Drugs of the Future 1998, 23(7): 767-811

CCC: 0377-8282/98

Information Update

Volume 1-22, Number 7

Estimated developmental phase for this month's updated products:

Preclinical

Dehydroevodiamine chloride (antihypertensive; Chinese Univ. Hong Kong)
T-440 (antiasthmatic, phosphodiesterase IV inhibitor; Tanabe Seiyaku)
Triptolide (immunosuppressant; Kunming Inst.)

Phase I

AK-2123 (radiosensitizer; Adeka Argus, Kyoto Univ.)
NS-398 (antiinflammatory, cyclooxygenase-2 inhibitor; Taisho)
Oltipraz (chemopreventive; Rhône-Poulenc Rorer)
Quercetin (cardioprotectant, antineoplastic, antioxidant; Beijing Chem. Reagent Fact., Taiyun Second Pharm. Fact.)

Phase II

1263W94 (antiviral; Glaxo Wellcome)
Daptomycin (antibiotic; Lilly, Cubist)
Moguisteine (antitussive; Boehringer Mannheim)
Ramoplanin (glycopeptide antibiotic, antiacne; Hoechst Marion Roussel, Lepetit, Intrabiotics)
Saredutant (antiinflammatory, tachykinin antagonist; Sanofi)
l-Stepholidine (analgesic, antidyskinetic; Yunnan Inst. Drug Control, Shanghai Inst. Materia Med.)
TYB-2285 (antiallergy; Toyobo)

Phase III

AE0047 (antihypertensive, neuroprotectant, calcium channel blocker; Green Cross)
Azelnidipine (antihypertensive, antianginal, calcium channel blocker; Sankyo, Ube)
Biapenem (carbapenem; Lederle)
Brivudine (antiviral; Rega Inst. Med. Res., Menarini, Berlin-Chemie, Viñas)
Bucindolol hydrochloride (β-adrenergic blocker, treatment of congestive heart failure; Bristol-Myers Squibb, Astra Merck, Intercardia, Knoll)
Cefluprenam (cephalosporin; Eisai)
Celecoxib (antiinflammatory, cyclooxygenase-2 inhibitor; Searle, Yamanouchi, Pfizer)
Desmin-370 (antithrombotic; Alfa Wassermann, Opocrin)
Ecabapide (antiulcerative, anti-*Helicobacter pylori*; Daiichi Pharm.)
Entacapone (antiparkinsonian, COMT inhibitor; Orion, Novartis)
Epristeride (5α-reductase inhibitor, treatment of BPH; SmithKline Beecham, Ono, Recordati)
Idoxifene (antiestrogen, antineoplastic, treatment of osteoporosis; Natl. Res. Dev. Corp., British Technol. Group, SmithKline Beecham, Ono, Recordati)
Idoxuridine (antineoplastic; Natl. Cancer Inst., Oncomed)
Ipsapirone (anxiolytic, antidepressant, 5-HT_{1A} agonist; Troponwerke)
KE-298 (antiarthritic; Taisho)
SB-209509/VML-251 (antimigraine, 5-$HT_{1B/1D}$ receptor agonist; SmithKline Beecham, Vanguard Medica)
Thrombopoietin (treatment of thrombocytopenia; Genentech, Novo Nordisk, Zymogenetics, Amgen, Kirin Brewery, Pharmacia & Upjohn)
Zaldaride maleate (calmodulin inhibitor, antidiarrheal; Novartis, Zyma, Kyowa Hakko)

Registered/Year

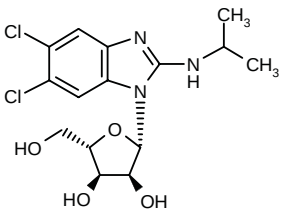
Risedronate sodium (bisphosphonate, treatment of osteoporosis; Procter & Gamble, Takeda, Ajinomoto, Hoechst Marion Roussel)/1998
Rizatriptan benzoate (antimigraine, 5-HT_{1D} agonist; Merck & Co.)/ 1998

Launched/Year

Brimonidine tartrate (antiglaucoma, α_2-adrenergic agonist; Pfizer, Allergan)/1996
Candesartan cilexetil (antihypertensive, angiotensin II agonist; Takeda, Astra Merck)/1997
Cetirizine hydrochloride (antihistaminic; UCB, Pfizer, Synthélabo, Sumitomo, Daiichi Pharm., Menarini, Lacer)/1987
Ebastine (antihistaminic; Almirall Prodesfarma, Dainippon, Meiji Seika, Rhône-Poulenc Rorer, Merck GKaA, Boryung)/1990
Fosphenytoin sodium (anticonvulsant, neuroprotectant; DuPont Merck, Warner-Lambert)/1996
Lansoprazole (gastric antisecretory H^+/K^+-ATPase inhibitor; Takeda, TAP, Houdé, Almirall Prodesfarma, Tecnobio, Roussel-Uclaf, American Home Prod.)/1991
Levofloxacin (fluoroquinolone antibacterial; Daiichi Pharm., Johnson & Johnson, Glaxo Wellcome, Hoechst Marion Roussel)/1993
Raloxifene hydrochloride (antiestrogen, treatment of osteoporosis, antineoplastic; Lilly, Chugai)/1998
Repaglinide (antidiabetic; Boehringer Ingelheim, Novo Nordisk, Schering Plough)/1998
Ritonavir (anti-HIV, HIV-1 protease inhibitor; Abbott, Dainippon)/1996
SDZ-ENS-713 (cognition enhancer, acetylcholinesterase inhibitor; Novartis)/1997
Tolterodine (agent for urinary incontinence, muscarinic receptor antagonist; Pharmacia & Upjohn)/1997
Valaciclovir (antiviral; Glaxo Wellcome; Hoechst, Theraplix)/1995
Zileuton (antiallergic/antiasthmatic, 5-lipoxygenase inhibitor; Abbott)/1997

1263W94 *Antiviral*
Benzimidavir
BW-1263W94

EN: 233414



$C_{15}H_{19}Cl_2N_3O_4$ **Glaxo Wellcome**

In vitro evaluation of GW-1263 in combination with other antiviral agents in human lung fibroblasts infected with human cytomegalovirus demonstrated additive effects of GW-1263 in combination with ganciclovir, foscarnet or acyclovir when evaluated in a DNA-DNA hybridization assay (average IC_{50} = 0.11 μM). AZT, didanosine, zalcitabine, lamivudine and GW-141 had no effect on the activity of GW-1263 (1).

GW-1263 inhibited the accumulation of linear and high molecular DNA in Akata cells with an IC_{50} of 0.2-1.1 μM, while Epstein-Barr virus DNA replication was completely inhibited at 10 μM. No effects were observed on Epstein-Barr virus DNA maturation. The compound also inhibited Epstein-Barr virus early antigen accumulation in a dose-dependent manner (2).

GW-1263 at doses of 100, 200 and 400 mg t.i.d. increased the range and extent of virus titer reductions in semen, and demonstrated antiviral activity in urine when evaluated in male HIV-infected patients with asymptomatic cytomegalovirus shedding. The drug demonstrated a favorable safety profile, with taste disturbance, fatigue, headache and nausea being the most frequently reported side effects (3).

Results from an ongoing phase I/IIa trial evaluating the activity against cytomegalovirus (CMV), safety and pharmacokinetics of 1263W94 have been presented. Male HIV-positive patients with asymptomatic CMV shedding received 1263W94 at doses of 100, 200 or 400 mg or placebo 3 times daily for 28 days; although none of the patients had CMV disease or positive blood cultures, about half of the patients had semen CMV titers and positive CMV urine culture at entry. Treatment was well tolerated, taste disturbances, headache, fatigue, nausea and diarrhea being the most frequently reported side effects; 2 patients withdrew due to diffuse maculopapular rash. 1263W94 dose-dependently reduced semen CMV titers and induced culture conversion in urine (4).

1. Selleseth, D.W., Talarico, C.L., Lutz, M.W., Biron, K., Miller, T., Harvey, R.J. *Interactions of GW1263 with other antiviral agents in the inhibition of HCMV.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst H-64.

2. Zacny, V.L., Davis, M.G., Chamberlain, S.D., Townsend, L.B., Biron, K.K., Pagano, J.S. *Activity against Epstein-Barr virus of benzimidazole riboside 1263W94 (5, 6-dichloro-2(isopropylamino)-1-β-L-ribofuranosyl-1H-benzimidazole).* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst H-69.

3. Drew, W.L., Lalezari, J.P., Wang, L.H., Miner, R.C., Aberg, J.A., Wire, M.B., Jacobson, M.A. *In vivo anti-CMV activity and safety of oral 1263W94 in HIV-infected subjects with asymptomatic CMV shedding.* Antivir Res 1998, 37(3): Abst 110.

4. Lalezari, J.P., Aberg, J.A., Wang, L.H., Miner, R.C., Wire, M.B., Jacobson, M.A., Drew, W.L. *In vivo anti-CMV activity, safety and pharmacokinetics (PK) of oral 1263W94 in HIV-infected subjects with asymptomatic CMV shedding.* 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 762.

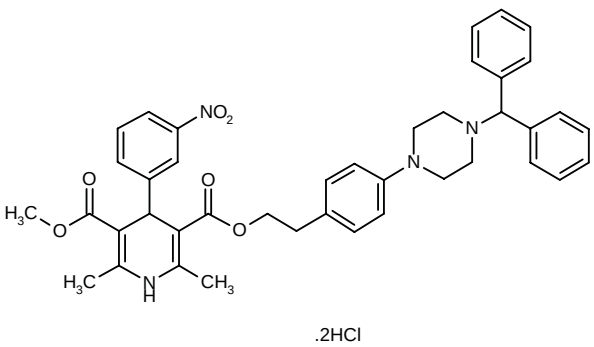
Original monograph – Drugs Fut 1997, 22: 707.

Additional Reference

Biron, K.K. *Development and testing of novel drugs for treatment of cytomegalovirus infections.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst S-53.

