vitro drug selection studies have failed to reveal a consistent genotypic resistance pattern for tipranavir.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst I-2113.

2. Rusconi, S., La Seta Catamancio, S., Citterio, P. et al. *Susceptibility to PNU-140690 (tipranavir) of human immunodeficiency virus type 1 isolates derived from patients with multidrug resistance to other protease inhibitors.* Antimicrob Agents Chemother 2000, 44(5): 1328.

3. Back, N.K.T., van Wijk, A., Remmerswaal, D., van Monfort, M., Nijhuis, M., Schuurman, R., Boucher, C.A.B. *In-vitro tipranavir susceptibility of HIV-1 isolates with reduced susceptibility to other protease inhibitors.* AIDS 2000, 14(1): 101.

4. Bulgheroni, E., Le Seta Catamancio, S., Citterio, P., Galazzi, M., Croce, F., Galli, M., Rusconi, S. *Tipranavir (PNU-140690) retains a potent antiviral in vitro activity against HIV-1 isolates derived from PI-naive or PI-experienced patients.* AIDS 2000, 14(Suppl. 4): Abst P14.

5. Wood, R. *Tipranavir - the protease inhibitor for the 21st century.* AIDS 2000, 14(Suppl. 4): Abst CS3.6.

Original monograph - Drugs Fut 1998, 23: 146.

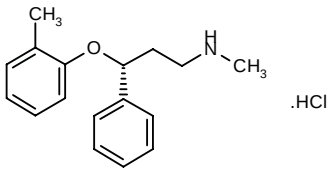
Additional References

Gao, P. et al. *Enhanced bioavailability of tipranavir in a self-emulsifying drug delivery system (SEDDS) Part I: Formulation dispersion and relevance on oral bioavailability.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 3018.

Gao, P. et al. *Enhanced bioavailability of tipranavir in a self-emulsifying drug delivery system (SEDDS) Part II: Lipid content and influence on oral bioavailability.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 3019.

Tomoxetine Hydrochloride *Treatment of ADHD*

EN: 090043



$C_{17}H_{21}NO.HCl$ **Lilly; Chugai**

A new synthesis of tomoxetine has been described: The reduction of ω-chloropropiophenone (I) with $NaBH_4$ in ethanol gives 3-chloro-1-phenyl-1-propanol (II), which is treated with butyric anhydride and pyridine in dichloromethane to yield the corresponding racemic ester (III). The optical resolution of (III) with immobilized lipase B from *Candida antarctica* (CALB) affords a mixture of unreacted (*S*)-ester and (*R*)-alcohol (IV) that are separated by column chromatography. Condensation of the (*R*)-alcohol (IV) with 2-methylphenol (V) by means of PPh_3 and diethyl azodicarboxylate (DEAD) in THF gives the corresponding ether (VI), which is finally treated with methylamine in refluxing ethanol (1). Scheme 3.

Tomoxetine hydrochloride, is being studied in phase III trials for the treatment of attention deficit hyperactivity disorder in children and adults (2).

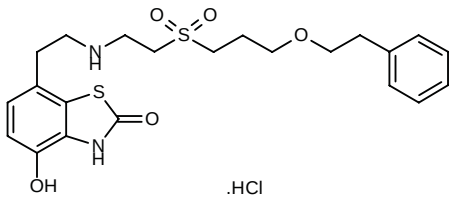
1. Liu, H.L., Ho, B.H., Anthonsen, T. *Chemoenzymatic synthesis of the non-tricyclic antidepressants fluoxetine, tomoxetine and nisoxetine.* J Chem Soc - Perkins Trans I 2000, (11): 1767.

2. *Lilly details late-stage product pipeline.* DailyDrugNews.com (Daily Essentials) June 21, 2000.

Original monograph - Drugs Fut 1986, 11: 134.

Viozan® *Treatment of COPD*
AR-C68397AA
FPL-68397

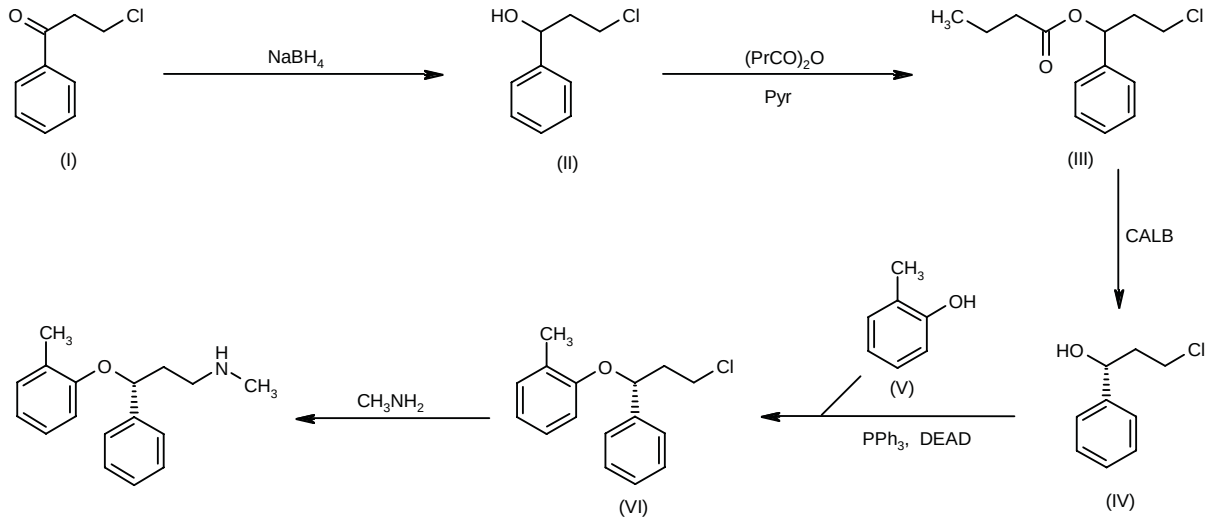
EN: 211502



$C_{22}H_{28}N_2O_5S_2.HCl$ **AstraZeneca**

A novel time-resolved fluorescence immunoassay using a complex of the DTPA derivative of Viozan® and free europium cation has been described for determination of Viozan® concentrations in human plasma. The

Scheme 3: Synthesis of Tomoxetine



method is an alternative to solid phase RIA procedures and is sensitive for pg/ml concentrations of the agent. The calibration range of the assay was 10-2000 pg/ml and the LOQ obtained was 50 pg/ml using 50 mcl of diluted human plasma (1).

Viozan® was shown to suppress sensory nerve activity in a study incorporating several canine models of airway disease. Viozan® dose-dependently inhibited histamine (aerosol)-induced tachypnoea for 4.5 h or more in anesthetized beta-blocked dogs. This inhibition was reversed by dopamine antagonists (*e.g.*, domperidone) and cooling of the vagi; salbutamol had no effect in this model. Both Viozan® and cooling of the vagi inhibited increases in mucus secretion while salbutamol and ipratropium had no effect in isolated perfused trachea taken from anesthetized dogs exposed to an ammonia vapor challenge. In addition, pretreatment with Viozan® or cooling of the vagi reduced capsaicin (aerosol)-induced coughing in tracheotomized, conscious β-blocked dogs (2).

A review was published describing novel dual dopamine D_2- and β_2-receptor agonists as a treatment for COPD. The summary includes results from multicenter, double-blind, placebo-controlled, group-comparator, 6-week phase II studies on Viozan® conducted in about 800 patients with symptomatic COPD and a history of smoking. The agent was well tolerated with no nausea reported in treated patients. Dose-dependent improvements in total symptom scores and scores for cough, sputum production and breathlessness were observed in Viozan®-treated patients. Morning and evening peak flow, requirement for rescue medication and health status/quality of life were also improved with treatment (3).

A randomized, double-blind, parallel-group study conducted in 15 COPD patients (habitual smokers) compared the effects of multiple doses of nebulized solutions of Viozan® (3 mg t.i.d.) and salbutamol (5 mg t.i.d.) for 10 days. Viozan® treatment markedly reduced 24-h sputum volume as compared to salbutamol (–11 *vs.* –1 ml). Increases in mucociliary clearance were similar for both treatment groups (4).

A randomized, double-blind, placebo-controlled, 6-week study in 872 COPD patients (current or ex-smokers; mean predicted FEV_1 = 42%; mean FEV_1/FVC = 49%) on established therapy showed the tolerability of Viozan® (45, 270 or 465 μg t.i.d. as pMDI ex actuator). The most common adverse events in patients given 495 mcg were taste of treatment (18 *vs.* 0% in placebo), headache (9 *vs.* 12%), tremor (8 *vs.* 0%), respiratory infection (8 *vs.* 13%), chronic obstructive airways disease (5 *vs.* 11%) and nausea (4 *vs.* 2%) (5).