AE0047 *Antihypertensive*
Vatanidipine Hydrochloride *Neuroprotectant*
Calcium Channel Blocker

EN: 163664



.2HCl

$C_{41}H_{42}N_4O_6.2HCl$ **Green Cross**

Findings from a study in rat aortic strips indicate that the vasodilating and antihypertensive effects of racemic AE0047 are mainly due to (+)-AE0047 and that (–)-AE0047 is pharmacologically inactive (1).

Evaluation of orally and intravenously administered AE0047 (0.3, 1, 3 and 10 mg/kg p.o. and 10, 30 and 100 mcg/kg i.v.) in various models of hypertension in rats and dogs showed that the compound has a slow onset of action and produces long-lasting antihypertensive effects in a dose-dependent manner (2).

Results from studies using various hypertensive models of rats and dogs have shown that long-term treatment

with AE0047 (0.3, 1 and 3 mg/kg/day for 8 weeks) caused a dose-dependent decrease in systolic blood pressure and a regression of left ventricular hypertrophy. Lipid and glucose metabolism were not influenced by the drug (3).

Results from studies evaluating the absorption and excretion of a single dose of [^{14}C]-AE0047 (3.0 mg/kg) in rats and dogs have shown that the absorption and bioavailability rates were 24.5% and 22.0% (rats) and 23.9 and 21.2% (dogs). The amounts of radioactivity excreted in urine and feces within 168 h postadministration were 4.2% and 96.1% (rats) and 11.1% and 83.2% (dogs). Unchanged drug was mainly detected in plasma in rats and dogs and was not detected in the urine of rats (4).

Studies of the lymphatic absorption and distribution of single and multiple oral doses of [^{14}C]-AE0047 in rats have shown that the highest levels of radioactivity, found in the lymph, liver and adrenals, were reached at 3 h after administration. Levels in muscle, fat, brown fat, skin, bone marrow, testis and eyeball reached the maximum at 6 h after administration. The lowest levels of radioactivity were found in the CNS. Within 48 h after dosing, 5.3% of the total dose was transferred to the lymphatic system (5).

After a single oral dose of [^{14}C]-AE0047 (3 mg/kg) to pregnant rats, maximum levels of radioactivity were reached at 6 h postdosing in the fetus and accounted for 6.0% of maximum concentrations found in the maternal plasma. In lactating rats, maximum levels in milk, also reached at 6 h postdosing, were lower than those in the maternal plasma (6).

In studies in anesthetized dogs, AE0047 (100 ng/kg/min) was found to dose-dependently inhibit the elevation of glomerular filtration fraction and abolish the decreases in urine flow, urinary excretion of electrolytes and fractional excretion of electrolytes induced by angiotensin II. These results indicate that AE0047 may prevent renal disease without reducing renal function in hypertensive patients (7).

In stroke-prone spontaneously hypertensive rats, AE0047 (1 or 3 mg/kg p.o.) dose-dependently attenuated the deterioration of neurological status caused by middle cerebral artery occlusion, reducing mortality to 0-10%. Infarct size and left/right hemispheric area ratio were also significantly reduced (8).

Results of a study in conscious spontaneously hypertensive rats showed that systemically administered AE0047 (10 and 30 μg/kg) produced diuresis and natriuresis, partly through inhibition of sodium and water reabsorption in the proximal tubules (9).

Long-term treatment of spontaneously hypertensive rats with AE0047 (0.013 or 0.04% in diet for 8 weeks) resulted in a significant and dose-dependent decrease in the lower blood pressure limit while preserving cerebral blood flow, indicating that the drug may improve tolerance to blood pressure reduction in patients with hypertension (10).

Results of studies in stroke-prone spontaneously hypertensive rats demonstrated that daily administration of AE0047 (1 and 3 mg/kg) was more effective than nicardipine (10 mg/kg) and hydralazine (10 mg/kg) in improving neurological symptoms and preventing mortality (11).

Studies in stroke-prone spontaneously hypertensive rats showed that treatment with AE0047 (1 and 3 mg/kg) before renal injury dose-dependently reduced systolic blood pressure. In animals with renal injury, treatment for 6 weeks prevented proteinuria and attenuated the development of renal lesions (12).

The effects of AE-0047 against cerebral ischemia and edema have been assessed in cats subjected to middle cerebral artery (MCA) occlusion. When given 20 min after MCA occlusion, AE-0047 (10 μg/kg i.v.), similar to nilvadipine (30 μg/kg), significantly increased local cerebral blood flow in moderately and severely ischemic brain regions, whereas nicardipine (5 μg/kg by bolus + 3 μg/kg/min for 60 min) had no effect. In contrast to the other dihydropyridines, AE-0047 also tended to prevent the increase in cortical water content in severely ischemic regions. These results indicate that the effects of dihydropyridine calcium antagonists on cerebral ischemia/edema differ depending on their side-chain structures (13).

In cholesterol-fed rabbits, treatment with AE-0047 (3 and 10 mg/kg p.o.) during 7 weeks reduced the lipid deposition area, without altering serum lipid levels. In rabbits on a high-fat diet, AE-0047 reduced total and esterified cholesterol and calcium content in the aorta to levels observed in rabbits fed a normal diet. Furthermore, the drug inhibited Cu^{2+}-induced LDL oxidation and aggregation of apolipoprotein B-100 *in vitro*, and inhibited the degradation of oxidized LDL by macrophages. Nilvadipine showed no effect in these tests (14).

Vatanidipine hydrochloride is the new proposed nonproprietary name for AE-0047 (15).

1. Nishikawa, M., Ohtaki, Y., Kido, H., Fujino, Y., Inoue, S., Nakamura, N. *Vasodilating and antihypertensive effects of the optical isomers of AE0047, a calcium antagonist.* Jpn Pharmacol Ther 1997, 25(5): 115.

2. Kido, H., Nishikawa, M., Hayashi, K. et al. *Antihypertensive effects of a novel calcium antagonist, AE0047, in various hypertensive models.* Folia Pharmacol Jpn 1997, 109(6): 279.

3. Kido, H., Nishikawa, M., Hayashi, K., Kubo, Y., Ebisu, H., Egi, Y., Shinyama, H., Nakamura, N. *Antihypertensive effects of long term treatment with AE0047, a novel long-lasting calcium antagonist, in hypertensive models of rats and dogs.* Folia Pharmacol Jpn 1997, 109(6): 291.

4. Ohkubo, M., Hirata, T., Sogame, Y., Tanaka, M., Okano, K., Tsuda, Y. *Metabolic fate of a new dihydropyridine calcium antagonist AE0047 (I): Absorption and excretion of AE0047, in rats and dogs.* Xenobiotic Metab Dispos 1997, 12(3): 178.

5. Ohkubo, M., Hirata, T., Sogame, Y., Tanaka, M., Okano, K., Tsuda, Y. *Metabolic fate of a new dihydropyridine calcium antagonist, AE0047 (II): Lymphatic absorption and distribution of AE0047 in rats.* Xenobiotic Metab Dispos 1997, 12(3): 192.

6. Ohkubo, M., Hirata, T., Sogame, Y., Tanaka, M., Okano, K., Tsuda, Y. *Metabolic fate of a new dihydropyridine calcium antagonist, AE0047 (III): Placental transfer and milk transfer of ^{14}C-AE0047.* Xenobiotic Metab Dispos 1997, 12(3): 204.

7. Hayahi, K., Egi, Y., Kubo, Y., Kido, H., Nakamura, N., Kagitani, Y. *A calcium channel blocker, AE0047 dilates the efferent arterioles in angiotensin II-infused anesthetized dogs.* Jpn Pharmacol Ther 1997, 25(5): 99.

8. Shinyama, H., Kawamura, T., Iwamoto, M., Egi, Y., Tanaka, H., Kawabata, Y., Nakamura, N., Kagitani, Y. *Effects of the calcium antagonist AE0047 on the development of neurological deficit and infarction after middle cerebral artery occlusion in stroke-prone spontaneously hypertensive rats.* J Pharm Pharmacol 1997,49(9): 919.

9. Hayashi, K., Kido, H., Kubo, Y., Shinyama, H., Nakamura,N., Kagitani, Y. *Effects of the calcium channel blocker AE0047 on renal function in conscious spontaneously hypertensive rats: Focus on renal proximal tubules.* Drug Develop Res 1997, 41(2): 91.

10. Shinyama, H., Nagai, H., Kawamura, T., Narita, Y., Nakamura, N., Kagitani, Y. *Effects of long-term treatment with the calcium antagonist AE0047 on cerebrovascular autoregulation and hypertrophy in spontaneously hypertensive rats.* J Cardiovasc Pharmacol 1997, 30(5): 616.

11. Shinyama, H., Nagai, H., Kawamura, T., Narita, Y., Nakamura, N., Kagitani, Y. *Therapeutic effects of AE0047, a novel calcium antagonist, on progression of brain damage after stroke in stroke-prone spontaneously hypertensive rats.* Gen Pharmacol 1998, 30(3): 379.

12. Hayashi, K., Koyama, M., Kido, H., Egi, Y., Shinyama, H., Iwamoto, M., Hanada, S., Nakamura, N. *Preventive and therapeutic effects of AE0047 on renal injury in stroke-prone spontaneously hypertensive rats.* Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-462.

13. Shinyama, H., Hayashi, K., Kawamura, T., Nakamura, N., Kagitani, Y. *Effects of AE0047 on cerebral ischaemia and oedema after middle cerebral artery occlusion in cats.* Clin Exp Pharmacol Physiol 1997, 24(11): 824.

14. Hayashi, K., Imada, T., Yamauchi, T., Kido, H., Shinyama, H., Matzno, S., Nakamura, N., Kagitani, Y. *Possible mechanism for the anti-atherosclerotic action of the calcium channel blocker AE0047 in cholesterol-fed rabbits.* Clin Exp Pharmacol Physiol 1998, 25(1): 17.