Results from a randomized, double-blind, 6-week study involving 872 COPD patients (current or ex-smokers; mean predicted FEV_1 = 42%; mean FEV_1/FVC = 49%) showed the efficacy of Viozan® (45, 270 or 465 μg t.i.d. as pMDI ex actuator) in reducing breathlessness, cough and sputum production. Dose-dependent and significant decreases in total symptom scores were observed in the groups receiving doses of 270 and 465 μg as compared to placebo; these doses were associated with a decreased need for use of a rescue bronchodilator. The 495 μg dose also significantly reduced individual scores of breathlessness, cough and sputum (6).

Results from a randomized, double-blind, 6-week study involving a total of 872 COPD patients given Viozan® (45, 270 or 465 μg t.i.d. as pMDI ex actuator) showed that the 2 higher doses significantly improved health-related quality of life as assessed by scores from 765 of the patients given the St. George's Respiratory

Questionnaire. Mean baseline scores for all groups for symptoms, activity, impacts and total components were 57.4, 64.3, 36.8 and 48.5, respectively. Treatment with 270 and 495 μg significantly improved symptoms (–5.7 and –7.1), activity (–4.4 and –3.5), impacts (–4.2 and –3.1) and total components (–4.5 and –3.9) as compared to placebo (7).

A randomized, double-blind, placebo-controlled, 4-week study in 701 COPD patients (current or ex-smokers; mean predicted FEV_1 = 43%; mean FEV_1/FVC = 51%) on established therapy compared the efficacy and tolerability of Viozan® (400, 600 or 1000 μg t.i.d. as pMDI ex valve) with salbutamol (200 μg t.i.d.) and ipratropium bromide (40 μg t.i.d.). Viozan® at a dose of 600 μg significantly reduced the total symptom score (including daily breathlessness, cough and sputum production scores) as compared to placebo, salbutamol and ipratropium bromide. Salbutamol and ipratropium bromide only showed slight efficacy as compared to placebo (8).

1. Willson, V.J.C., Lockley, W.J.S., Mather, A., Singh, J., Gilbert, C.M., Bayliss, M.A., Wilkinson, D. *A time-resolved fluorescence immunoassay for the determination of a novel respiratory therapeutic agent, AR-C68397XX (Viozan™) in human plasma.* J Pharm Biomed Anal 2000, 23(6): 947.

2. Young, A., Dougall, I., Jackson, D., Blackham, A., Hallam, C., Harper, S., Brown, R., Leff, P., Eady, R. *Viozan™, a novel dual D_2-receptor and β-adrenoceptor agonist, inhibits clinically relevant parameters in animal models of airways disease.* Am J Respir Crit Care Med 2000, 161(3, Part 2): A820.

3. Young, A. *Dual dopamine D_2- and β_2-receptor agonists: A novel therapeutic approach in COPD.* Conquering Airw Inflamm 21st Century (Sept 11-13, London) 2000.

4. Hasani, A., Toms, N., Agnew, J.E., LLoyd, J., Sabin, A., Dilworth, J.P. *The effect of multiple doses of Viozan™ (AR-C68397AA) compared with salbutamol on lung mucociliary clearance and sputum production in smokers with COPD.* Am J Respir Crit Care Med 2000, 161(3, Part 2): A820.

5. Ind, P.W., Sandström, T., Wallaert, B., Deamer, L., Nyström, P., Rocchiccioli, K. *Tolerability profile of Viozan™ (AR-C68397AA): A novel therapy for symptomatic treatment of COPD.* Am J Respir Crit Care Med 2000, 161(3, Part 2): A821.

6. Wenzel, S., Ind, P.W., Laursen, L.C., Deamer, L., Nyström, P., Rocchiccioli, K. *Viozan™ (AR-C68397AA) reduces breathlessness, cough and sputum production in COPD patients.* Am J Respir Crit Care Med 2000, 161(3, Part 2): A490.

7. Wenzel, S., Lindqvist, A., Sandström, T., Deamer, L., Nyström, P., Rocchiccioli, K. *Viozan™ (AR-C68397AA) improves health-related quality of life in patients with COPD.* Am J Respir Crit Care Med 2000, 161(3, Part 2): A490.