15. *Proposed international nonproprietary names (Prop. INN): List 77.* WHO Drug Inform 1997, 11(2): 103.

Original monograph – Drugs Fut 1994, 19: 627.

Additional References

Hayashi, K. et al. *Possible mechanism of action of AE0047, a calcium antagonist, on triglyceride metabolism.* J Pharmacol Exp Ther 1997, 282(2): 882.

Shinyama, H. et al. *Prophylactic effect of the calcium antagonist AE0047 on stroke in salt-loaded stroke-prone spontaneously hypertensive rats.* Jpn Pharmacol Ther 1997, 25(5): 85.

Shinyama, H. et al. *Ameliorating effect of the calcium antagonist AE0047 on circulatory disturbance in the organs of stroke-prone spontaneously hypertensive rats.* Jpn Pharmacol Ther 1997, 25(5): 93.

Shinyama, H. et al. *Effects of the calcium antagonist AE0047 on PGI_2 production in cerebral microvessels of stroke-prone spontaneously hypertensive rats.* Jpn Pharmacol Ther 1997, 25(5): 107.

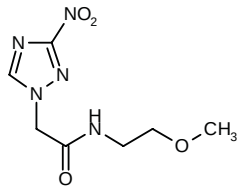
Otsuka, K. et al. *Hemodynamic effects of TN-891, a novel β-blocker, and GJ-0956, a dihydropyridine calcium antagonist in patients with essential hypertension.* Jpn J Clin Pharmacol Ther 1997, 28(1): 163.

Hayashi, K. et al. *Preventative and therapeutic effects of AE0047 on renal injury in stroke-prone spontaneously hypertensive rats.* Clin Exp Pharmacol Physiol 1997, 24(11): 831.

AK-2123

Radiosensitizer

EN: 140350



$C_7H_{11}N_5O_4$ **Adeka Argus; Kyoto Univ.**

Results of studies in syngenic mice demonstrated that AK-2123 (10 mg/kg/day i.p.) had a significant inhibitory effect on the growth of hepatic metastases induced by the intrasplenic injection of colon adenocarcinoma cells. The antimetastatic effect of the compound appeared to be related, at least in part, to the inhibition of active transport of calcium ions (1).

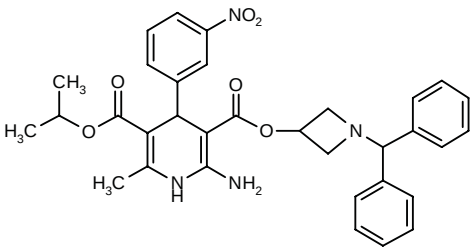
1. Konovalova, N.P., Volkova, L.M., Tatyanenko, L.V., Kotelnikova, R.A., Yakushchenko, T.N., Kagiya, T.V. *Inhibitory effect of radiosensitizer AK-2123 on experimental hepatic metastase and Ca^{2+} active transport.* Neoplasma 1997, 44(6): 361.

Original monograph – Drugs Fut 1995, 20: 659.

Azelnidipine

Antihypertensive
Antianginal
Calcium Channel Blocker

EN: 141329



$C_{33}H_{34}N_4O_6$ **Sankyo; Ube**

  CCC: 0377-8282/98

Azelnidipine did not induce gene mutations or clastogenic activity in *in vitro* assays, including the reverse mutation test in bacteria, chromosome aberration test in cultured cells and micronucleus test in mice. These results indicate that azelnidipine is not genotoxic (1).

Single-dose toxicity studies of azelnidipine have reported LD_{50} values of 979 mg/kg and 1971 mg/kg for male mice and rats, respectively, and 785 mg/kg and 1267 mg/kg for female mice and rats, respectively; the LD_{50}s for dogs were greater than 800 mg/kg (for males and females) and there was no incidence of death. Numerous side effects such as irregular respiration, crouching, staggering gait, watery stool, abdominal distention, emaciation, and/or clonic convulsions were observed in mice and rats and vomiting and decreased activity were seen in treated dogs (2).

In a toxicity study, rats were administered azelnidipine (1, 3, 10 or 30 mg/kg/day p.o.) for 90 days and several adverse effects with doses of 10-30 mg/kg/day were observed, including death, abdominal distension, inhibition of weight gain, increased water consumption, increased urine volume and excretion of sodium and chloride, decreased potassium excretion, and/or elevated urine pH creatinine, GOT and GPT, and glucose plasma levels. The no-effect dose was determined to be 3 mg/kg/day (3).

In a 13-week toxicity study, dogs were administered 1, 3 or 10 mg/kg/day azelnidipine. The minimum effective dose was determined to be 10 mg/kg/day and resulted in a decrease in food intake, an increase in heart rate, necrosis and fibrosis (4).

In a 52-week toxicity study, dogs were administered 1, 3 or 10 mg/kg/day azelnidipine. Treatment with 1 mg/kg/day was ineffective and 1 male dog treated with 10 mg/kg died on day 9 from cardiovascular and pulmonary dysfunction. A female receiving 3 mg/kg displayed calcification of the heart papillary muscle. The no-effect dose was determined to be 3 mg/kg/day (5).

In an *in vivo* study, azelnidipine (1, 10 or 30 mg/kg/day p.o.) was administered to 6-week old male rats (9 weeks prior to mating) for 2 weeks and 8-week old female rats (2 weeks prior to mating) until day 7 of pregnancy. Azelnidipine treatment did not affect copulation behavior or pregnancy rates. Moreover, no lethal or adverse effects were detected in parental animals or 20-day old fetuses. It was concluded that the no-effect dose in parents, reproductive activity and offspring must be greater than 30 mg/kg (6).

In an *in vivo* study, azelnidipine (3, 10 or 30 mg/kg/day) was administered via gavage to pregnant rats from day 7-17 of pregnancy. Maternal decreases in food intake and weight gain, in addition to death, were observed in rats receiving 30 mg/kg; treatment did not affect maintenance of pregnancy, parturition or lactation. Moreover, no adverse effects were detected in embryos or fetuses from any of the treated groups. The no-effect doses were determined to be 10 mg/kg and greater than 30 mg/kg for parental females and offspring, respectively (7).

In an *in vivo* study, pregnant rabbits were administered azelnidipine (10, 30 or 100 mg/kg/day via gavage) from days 6-18 of pregnancy. Treatment with 100 mg/kg resulted in maternal decreases in food intake. No lethal or adverse effects were observed in embryos and fetuses in any of the treated groups. Thus, the no-effect doses in maternal animals and offspring were determined to be 10 mg/kg and greater than 100 mg/kg, respectively (8).

Pregnant rats were administered azelnidipine (1, 3 or 10 mg/kg/day via gavage) from day 17 of pregnancy (perinatal) to day 21 postpartum (lactation). Treatment with 10 mg/kg resulted in decreased maternal food intake and a decrease in body weight gain. In addition, decreased locomotor activity, deep respiration, piloerection, paleness of pinna and limbs and discoloration of eyeballs was observed from late pregnancy to lactation. Pregnancy was prolonged in some females and 6 females died in late pregnancy or postpartum. Moreover, an increased number of dead fetuses was also observed in treated animals. Azelnidipine doses of 3 mg/kg and 10 mg/kg were considered to be the no-effect doses in maternal animals and offspring, respectively (9).

Azelnidipine treatment was found to have low antigenicity in a study using guinea pigs and mice. Guinea pigs were administered either a single oral dose of azelnidipine (0.1 or 1 mg) or Freund's complete adjuvant or ovalbumin (s.c.) at the same doses, and mice received either a single oral dose of azelnidipine (0.01 or 0.1 mg), the same doses of azelnidipine plus Alum or TNBS plus Alum (0.3 m/body i.p.). No antibody titers were detected in any of the treated groups (10).

Azelnidipine treatment in mice (3, 10 or 30 mg/kg/day) and rats (1, 3, 10 mg/kg/day) via oral gavage did not result in any oncogenic effects. Drug-treated male and female mice and male rats had lower body weights as compared to control animals and male rats treated with 10 mg/kg exhibited suppressed body weight gain. Although a higher incidence of alveolar/bronchiolar adenomas was observed in mice treated with 30 mg/kg, no significant differences in survival, hematology parameters, urinalysis, type of lesions observed at necropsy, incidence of malignant neoplasmas or tumors were observed between treatment groups (11).

Pharmacological studies of azelnidipine in mice, rats, guinea pigs, rabbits and dogs demonstrated that doses higher (100 and 300 mg/kg) than the effective *in vitro* (0.1-1 μg/ml) and *in vivo* (0.03-10 mg/kg) doses resulted in pharmacological effects in the central nervous system, respiratory and cardiovascular systems, and smooth muscle and renal function common to most dihydropyridine calcium channel antagonists (12).

Contractile dysfunction of stunned myocardium was significantly improved when azelnidipine was administered i.v. to dogs 20 min before coronary artery ligation. Although 0.03 mg/kg azelnidipine was ineffective, 0.1 and 0.3 mg/kg significantly reduced diastolic blood pressure and increased percentage segment shortening. An enhanced recovery of decreases in ischemia-induced segment shortening was also observed in treated animals (13).

Azelnidipine was shown to have possible vasculoprotective properties in a study in which salt-sensitive rats were administered 3 mg/kg/day of the drug for 12 days. Blood pressure, LDH/HDL cholesterol ratios, urinary albumin excretion and thoracic aorta wall/lumen thickness/diameter were all significantly decreased in treated animals. Endothelium monocyte adherence was also inhibited in azelnidipine-treated animals as compared to controls (14).

1. Hirano, K., Hagiwara, T., Uchida, T., Kawaguchi, A. *Genotoxicity test on azelnidipine.* Jpn Pharmacol Ther 1997, 25(Suppl. 5): 137.

2. Totsuka, S., Sugano, A., Suzuki, M. et al. *Single dose oral toxicity studies on azelnidipine in mice, rats and dogs.* Jpn Pharmacol Ther 1997, 25(Suppl. 5): 5.