8. Laitinen, L.A., Laursen, L.C., Woulters, E., Lloyd, J., Blackshaw R., Rocchiccioli, K. *Efficacy of Viozan™ (AR-C68397AA) versus salbutamol and ipratropium bromide in the management of COPD.* Am J Respir Crit Care Med 2000, 161(3, Part 2): A490.

Original monograph - Drugs Fut 2000, 25: 165.

Additional References

Holt, P.R. et al. *AR-C68397AA: A novel approach to the management of COPD.* Eur Respir J 2000, 16(Suppl. 31): Abst P509.

Ince, F. et al. *Viozan™: The discovery of a novel dual D_2-receptor and β_2-adrenoceptor agonist for the treatment of the symptoms of COPD.* 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 198.

Ind, P.W. et al. *Symptomatic relief of COPD with AR-C68397AA.* Eur Respir J 2000, 16(Suppl. 31): Abst P512.

Laursen, L.C. et al. *Dose-ranging study to determine the effects of AR-C68397AA administered via turbuhaler in COPD patients.* Eur Respir J 2000, 16(Suppl. 31): Abst P511.

Young, A. et al. Dual *D_2-dopamine receptor, β_2-adrenoceptor agonists: A novel therapeutic class for the management of COPD.* Eur Respir J 2000, 16(Suppl. 31): Abst P510.

Young, A. et al. *Novel dual D_2-receptor and β_2-adrenoceptor agonists for the treatment of airways diseases.* Am J Respir Crit Care Med 2000, 161(3, Part 2): A436.

Ziconotide *Analgesic*

EN: 197367

H-Cys-Lys-Gly-Lys-Gly-Ala-Lys-Cys-Ser-Arg-Leu-Met-Tyr-Asp-Cys-Cys-Thr-Gly-Ser-Cys-Arg-Ser-Gly-Lys-Cys-NH_2
cyclic (1-16),(8-20),(15-25)-tris(disulfide)

$C_{102}H_{172}N_{36}O_{32}S_7$ **Elan; Draxis Health**

A study examined the bioavailability of ziconotide in the brain. Maximum brain concentrations of the agent at 3-20 min after i.v. injection were between 0.003 and 0.006% of the injected material/g tissue; this rate decreased to 0.001% at 2 h postinjection. In contrast, SNX-185 persisted in the brain with 0.0035 and 0.0015% present at 2-4 and 24 h postinjection, respectively. Similar results were observed when the agents were administered via dialysis probes implanted in the hippocampus. Results from both *in vitro* studies examining diffusion of SNX-194 (a close structural analog of ziconotide) through cultured bovine brain microvessel endothelial cells and *in situ* studies observing perfusion through the carotid artery indicated that the agent could pass through the blood-brain barrier (1).

The pharmacokinetics of ziconotide in cerebrospinal fluid (CSF) and plasma were examined in 22 patients with chronic stable pain (1-10 μg 1-h intrathecal infusion into the lumbar region), healthy volunteers (3-30 mg/h 24-h i.v. infusion) and dogs (10 μg bolus + [^{3}H]-inulin and 1-5 mg/h lumbar infusions for 48 h). The CSF pharmacokinetics in patients were linear but variable. Median CSF clearance, steady-state volume and terminal half-life values obtained for the agent were 0.26 ml, 99 ml and 4.5 h, respectively; the agent was not detected in 95% of the plasma samples of these patients. In dogs, CSF

clearance rates for the agent and inulin were similar with bulk flow identified as the primary CSF clearance pathway. The cisternal:lumbar CSF ratio was < 0.02 in dogs, indicating limited mixing of CSF. Pharmacokinetics in volunteers were linear and showed little variability (2).

The pharmacokinetics of intrathecal ziconotide (1-10 mg into the lumbar region) were reported from a study conducted in 22 patients with chronic intractable pain of nonmalignant origin. CSF AUC and C_{max} values significantly correlated with summed differences from the visual analog scale of pain intensity (VASPI) after 12 h, with the correlation improving after 48 h. Results indicate a delay in maximal responses. These parameters were also significantly correlated with incidence of CNS adverse events such as dizziness, nausea and abnormal gait; there was no correlation with vital signs. It was concluded that for ziconotide to be effective, CSF concentrations must be maintained for a few hours (3).