3. Suzuki, T., Koike, Y., Kitagaki, T., Yamoto, T. *A 90-day oral repeated dose toxicity study of azelnidipine in rats followed by a 28-day recovery period.* Jpn Pharmacol Ther 1997, 25(Suppl. 5): 13.

4. Mori, M., Muramatsu, T., Yamashita, K., Miyakoshi, N., Kudo, K., Yasuda, M. *A 13-week oral repeated dose toxicity study of azelnidipine in beagle dogs.* Jpn Pharmacol Ther 1997, 25(Suppl. 5): 41.

5. Yasuda, M., Koyanagi, F., Yamashita, K., Ohashi, Y., Takaoka, M. *A 52-week oral repeated dose toxicity study of azelnidipine in beagle dogs.* Jpn Pharmacol Ther 1997, 25(Suppl. 5): 65.

6. Hirose, K., Tanase, H. *Reproductive study of azelnidipine administered prior to and in the early stages of pregnancy in rats.* Jpn Pharmacol Ther 1997, 25(Suppl. 5): 93.

7. Hirose, K., Tanase, H. *Reproductive and developmental toxicity study of azelnidipine administered during the period of fetal organogenesis in rats.* Jpn Pharmacol Ther 1997, 25(Suppl. 5): 103.

8. Asai, M., Kimura, T., Hirose, K., Tanase, H. *Reproductive and developmental toxicity study of azelnidipine administered during the period of fetal organogenesis in rabbit.* Jpn Pharmacol Ther 1997, 25(Suppl. 5): 113.

9. Kaneko, Y., Hirose, K., Tanase, H. *Reproductive study of azelnidipine administered during the perinatal and lactation periods in rats.* Jpn Pharmacol Ther 1997, 25(Suppl. 5): 119.

10. Shinkai, K., Kimura, T., Ishikawa, N., Muramatsu, K., Kurita, Y. *Antigenicity studies on azelnidipine in guinea pigs and mice.* Jpn Pharmacol Ther 1997, 25(Suppl. 5): 129.

11. Takaoka, M., Matsuura, T., Yamashita, K., Ohashi, Y., Matsunuma, N. *Oncogenicity studies in mice and rats with azelnidipine.* Jpn Pharmacol Ther 1997, 25(Suppl. 5): 149.

12. Miyamoto, M., Miyake, S., Koike, H., Iwata, N., Kamoshita, K., Fukami, M. *General pharmacological studies on azelnidipine, a novel dihydropyridine calcium channel antagonist.* Jpn Pharmacol Ther 1997, 25(Suppl. 5): 163.

13. Satoh, K., Yamamoto, A., Hoshi, K., Ichihara, K. *Effects of azelnidipine, a dihydropyridine calcium antagonist, on myocardial stunning in dogs.* Jpn J Pharmacol 1998, 76(4): 369.

14, Yamakado, M., Yamazaki, I. *Experimental study of calcium antagonist on vasculoprotection: Effect of azelnidipine on hypertensive vascular injury in Dahl salt sensitive rat.* Amer J Hypertension 1998, 11(4, Part 2): 92A.

Original monograph – Drugs Fut 1990, 15: 671.

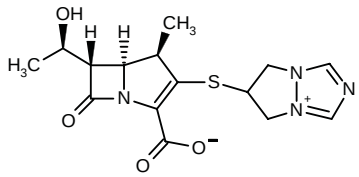
Additional Reference

Okamura, A. et al. *Study of the participation of renin-angiotensins (RA) system on the formation of cardiac hypertrophy in fructose-fed rats.* Jpn Circ J 1997, 61(Suppl. 1): Abst 0965.

Biapenem

Carbapenem

EN: 148321



$C_{15}H_{18}N_4O_4S$ **Lederle**

Results of *in vitro* studies against 535 clinical isolates showed that biapenem was more active than imipenem against *Enterobacteriaceae* (MIC_{90}s = 0.12-2 and 0.25-4 mg/l, respectively) and *Pseudomonas aeruginosa* (MIC_{90}s = 8 and 16 mg/l, respectively) (1).

A pharmacokinetic study in which 8 healthy volunteers and 30 patients with varying degrees of renal failure were administered biapenem (500 mg i.v. over 30 min) showed that 46% of the compound was eliminated extrarenally in healthy subjects, while elimination in treated patients was prolonged due to a decrease in both extrarenal and renal clearance. In addition, a significant amount of biapenem was eliminated in patients on hemodialysis, suggesting that the agent should be given following hemodialysis or dosages should be increased (2).

The pharmacokinetics and safety of biapenem have been compared in subjects with normal and impaired renal function and in the elderly. Patients with end-stage renal disease undergoing long-term hemodialysis treatment and healthy elderly and young volunteers received single i.v. doses of biapenem, which was well tolerated in all study groups. Age-related changes were observed in some pharmacokinetic parameters (AUC, total body clearance and renal clearance), while others (elimination $t_{1/2}$ and urinary recovery of unchanged drug) were not affected by age. Steady-state volume of distribution decreased, but not to a significant extent, with age. These age-related changes were attributed to decreased lean body mass and lower renal function in the elderly volunteers, but these differences are not sufficient to require dosage adjustment in elderly patients with normal renal function. Furthermore, the results obtained following single i.v. administration of biapenem to patients with renal

impairment, studied both on and off hemodialysis, indicated that the drug may also be used safely in this patient group (3).

1. Bonfiglio, G., Maccarone, G., Mezzatesta, M.L., Privitera, A., Carciotto, V., Santagati, M., Stefani, S., Nicoletti, G. *In vitro activity of biapenem against recent Gram-negative and Gram-positive clinical isolates.* Chemotherapy 1997, 43(6): 393.

2. Koeppe, P., Höffler, D., Fitzen, B. *Biapenem pharmacokinetics in healthy volunteers and in patients with impaired renal function.* Arzneim-Forsch-Drug Res 1997, 47(11): 1250.

3. Uematsu, T., Kozawa, O., Niwa, M., Matsuno, H. *Comparative pharmacokinetics of a new carbapenem, biapenem, in the subjects with normal and impaired renal functions and in the elderly.* Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-388.

Original monograph – Drugs Fut 1994, 19: 631.

Additional References

Aralar, P.A. et al. *The antimycobacterial activity of the carbapenems, biapenem, imipenem, meropenem, panipenem and BO2727 against Mycobacterium avium complex (MAC).* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst E-165.

Ozawa, O. et al. *Study on the tolerance and pharmacokinetics of a novel carbapenem antibacterial agent (biapenem) in elderly subjects.* Jpn J Clin Pharmacol Ther 1997, 28(1): 237.

Horii, T. et al. *An in-vitro study of carbapenem-induced morphological changes and endotoxin release in clinical isolates of Gram-negative bacili.* J Antimicrob Chemother 1998, 41(4): 435.

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Antiglaucoma
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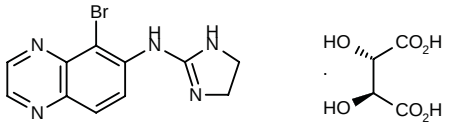

$C_{11}H_{10}BrN_5.C_4H_6O_6$

Pfizer; Allergan

In studies in rats, both single (1 mg/kg i.p.) and multiple (10 µl 1% b.i.d. for 15 days) doses of brimonidine were found to significantly upregulate retinal bFGF expression and improve neuronal survival following kainic acid-induced toxicity. These results indicate that brominidine has neuroprotective properties in addition to its ability to lower intraocular pressure (1).

In studies in conscious cynomolgus monkeys with normal or elevated intraocular pressure, brimonidine, timolol and betaxolol all reduced intraocular pressure, with brimonidine and timolol being equipotent and more potent than betaxolol. In normotensive monkeys, brimonidine was much more potent than the other two drugs. In guinea pig bronchi rings, timolol produced a concentration-dependent constrictive response (EC_{50} = 12 nM). Betaxolol produced a 50% response at 10 µM, while brimonidine had no activity at this concentration. Isoproterenol-induced inotropic response was inhibited by timolol and betaxolol (EC_{50} = ~ 300 nM), while brimonidine at concentrations up to 10 µM had no effect (2).

Administration of brimonidine (0.2% b.i.d. for 29 days) in 27 patients with ocular hypertension reduced intraocular pressure from 20.5 to 15.9 mmHg, reduced aqueous flow from 2.4 to 2.1 µl/min and increased uveoscleral outflow from 0.65 to 1.09 µl/min (3).

In a 12-month, multicenter, randomized, parallel-group study in 483 patients with glaucoma and ocular hypertension, treatment with brimonidine (0.2% b.i.d.) or timolol (0.5% b.i.d.) resulted in mean reductions from baseline in intraocular pressure of 6.8 and 5.9 mmHg, respectively. Both drugs were well tolerated and did not produce clinically significant changes in systolic or diastolic blood pressure (4).

Brimonidine (0.2%) was shown to be as effective as apraclonidine (0.1%) in preventing intraocular pressure spikes in patients undergoing argon laser trabeculoplasty. The average maximum reductions in intraocular pressure were 6.3 and 4.8 mmHg in the brimonidine- and apraclonidine-treated groups, respectively (5).

In a 3-month, multicenter, randomized, parallel-group study in 206 patients with open-angle glaucoma or ocular hypertension, brimonidine (0.2% b.i.d.) was found to be more effective than betaxolol (0.25% b.i.d.) in lowering intraocular pressure. Overall mean decreases in intraocular pressure at trough were 3.9 and 3.2 mmHg, respectively, for brimonidine and betaxolol (6).

Brimonidine 0.2% b.i.d. was compared to timolol 0.5% in terms of clinical success rate and quality of life in patients with previously untreated open-angle glaucoma or ocular hypertension. Assessment of intraocular pressure, SF-36 Health Survey, the Glaucoma Disability Index and safety evaluations showed that brimonidine is a safe and effective initial treatment of ocular hypertension. Of the 206 patients who completed the study, 178 (86%) were considered clinically successful (7).

In a multicenter, double-masked, unevenly randomized comparison of brimonidine (0.2% b.i.d.) and timolol (0.5% b.i.d.) in 926 patients with open-angle glaucoma or ocular hypertension, mean reductions in intraocular pressure from baseline were 6.7 and 6.2 mmHg for brimonidine and timolol, respectively. Both treatments were well tolerated and their effects were sustained throughout the 1-year follow-up period. Brimonidine therapy did not affect heart rate, while timolol produced significant reductions from baseline values. More patients treated with timolol reported burning and stinging, while the incidence of oral dryness was more frequent in the brimonidine group (8).

The effects of brimonidine (0.2% b.i.d. for 2 weeks) on ocular blood flow were evaluated in 18 patients with ocular hypertension in a randomized, double-masked, crossover study. Brimonidine therapy produced a 0.4% reduction in pulsatile ocular blood flow, compared to 4%

in the placebo group. Respective reductions in intraocular pressure were 17.7% and 9 % for brimonidine and placebo (9).

Allergan has introduced brimonidine tartrate (Alphagan®) in Germany for the treatment of open-angle glaucoma and ocular hypertension (10).

1. Lai, R.K., Hasson, D.W., Wheeler, L.A. *Neuroprotective effect of brimonidine.* Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 2750.

2. Manlapaz, C.A., Kharlamb, A.B., Williams, L.S., Burke, J.A., Wheeler, L.A. *IOP, pulmonary and cardiac effects of anti-glaucoma drugs brimonidine (Alphagan®), timolol and betaxolol.* Invest Ophthalmol Visual Sci 1997, 38(4, Part 2): Abst 3792.

3. Toris, C.B., Camras, C.B., Yablonski, M.E., Garden, V.S. *Acute versus chronic effects of brimonidine on aqueous humor dynamics in human eyes.* Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 1129.

4. Lewis, R.A. *Comparative safety and ocular hypotensive efficacy of brimonidine tartrate 0.2% and timolol maleate 0.5% in patients with glaucoma or ocular hypertension: 12-Month results from an ongoing study.* Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 1149.

5. Barnes, S.D., Campagna, J.A., Dirks, M.S., Geanon, J.D.,Doe, E.A. *Comparison of brimonidine 0.2% to apraclonidine 1.0% for the control of intraocular pressure spikes after argon laser trabeculoplasty.* Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 2597.

6. Sherwood, M. *A comparison of the safety and ocular hypotensive efficacy of twice daily brimonidine 0.2% versus betaxolol 0.25% suspension in patients with open-angle glaucoma or ocular hypertension.* Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 2598.

7. Javitt, J. *The clinical success rate and quality of life assessment of brimonidine tartrate 0.2% compared with timolol 0.5%, administered twice-daily, in patients with previously untreated open-angle glaucoma or ocular hypertension.* Invest Ophthalmol Visual Sci 1997, 38(4, Part 2): Abst 3363.

8. Crichton, A. *Brimonidine tartrate 0.2% compared with timolol 0.5% administered twice-daily in patients with open-angle glaucoma or ocular hypertension.* Invest Ophthalmol Visual Sci 1997, 38(4, Part 2): Abst 3364.

9. Lachkar, Y., Migdal, C., Dhanjil, S., Griffin, M. *The effect of brimonidine on ocular blood flow.* Invest Ophthalmol Visual Sci 1997, 38(4, Part 2): Abst 3602.

10. *Another European launch for Alphagan*. Prous Science Daily Essentials April 23, 1998.

Original monograph – Drugs Fut 1985, 10: 578.

Additional References

Miguel, T.T. et al. *Central UK-14,304 and imidazolacetic acid and hydrosaline intake.* Soc Neurosci Abst 1996, 22(Part 1): Abst 182.6.

Gordon, R.N. et al. *α-Agonist allergy: Is there cross reactivity between apraclonidine and brimonidine?* Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 2601.

Brown-Istvan, L., Samples, J.R. *Effect of brimonidine on trabecular cell production of stromelysin.* Invest Ophthalmol Visual Sci 1997, 38(4, Part 1): Abst 2618.

Bhandari, A. et al. *Effect of brimonidine on optic nerve blood flow in rabbits.* Invest Ophthalmol Visual Sci 1997, 38(4, Part 2): Abst 3631.

Zhan, G.-L. et al. *Effects of apraclonidine and brimonidine on rabbit ocular blood flow.* Invest Ophthalmol Visual Sci 1997, 38(4, Part 2): Abst 3632.

Schuman, J.S. et al. *A 1-year study of brimonidine twice daily in glaucoma and ocular hypertension: A controlled, randomized, multicenter clinical trial.* Arch Ophthalmol 1997, 115(7): 847.

Greenfield, D.S. et al. *Brimonidine: A new α_2-adrenoreceptor agonist for glaucoma treatment.* J Glaucoma 1997, 6(4): 250.

Nunes, J.P., Guimaraes, S. *The influence of tone and pertussis toxin on the responses of the canine saphenous vein to phenylephrine, UK-14-304 and chloroethylclonidine.* Pharmacol Rev Commun 1997, 9: 41.

Stonel, L.S. et al. *The α_2-adrenergic receptor subtype in spinal adrenergic analgesia: A combined behavioral and anatomical study.* 2nd Cong Eur Fed Int Assoc Study Pain Chapters (Sept 23-27, Barcelona) 1997, 268.

Hasson, D. et al. *Functional protection of rat retinal from ischemic injury by brimonidine.* Soc Neurosci Abst 1997, 23(Part 1): Abst 72.4.

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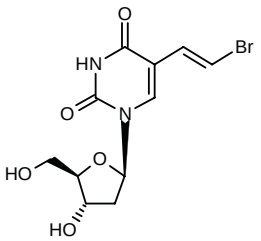

$C_{11}H_{13}BrN_2O_5$

Rega Inst. Med. Res. (BE); Menarini; Berlin-Chemie; Viñas

The pharmacokinetics of brivudin was evaluated in rats, monkeys and humans following oral and intravenous administration. Values for clearance and volume of distribution at steady state in rats, monkeys and humans were 3.85, 4.33 and 0.25 l/h/kg, and 9.93, 0.54 and 0.22 l/kg, respectively, while terminal half-life and absolute bioavailability were measured at 4.5-12.0, 0.1-0.4 and 3.7-16.4 h, and 60, 9.5 and 33.2%, respectively (1).

1. Urso, R., Crea, A., D'Aranno, V., Giachetti, A., Segre, G. *Pharmacokinetics of brivudin in rat, monkey and man.* Pharmacol Res 1997, 35(Suppl.): 98.

Original monograph – Drugs Fut 1980, 5: 334.

Additional References

Wutzler, P. et al. *Antiviral efficacies of famciclovir, valaciclovir, and brivudin in disseminated herpes simplex virus type 1 infection in mice.* Intervirology 1997, 40(1): 15.

Afouna, M.I. et al. *Assessment of the relationship between the skin target site free drug concentration (C*) and the in vivo efficacy for bromovinyldeoxyuridine and acyclovir formulations in the treatment of cutaneous HSV-1 infections in hairless mice.* Antivir Res 1998, 37(3): Abst 15.

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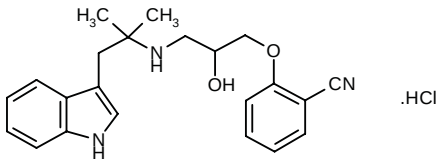

$C_{22}H_{25}N_3O_2.HCl$

Bristol-Myers Squibb; Astra Merck; Intercardia; Knoll

Results of a study evaluating intrinsic sympathomimetic activity (ISA) in pithed rats showed that bucindolol (10-1000 μg/kg i.v.) produced a significant dose-related increase in heart rate, which was inhibited by propranolol, indicating that the drug's effect on ISA is mediated through the stimulation of myocardial β-adrenoreceptors (1).

1. Willette, R.N., Mitchell, M.P., Ohlstein, E.H., Lukas, M.A., Ruffolo, R.R. *Evaluation of intrinsic sympathomimetic activity of bucindolol and carvedilol in rat heart.* Pharmacology 1998, 56(1): 30.

Original monograph – Drugs Fut 1981, 6: 405.

Candesartan Cilexetil
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Amias®
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Ratacand®

Antihypertensive
Angiotensin II Antagonist

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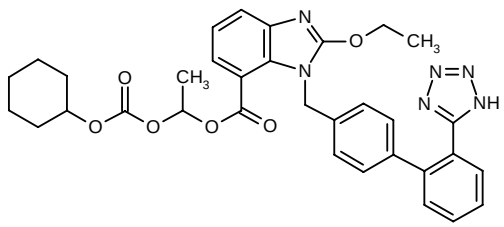


$C_{33}H_{34}N_6O_6$

Takeda; Astra Merck

In vitro studies using isolated rabbit thoracic aorta preparations showed that candesartan cilexetil (0.003, 0.03 and 1 nM) completely suppressed the contractile response to angiotensin II as compared to irbesartan (1, 10 and 100 nM), losartan (10, 100 nM) and its active metabolite EXP-3174 (0.01, 0.1 and 1 nM) (1).

Evaluation of the effects of candesartan cilexetil on myocardial function, infarct size and blood flow following myocardial ischemia and reperfusion in pigs showed that the drug did not produce significant changes in hemodynamics, but did improve functional recovery of the ischemic myocardium and reduce infarct size (2).

In studies in stroke-prone, spontaneously hypertensive rats, candesartan cilexetil at a dose of 0.1 mg/kg reduced the incidence of stroke and urinary protein excretion without affecting blood pressure. Higher doses of candesartan (1 and 10 mg/kg) and enalapril maleate (10 mg/kg) reduced blood pressure, stroke incidence, urinary indices and left ventricular weight. Furthermore, a low dose of candesartan reduced circulating renin-angiotensin system indices while the high dose increased them (3).