A randomized, double-blind, placebo-controlled, pilot study in patients undergoing elective total abdominal hysterectomy, radical prostatectomy or total hip replacement showed the safety and efficacy of ziconotide (0.7 or 7 μg/h continuous intrathecal injection for 48-72 h postoperatively). Thirty patients received ziconotide and 26 were evaluable for efficacy. The mean daily patient controlled analgesia morphine equivalent consumption was significantly less in ziconotide-treated patients between 24 and 48 h as compared to placebo and the VASPI scores for the first 8 h postsurgery were lower in ziconotide-treated patients. Adverse events including dizziness, blurred vision, nystagmus and sedation caused 4 patients in the higher dose group to discontinue treatment after 24 h (4).

Ziconotide is currently under evaluation for the treatment of chronic pain and has shown analgesic efficacy in cancer and AIDS patients unrelieved by opioids. Adverse events have appeared to be manageable by dose reduction or symptomatic treatment. Now serious side effects from the intrathecal delivery of ziconotide have been reported. An examination of 3 case studies revealed that symptoms of adverse events were often cerebellar in origin and also affected the brainstem, cortical and other systems. Symptoms often required days or weeks to subside after the dose was reduced or the drug was withdrawn, and great lengths of time were needed for recovery. These side effects indicate that further trials should be designed with extreme caution (5).

Results from a multicenter, randomized, double-blind, placebo-controlled, crossover trial conducted in 112 patients with moderate to severe pain on the VASPI of > 50 mm showed the analgesic efficacy of intrathecal ziconotide (0.1 mg/h titrated every 12-24 h up to 2.4-3.9 mg/h over 5-6 days) against refractory, intractable cancer and AIDS-related pain. Ziconotide treatment significantly improved VASPI over placebo (53.1 *vs.* 18.1%). Adverse events including dizziness, nystagmus, nausea, fever, postural hypotension, somnolence and confusion were mild to moderate and reversible with dose adjustments (6).

Pooled results from 2 randomized, double-blind, placebo-controlled trials in 111 patients with chronic intractable pain from cancer or AIDs and 225 patients with nonmalignant pain showed the analgesic efficacy of ziconotide. A significantly higher change in VASPI was seen in the ziconotide group as compared to placebo (–37.3 *vs.* –9.8) (7).

An open-label, feasibility, dose-titration study conducted in 31 patients with chronic pain of malignant or nonmalignant origin showed the analgesic efficacy of intrathecal ziconotide (0.1 mg/h titrated to 2.4 g/h over 5-6 days). Patients were started on 0.3 ng/kg/h (to be titrated to 300 ng/kg/h) but because analgesia and adverse events were observed at lower doses, the starting dose was changed to 0.1 mg/h to be titrated to 2.4 g/h. Preliminary results indicated good tolerability and a decrease in incidence of adverse events as compared to other studies. The study is ongoing (8).

A report has summarized the safety profile of intrathecal ziconotide from a number of trials involving over 1000 patients with chronic pain of malignant or nonmalignant origin. Rates of adverse events from placebo-controlled, inpatient, fixed-titration studies were 72 and 96% for placebo and ziconotide, respectively. Adverse events related to ziconotide treatment included dizziness, nausea, nystagmus, abnormal gait, constipation, urinary retention, headache, somnolence, postural hypotension, vomiting, confusion, fever and pain. Results from open-label, long-term studies with gradual titration schedules in outpatients showed less incidence of adverse events. Adverse events were managed by dose adjustment and were mild to moderate in 89% and serious in only 2% of the cases. Only 7.8% of the patients required discontinuation, which resulted in reversal of adverse events. No evidence of cumulative adverse events was observed and no respiratory depression, hemodynamic effects or effects on cardiac conduction, rate or rhythm have been noted (9).

The efficacy of ziconotide (2.4 mg/day intrathecal titrated every 24 h to 7.2 mg/day) in relieving opioid-refractory neuropathic and cancer pain was shown in a 27-year old woman with metastatic carcinoma and severe intractable neuropathic pain secondary to intrapelvic disease. Previous treatment with oral morphine/transdermal fentanyl/oral hydrocodone, intrathecal morphine/transdermal clonidine/oral baclofen and intrathecal bupivacaine/i.v. morphine were ineffective. Within 24 h of initiation of ziconotide, a 25% reduction in VASPI was noted. The patient was discharged as an outpatient 6 days later and reported a 53% reduction in VASPI. Adverse events included mild ataxia and vertigo. Dose adjustments to a final dose of 4.1 mg/day were made according to adverse events and deterioration in condition and good pain control was observed. The patient died after developing small bowel obstruction and becoming icteric and cachectic. Pain relief remained acceptable (10).