The effects of candesartan on infarct size were evaluated and compared to placebo in a model of severe regional myocardial ischemia in anesthetized pigs induced by 90 min of ischemia and 120 min of reperfusion. At a dose of 1 mg/kg i.v., candesartan reduced infarct size from 17.7 ± 8.6% of the area at risk in the placebo group to 9.7 ± 6.5%. No significant differences in heart rate, regional myocardial blood flow and area at risk were observed between the two groups (4).

Evaluation of the chronic effects of TCV-116 in 14 patients with congestive heart failure showed that the drug produced no significant changes in clinical parameters or neurohormonal and cytokine levels, while significant reductions in plasma TNFα, sICAM-1 and sVCAM-1 levels coincided with an increased ejection fraction (5).

The antihypertensive efficacy of candesartan cilexetil (4, 8 or 12 mg/day) was compared to enalapril (10 mg/day) in 380 patients with mild to moderate essential hypertension during 12 weeks of treatment. The 8 mg dose of candesartan was equally effective as enalapril in reducing sitting diastolic and systolic blood pressure. Both drugs were well tolerated and equally safe (6).

Candesartan cilexetil (8 and 16 mg once daily), alone or in combination with other drugs, was evaluated in 216 patients with moderate to severe essential hypertension. At the end of the 12-week treatment period, blood pressure was reduced from 166/104 to 138/87 mmHg with the 8-mg dose and from 165/105 to 142/88 mmHg with the 16-mg dose. The 16-mg dose of candesartan in combination with 5 mg amlodipine reduced blood pressure from 187/108 to 143/88 mmHg, while a regimen of candesartan 16 mg plus amlodipine 5 mg and hydrochlorothiazide 25 mg produced a reduction from 181/112 to 141/88 mmHg (7).

Escalating doses of 4, 8, 16 and 32 mg candesartan cilexetil were assessed for safety and efficacy in 19 patients with essential hypertension. The drug was safe at all doses tested, and the frequency of adverse events in the treatment group compared favorably to the placebo

group. Supine and standing systolic and diastolic blood pressures decreased 24 h after each dose, and the 32-mg dose produced a notable and smooth reduction throughout the 24-h period (8).

A combination regimen of candesartan cilexetil (2, 4, 8 or 16 mg) and hydrochlorothiazide (12.5 or 25 mg) in 1306 patients with mild to moderate hypertension produced superior results compared to regimens consisting of either drug alone. The treatments were well tolerated, with adverse events occurring in 21-40% of the patients (9).

The addition of 4 and 8 mg candesartan cilexetil to hydrochlorothiazide (12.5 mg) produced a significant reduction in sitting diastolic blood pressure when evaluated in 325 patients with mild to moderate hypertension. In addition, candesartan showed an excellent safety and tolerability profile (10).

The effects of candesartan cilexetil (8 or 16 mg once daily for 12 weeks) on glucose homeostasis and serum lipid profile were evaluated in a double-blind, crossover study in patients with mild hypertension and type II diabetes. The drug had no adverse effects on HbA1c, blood glucose or serum lipids as compared to placebo, and adverse events and withdrawals were similar in both groups. Blood pressure was controlled in most patients, with approximately 60% achieving diastolic blood pressure of less than 90 mmHg (11).

A multicenter, double-blind, randomized, comparative study evaluated the antihypertensive effects of candesartan cilexetil (4-8 mg once daily) and enalapril (10-20 mg once daily) in 205 patients with mild to moderate hypertension. Administration of candesartan for a period of 8 weeks produced significantly better reductions in systolic and diastolic blood pressure as compared to enalapril and placebo (12).

In patients with type II diabetes and mild hypertension, candesartan cilexetil had no effect on glomerular filtration rate, glucose homeostasis, blood lipid profile or body weight as compared to treatment with placebo. Furthermore, median urinary albumin decreased in candesartan-treated patients and increased in the placebo group. Blood pressure was reduced by 6.4 and 3.6 mmHg following treatment with candesartan and placebo, respectively (13).

In a study in 16 patients with essential hypertension, a single dose of candesartan cilexetil (16 mg) reduced mean arterial blood pressure as a consequence of decreased vascular resistance. The reduction in renal vascular resistance led to increased renal plasma flow even though systemic blood pressure was decreased (14).

In a double-blind, randomized trial in patients with mild to moderate hypertension, candesartan cilexetil 8 mg/day was as effective as losartan 50 mg/day in reducing sitting diastolic blood pressure, whereas 16 mg/day candesartan was significantly more effective than losartan 24 h after drug administration (15).

Increasing doses of candesartan cilexetil (2, 4, 8 and 16 mg/day) were evaluated in 1490 patients with hypertension during 4-12 weeks. The drug produced dose-related blood pressure reductions at all doses tested, with the 16 mg/day dose showing the greatest effect. The drug was well tolerated, and the incidence of adverse events was similar in candesartan- and placebo-treated groups (16).

The efficacy and tolerability of candesartan cilexetil (8 mg/day, increased to 16 mg/day) were evaluated in elderly hypertensive patients aged 65 or older. The drug proved to be effective and very well tolerated in this patient population, producing reductions in supine diastolic and systolic blood pressure of 7.5 and 13.6 mmHg 24 h postadministration (17).

A meta-analysis of 6 placebo-controlled, double-blind clinical trials in patients with mild to moderate hypertension showed that candesartan cilexetil administered at doses of 4, 8 or 16 mg dose-dependently lowered blood pressure and effectively controlled blood pressure, with the 16-mg dose producing the most pronounced blood pressure-lowering effects. The drug's efficacy is equivalent to that of enalapril (10-20 mg), amlodipine (5 mg) and hydrochlorothiazide (25 mg) and greater than that of losartan (50 mg). In combination with hydrochlorothiazide, candesartan is effective in patients previously unresponsive to hydrochlorothiazide monotherapy. The drug's tolerability profile is similar to that observed with placebo and appears not to be affected by sex or gender (18).

In 1490 hypertensive patients treated with candesartan cilexetil (2, 4, 8 or 16 mg/day) for 4-12 weeks, the drug produced dose-related antihypertensive effects at all doses studied. Therapy was well tolerated in both young and elderly patients, and the frequency of side effects was similar in both candesartan- and placebo-treated groups (19).

Pharmacokinetic evaluation of single and multiple doses of candesartan cilexetil (2-16 mg) administered in 51 young, healthy male volunteers and 33 elderly male and female healthy volunteers, produced dose-proportional AUC and C_{max}, indicating linear pharmacokinetics. Elimination half-life was 9 h, with no evidence of accumulation or gender-specific effects. Safety and tolerability were similar to those of placebo, with no significant treatment-related adverse events reported (20).

In an open-label, randomized study in 18 healthy male volunteers, administration of candesartan cilexetil (8 mg) either 30 min after intake of a high fat meal or after 10 h of fasting, produced no significant difference in AUC (642 *vs.* 636 ng/h/ml). Following the high fat meal, C_{max} increased (from 68.7 to 86.8 ng/ml), while t_{max} and mean residence time were reduced from 4.4 to 3.3 h and 11.6 to 9.8 h, respectively; these differences had no clinical significance. Renal clearance was similar under both fasting and fed conditions (10.7 and 10.9 ml/min, respectively) as was elimination half-life (9.4 and 9.1 h, respectively) (21).

Administration of 16 mg candesartan cilexetil in combination with nifedipine, warfarin, glibenclamide or digoxin in healthy male and female volunteers had no effect

  CCC: 0377-8282/98

on the pharmacokinetics of candesartan, although a combination of candesartan and hydrochlorothiazide produced a significant increase in the bioavailability of candesartan (22).

Pharmacodynamics and pharmacokinetics of candesartan cilexetil were evaluated in 232 patients of both sexes receiving doses of 2, 4, 8, 12 and 16 mg/day. All doses reduced both systolic and diastolic blood pressure with a maximum effect observed following repeated administration. Population pharmacokinetics best fit a two-compartment model in terms of clearance, central volume of distribution, peripheral volume and intercompartmental clearance, with acumulation half-life of 29 h. Elimination of the drug was age- and weight-dependent (23).

In an 8-week multicenter, double-blind study in 277 patients with mild to moderate hypertension, candesartan cilexetil (16 mg q.d. or 8 mg b.i.d.) produced comparable reductions in mean trough sitting diastolic and systolic blood pressures with both dosing regimens. The antihypertensive effects were persistent and diurnal variation was preserved over the 24-h dosing interval (24).

Administration of candesartan cilexetil (16 mg/day) during 6 weeks in patients with essential hypertension produced systemic and renal arterial vasodilatation as well as a reduction in blood pressure. Renal perfusion and filtration, as well as cardiac performance were not affected. An increase in angiotensin II levels and plasma renin activity and a decrease in aldosterone concentration were observed (25).

A meta-analysis of 6 phase II/III randomized, double-blind, placebo-controlled trials involving 1187 patients treated with candesartan cilexetil (8 or 16 mg/day) for 4-12 weeks, and 957 patients treated for at least 8 weeks showed that the drug reached 90% of its antihypertensive effect after 4 weeks. Continued treatment for another 4 weeks resulted in a further decrease in blood pressure. A clinically relevant reduction in blood pressure was observed within the first 2 weeks of therapy, with 67 and 80% being achieved after 1 and 2 weeks, respectively (26).

The efficacy and safety of tablet formulations of candesartan cilexetil and hydrochlorothiazide (8/12.5 mg once daily) and lisinopril and hydrochlorothiazide (10/12.5 mg once daily) were compared in 353 patients with primary hypertension. No significant and clinically relevant differences in blood pressure reductions were observed between the two regimens. Candesartan/hydrochlorothiazide was better tolerated with a lower incidence of cough than lisinopril/hydrochlorothiazide (27).

A multicenter, double-blind study in 209 patients with severe hypertension, which included a prospectively designed secondary analysis by race of 85 black and 124 nonblack subjects, showed that the addition of candesartan cilexetil (8 mg q.d.) to hydrochlorothiazide (12.5 mg q.d.) produced better blood pressure control in black patients responding poorly to hydrochlorothiazide monotherapy. Treatment was well tolerated, and no significant differences were observed between groups in regard to frequency and intensity of adverse events, and laboratory and clinical findings (28).

The addition of candesartan cilexetil to hydrochlorothiazide therapy reduced mean trough sitting diastolic blood pressure from 105.0 mmHg to 95.8 mmHg in patients with severe hypertension previosly responding poorly to hydrochlorothiazide. In patients receiving placebo in addition to hydrochlorothiazide, blood pressure was reduced from 105.6 to 102.2 mmHg. The frequency of adverse effects and changes from baseline in clinical and laboratory findings were similar in both groups (29).

The incidence and severity of cough induced by candesartan cilexetil was compared to enalapril in men and women aged 20-80 with a history of primary hypertension and treatment-related cough. Candesartan was associated with a lower frequency of cough than enalapril; the proportion of patients without cough at last visit was 64.5% and 31.8% in the candesartan- and enalapril-treated groups, respectively (30).

Astra has obtained mutual recognition approval for candesartan cilexetil (Atacand®) for the treatment of hypertension in the European Community countries (31).

Takeda received approval for candesartan cilexetil (Blopress®) for the treatment of essential hypertension in the European Community countries (32).

Candesartan cilexetil (Atacand®) has been launched in Sweden by Astra; it is supplied as tablets, 4, 8 and 16 mg (33).

Candesartan cilexetil (Atacand®) has been launched for the treatment of hypertension in its first market, Sweden. Candesartan will be comarketed by Astra and originator Takeda (Blopress®) in most countries, although Astra holds exclusive rights in certain European countries, Australia, Canada and the U.S., and Takeda holds exclusive rights in Japan and some Asian countries (34).

Takeda has introduced candesartan cilexetil (Amias®) in the U.K. for the treatment of essential hypertension and will be comarketed with Astra (35).

The FDA has cleared candesartan cilexetil (Atacand®) for the once-daily treatment of hypertension. The product will be marketed in the U.S. by Astra Merck, the 50/50 Astra and Merck & Co. joint venture. Candesartan has already been introduced in a number of European markets, including Germany, Sweden and the U.K. The drug is also known as Blopress® and Amias® (36).

1. Morsing, P., Brandt-Eliasson, U., Abrahamsson, T. *Candesartan, an insurmountable antagonist of angiotensin II mediated contractile effects in isolated vascular preparations: A comparison with irbesartan, losartan and its active metabolite (EXP 3174).* Amer J Hypertension 1998, 11(4, Part 2): 37A.

2. Shimizu, M., Wang, Q.-D., Sjöquist, P.-O., Rydén, L. *Angiotensin II type-1 receptor blockade with candesartan protects the myocardium from ischaemia/reperfusion injury.* Eur Heart J 1997, 18(Suppl.): Abst P1021.

3. Inada, Y., Wada, T., Ojima, M., Sanada, T., Shibouta, Y., Kanagawa, R., Ishimura, Y., Fujisawa, Y., Nishikawa, K. *Protective effects of candesartan cilexetil (TCV-116) against stroke, kidney dysfunction and cardiac hypertrophy in stroke-*

prone spontaneously hypertensive rats. Clin Exp Hypertension 1997, 19(7): 1079.

4. Jalowy, A., Schulz, R., Post, H., Dörge, H., Weidenbach,R., Behrends, M., Heusch, G. *The angiotensin II AT_1-receptor antagonist candesartan reduces infarct size in pigs.* J Mol Cell Cardiol 1998, 30: Abst 303.

5. Tsutamoto, T., Maeda, K., Mabuchi, N., Hisanaga, T., Wada, A., Fukai, D., Ohnishi, M., Sawaki, M. *Angiotensin II receptor antagonist improves the immune activations of patients with chronic heart failure.* J Amer Coll Cardiol 1998, 31(2, Suppl. A): Abst 1015-40.

6. Franke, H., Herrmann, W.M., Magin, S.G. *Comparison of the efficacy and safety of candesartan cilexetil 4, 8 and 12 mg with placebo and enalapril 10 mg in patients with mild to moderate essential hypertension.* J Hypertension 1997, 15(Suppl. 4): Abst 99.

7. MacGregor, G.A., Antonios, T.F.T., He, F.J. *The efficacy of candesartan cilexetil: An angiotensin II type I receptor antagonist alone or in combination with amlodipine or in combination with amlodipine and hydrochlorothiazide in patients with moderate-to-severe essential hypertension.* J Hypertension 1997, 15(Suppl. 4): Abst 192.

8. O'Kane, K.P.J. et al. *Tolerability and efficacy of candesartan cilexetil 32 mg once daily in hypertensive patients.* J Hypertension 1997, 15(Suppl. 4): Abst 244.

9. Philipp, T. et al. *Dose-finding study of candesartan cilexetil and hydrochlorothiazide in combination in patients with mild to moderate hypertension.* J Hypertension 1997, 15(Suppl. 4): Abst 274.

10. Plouin, P.F. et al. *Efficacy and safety of candesartan cilexetil in combination with hydrochlorothiazide in the treatment of patients with mild to moderate hypertension unresponsive to hydrochlorothiazide alone.* J Hypertension 1997, 15(Suppl. 4): Abst 280.

11. Trenkwalder, P. et al. *Long-term treatment with candesartan cilexetil does not affect glucose homeostasis or serum lipid profile in patients with mild hypertension and type II diabetes.* J Hypertension 1997, 15(Suppl. 4): Abst 372.

12. Zanchetti, A. et al. *Antihypertensive efficacy of candesartan cilexetil or enalapril in patients with mild to moderate hypertension: Clinic and ambulatory blood pressure data.* J Hypertension 1997, 15(Suppl. 4): Abst 406.

13. Forsblom, C., Trenkwalder, P., Dahl, K., Mulder, H. *Candesartan cilexetil, a novel angiotensin II antagonist reduces microalbuminuria in patients with type II diabetes mellitus and mild hypertension.* J Hypertension 1997, 15(Suppl. 4): Abst P3.91.

14. Andersson, O., Fridman, K., Wysocki, M., Friberg, P. *Acute effects of candesartan cilexetil on the systemic and renal haemodynamics in hypertensive patients.* J Hypertension 1997, 15(Suppl. 4): Abst P3.93.

15. Andersson, O.K., Neldam, S. *Candesartan cilexetil 16 mg provides greater antihypertensive effect than losartan 50 mg in patients with mild to moderate hypertension.* J Hypertension 1997, 15(Suppl. 4): Abst P3.97.

16. Hübner, R., Elmfeldt, D., George, M., Olofsson, B. *Candesartan cilexetil, a novel angiotensin II antagonist, provides dose-dependent antihypertensive effect with maintained tolerability.* J Hypertension 1997, 15(Suppl. 4): Abst P3.98.

17. McInnes, G.T., Jonker, J. *Antihypertensive effects and tolerability of candesartan cilexetil in an elderly population.* J Hypertension 1997, 15(Suppl. 4): Abst P3.105.

18. Mancia, G. *The clinical profile of candesartan cilexetil, a new long-acting angiotensin II receptor blocker.* 1st Int Symp Angiotensin II Antagon (Sept 28-Oct 1, London) 1997, Abst 5.5.

19. Hübner, R., George, M., Voet, B. *Candesartan cilexetil: Dose-dependent antihypertensive effect and maintained tolerability.* 1st Int Symp Angiotensin II Antagon (Sept 28-Oct 1, London) 1997, Abst P.40.

20. Riddell, J.G., Högemann, A.M. *Candesartan cilexetil: Single and multiple dose pharmacokinetics in healthy volunteers.* 1st Int Symp Angiotensin II Antagon (Sept 28-Oct 1, London) 1997, Abst P.41.

21. Riddell, J.G., Högemann, A.M. *Food interaction and candesartan cilexetil.* 1st Int Symp Angiotensin II Antagon (Sept 28-Oct 1, London) 1997, Abst P.42.

22. Jonkman, J.H.G., Högemann, A.M. *Drug interaction and candesartan cilexetil.* 1st Int Symp Angiotensin II Antagon (Sept 28-Oct 1, London) 1997, Abst P.43.

23. Meineke, I., Feltkamp, H., Hogemann, A., Gundert Remy, U. *Pharmacokinetics and pharmacodynamics of candesartan after administration of its pro-drug candesartan cilexetil in patients with mild to moderate hypertension - A population analysis.* Eur J Clin Pharmacol 1997, 53(3-4): 221.

24. Zuschke, C.A., Halim, A., Keys, I. *The angiotensin-II receptor blocker candesartan cilexetil provides 24-hour blood pressure control with once-a-day administration in mild-to-moderate hypertension*. Amer J Hypertension 1998, 11(4, Part 2): 107A.

25. Fridman, K., Wysocki, M., Friberg, P., Andersson, O. *Long-term effects of candesartan cilexetil on the systemic and renal haemodynamics in moderately hypertensive patients.* Amer J Hypertension 1998, 11(4, Part 2): 77A.

26. Sever, P., Michel, J., Voet, B. *Candesartan cilexetil (CC): A meta-analysis of time-to-effect relationship.* Amer J Hypertension 1998, 11(4, Part 2): 79A.

27. McInnes, G.T., Istad, H., Keinänen-Kiukaanniemi, S., van Mierlo, H.F.C.M. *Combination of candesartan cilexetil/hydrochlorothiazide 8/12.5 mg has a similar antihypertensive effect and is better tolerated than lisinopril/hydrochlorothiazide 10/12.5 mg.* Amer J Hypertension 1998, 11(4, Part 2): 109A.