Because patients administered ziconotide for neuropathic pain sometimes experience a decrease in lower and upper extremity reflexes, the drug was tested in

2 patients who suffered from intractable spasticity due to spinal cord injury. In 1 patient, ziconotide controlled spasticity and reduced pain. In the other, spasticity was controlled but pain was not resolved, and side effects required that use of the drug be discontinued. Further evaluations are needed before the appropriate use of ziconotide in the management of spinal cord spasticity is understood (11).

Elan has received an approvable letter from the FDA for ziconotide for the treatment of severe chronic pain via the intrathecal route (12).

1. Newcomb, R., Abbruscato, T.J., Singh, T., Nadasdi, L., Davis, T.P., Miljanich, G. *Bioavailability of ziconotide in brain: Influx from blood, stability, and diffusion.* Peptides 2000, 21(4): 491.

2. Hale, V., Ngo, L., Chao, S., O'Connell, D., Ellis, D., Mato, M., Wermeling, D. *Pharmacokinetic-pharmacodynamic relationships of ziconotide, a novel analgesic, following intrathecal administration to patients with chronic intractable pain.* 19th Annu Sci Meet Am Pain Soc (Nov 2-5, Atlanta) 2000, Abst 841.

3. Atanassoff, P.G., Hartmannsgruber, M.W.B., Thrasher, J. et al. *Ziconotide, a new N-type calcium channel blocker, administered intrathecally for acute postoperative pain.* Reg Anesth Pain Med 2000, 25(3): 274.

4. Wemeling, D., O'Connell, D., de Kater, A., Bowersox, S., Singh, T., Mayo, M., Hale, V.G. *Effect of the primary clearance mechanism and source of inter-patient variability in cerebrospinal fluid pharmacokinetics of ziconotide in chronic pain patients.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 2084.

5. Penn, R.D., Paice, J.A. *Adverse effects associated with the intrathecal administration of ziconotide.* Pain 2000, 85(1-2): 291.

6. Presley, R., Charapata, S., Staats, P., Yearwood, T., Mayo, M., Ellis, D., McGuire, D. *Intrathecal ziconotide in the treatment of opioid-resistant pain: A controlled clinical trial.* 19th Annu Sci Meet Am Pain Soc (Nov 2-5, Atlanta) 2000, Abst 628.

7. Mayo, M., Ellis, D.J. *Analgesic efficacy of intrathecal ziconotide in common painful conditions.* Worldwide Pain Conf (July 15-21, San Francisco) 2000, 122.

8. Wallace, M., Presley, R., Fisher, R., Mayo, M., Ellis, D., McGuire, D. *Intrathecal dose titration evolution of ziconotide, a novel analgesic N-type calcium channel blocker.* 19th Annu Sci Meet Am Pain Soc (Nov 2-5, Atlanta) 2000, Abst 840.

9. Staats, P., Charapata, S., Royal, M., Fisher, R., Ellis, D., Mayo, M. *The safety profile of intrathecal ziconotide: A new non-opioid analgesic.* 19th Annu Sci Meet Am Pain Soc (Nov 2-5, Atlanta) 2000, Abst 839.

10. Presley, R., Mayo, M., Ellis, D., McGuire, D., Clay, D.A. *Intrathecal ziconotide relieves opioid-refractory neuropathic and cancer pain: A case report.* 19th Annu Sci Meet Am Pain Soc (Nov 2-5, Atlanta) 2000, Abst 627.

11. Ridgeway, B., Wallace, M., Gerayli, A. *Ziconotide for the treatment of severe spasticity after spinal cord injury.* Pain 2000, 85(1-2): 287.

12. *Elan receives FDA approvable letter for ziconotide.* DailyDrugNews.com (Daily Essentials) June 29, 2000.

Original monograph - Drugs Fut 1994, 19: 128.

Additional References

Gould, H.J. III. *Approaches to the management of neuropathic pain.* Worldwide Pain Conf (July 15-21, San Francisco) 2000, 319.

Leong, M.S. *Intrathecal ziconotide: A brief overview.* Worldwide Pain Conf (July 15-21, San Francisco) 2000, 332.

Wang, Y.X. et al. *Effects of intrathecal administration of ziconotide, a selective neuronal N-type calcium channel blocker, on mechanical allodynia and heat hyperalgesia in a rat model of postoperative pain.* Pain 2000, 84(2-3): 151.