28. Ripley, E., Oparil, S. *The addition of candesartan cilexetil to HCTZ enhances blood pressure reduction in black patients with severe (stage 3, JNC-VI) hypertension.* Amer J Hypertension 1998, 11(4, Part 2): 119A.

29. Oparil, S., Ripley, E. *Candesartan cilexetil enhances blood pressure reduction in severe (stage 3, JNC-VI) hypertensive patients inadequately controlled with HCTZ.* Amer J Hypertension 1998, 11(4, Part 2): 121A.

30. Tanser, P., Campbell, L.M., Carranza, J., Karrasch, J., Toutouzas, P., Watts, R. *Candesartan cilexetil is not associated with cough in patients with enalapril-induced cough.* Amer J Hypertension 1998, 11(4, Part 2): 122A.

31. *Mutual recognition approval obtained for Astra's angiotensin II blocker.* Prous Science Daily Essentials October 9, 1997.

32. *Takeda's Blopress approved in EC*. Prous Science Daily Essentials October 16, 1997.

33. *New product intros.* Drug News Perspect 1997, 10(9): 543.

34. *Atacand launched in Sweden.* Prous Science Daily Essentials November 13, 1997.

35. *Candesartan introduced in U.K., Germany.* Prous Science Daily Essentials December 5, 1997.

36. *Atacand: New antihypertensive agent approved for marketing in U.S*. Prous Science Daily Essentials June 8, 1998.

Original monograph – Drugs Fut 1993, 18: 609.

Additional References

Takeda's Atacand scheduled for European launch later this year. Prous Science Daily Essentials July 22, 1997.

Mutschler, E. et al. *Receptor pharmacology, angiotensin II antagonism and kinetics of candesartan cilexetil.* 1st Int Symp Angiotensin II Antagon (Sept 28-Oct 1, London) 1997, Abst 5.1.

Maeda, Y. et al. *Comparison of the therapeutic effects of long-term administration with an angiotensin II receptor antagonist (TCV-116) and an ACE inhibitor in congestive heart failure.* Jpn Circ J 1997, 61(Suppl. 1): Abst 1074.

Yusuf, S. et al. *Effects of candesartan, enalapril or their combination on exercise capacity, ventricular function, clinical deterioration and quality of life in heart failure: Randomized evaluation of strategies for left ventricular dysfunction (RESOLVD).* Circulation 1997, 96(8, Suppl.): Abst 2527.

Meyer-Lehnert, H. et al. *The AT_1-receptor antagonist candesartan inhibits angiotensin II-induced expression of endothelin-1-mRNA in vascular smooth muscle.* J Amer Soc Nephrol 1997, 8: Abst A1397.

Miwa, K. et al. *In vitro metabolism of a new angiotensin II receptor antagonist, candesartan cilexetil.* 1st Int Symp Angiotensin II Antagon (Sept 28-Oct 1, London) 1997, Abst P.11.

Kobayashi, M. et al. *Influence of angiotensin II receptor antagonist (TCV-116) on medial arterial hypertrophy and left ventricular hypertrophy in pressure-overloaded rat heart.* Jpn Circ J 1997, 61(Suppl. 1): Abst 0487.

Watanabe, M. et al. *Effect of chronic administration of angiotensin II receptor antagonist (TCV-116) and calcium antagonist on myocardial remodeling.* Jpn Circ J 1997, 61(Suppl. 1): Abst P343.

Fujii, N. et al. *Effects of exercise on antihypertensive effects of long-term administration of angiotensin II-type 1 (AT_1) receptor antagonist in rats.* Jpn Circ J 1997, 61(Suppl. 1): Abst P680.

Atsumoto, N. et al. *Long-term effects of angiotensin II (Ang II) receptor antagonist as therapeutic agent for heart failure. Influence on neurohumoral factor.* J Cardiol 1997, 30(Suppl. 1): Abst 303.

Noda, M. et al. *Effects of candesartan cilexetil (TCV-116) and enalapril in 5/6 nephrectomized rats.* Kidney Int 1997, Suppl. 63: S136.

Nakamura, T. et al. *Candesartan prevents the progression of mesangioproliferative nephritis in rats*. Kidney Int 1997, Suppl. 63: S226.

Obata, J.E. et al. *Candesartan prevents the progression of glomerulosclerosis in genetic hypertensive rats*. Kidney Int 1997, Suppl. 63: S229.

Moriyama, T. et al. *TCV-116 inhibits interstitial fibrosis and HSP47 mRNA in rat obstructive nephropathy.* Kidney Int 1997, Suppl. 63: S232.

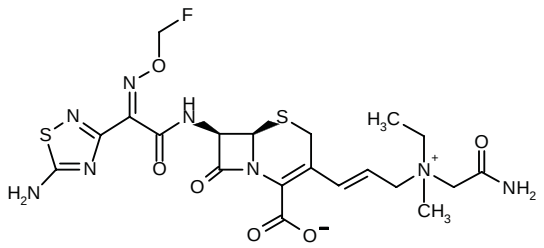
Okazaki, M. et al. *Effect of chronic administration of TCV-116, a novel nonpeptide angiotensin II receptor antagonist, on vasoconstrictor response to sympathetic nerve stimulation in spontaneously hypertensive rats (SHR).* Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-330.

Tsuyuki, R.T. et al. *Combination neurohormonal blockade with ACE inhibitors, angiotensin II antagonists and β-blockers in patients with congestive heart failure.* Can J Cardiol 1997, 13(12): 1166.

Cefluprenam
Cefprenam

Cephalosporin

EN: 142510



$C_{20}H_{25}FN_8O_6S_2$ **Eisai**

In vitro studies using vibration-culture methods to compare the morphologic changes and bactericidal activities of cefluprenam, ceftazidime and cefotaxime against *Escherichia coli*, *Bacteroides fragilis* and *Prevotella bivia* have demonstrated that cefluprenam induced time and dose-dependent morphological filamentous changes. Although bactericidal actions were similar for all cephalosporins, the bactericidal activities of cefotaxime against *B. fragilis* were more potent than cefluprenam and ceftazidime (1).

An *in vitro* study has described the efficacy of cefluprenam and ceftazidime treatment (20 mg/kg p.o. b.i.d. for 3 days) in a new rat model of uterine endometrial cancer. Both cefluprenam and ceftazidime decreased bacterial activity (MIC = 0.025 and 0.05 μg/ml, respectively), suggesting that the two cephalosporins may be useful as a therapy for uterine endometritis in endometrial cancer patients (2).

In vitro studies have shown that cefluprenam has potent antibacterial effects on a wide variety of bacteria. The drug was 2- to 4-fold more active than cefozopran and cefpirome and 16-fold more active than ceftazidime against *Staphylococcus aureus*. High antibacterial activity was also observed against *Enterococcus faecalis*, *Pseudomonas aeruginosa* and *Escherichia coli*. Concentrations of ≤ 0.78 μg/ml cefluprenam potently inhibited 90% of streptococci and most *Enterobacteriaceae*; higher MIC_{90}s were observed against *Enterobacter cloacae*, *Serratia marcescens* and

Providencia rettgeri (3.13, 6.25 and 6.25 μg/ml, respectively) (3).

The antibacterial properties of cefluprenam against Gram-positive and Gram-negative bacteria were evaluated *in vitro*. The drug had higher affinities for high molecular weight penicillin-binding proteins and treatment resulted in filamentous changes in cell morphology and lysis. Cefluprenam had a low affinity for and high resistance to hydrolysis by β-lactamases. In addition, it exhibited potent antibacterial activity against *Enterobacter cloacae* and *Citrobacter freundii* (4).

Cefluprenam treatment was shown to be effective against polymicrobial infections in the pyometra rat model. Rats receiving either 40 mg/kg q.i.d. or 80 mg/kg b.i.d. i.v. for 5 days immediately following inoculation with *Enterococcus faecalis* plus *Bacteroides fragilis* or *Prevotella bivia* had decreased bacterial counts, with the 40 mg/kg regimen being significantly more effective. *B. fragilis* was not reduced in animals receiving the 80 mg/kg regimen. An adequate tissue concentration of 3 μg/g was observed for 1 h following drug treatment (5).

In vivo studies of cefluprenam in mice have demonstrated potent antibacterial actions similar to those observed *in vitro*. Treatment with the drug reduced bacterial counts against polymicrobial pyelonephritis and was more potent than ceftazidime although cefozopran had simlar antibacterial activity. Cefluprenam was also effective against polymicrobial respiratory tract infections, penicillin-resistant *Streptococcus pneumoniae* and *Staphylococcus aureus*-induced thigh infections, with efficacy similar to that of ceftazidime (6).

A pharmacokinetic study has demonstrtaed rapid tissue distribution of [^{14}]C-cefluprenam 5 min after administration (20 mg/kg i.v.) in male rats. The highest level of radioactivity was observed in the renal medulla which was 12 times higher than plasma concentrations (65.62 μg/ml). Radioactivity was also detected in (from highest concentration to lowest): urinary bladder, renal cortex, aorta, plasma blood, vein, trachea, skin and lung. Five minutes after administration, 84.2% of radioactivity found in plasma was the unchanged compound; a decrease to 6.6% was observed 3 h after administration. Two h after treatment, 86% of the unchanged compound was detected in urine which decreased 2-24 h after dosing, indicating that the tissue metabolism of cefluprenam was not extensive; lower percentages (0.05-0.2%) of radioactivity were detected in feces and bile 2 -24 h after treatment (7).

A pharmacokinetic study using monkeys injected with cefluprenam (5, 20 or 80 mg/kg i.v.) has shown that at all doses, the drug had a half-life of 0.10-0.29 and 1.02-1.23 h for α and β phases, respectively. No sex differences were observed in half-lives, mean clearance values (174.69-206.88 ml/kg/h for all doses) and mean AUC values (29.97 and 26.28 μg/h/ml for 5 mg/kg; 101.47 and 111.20 μg/h/ml for 20 mg/kg; and 414.03 and 440.76 μg/h/ml for 80 mg/kg). The results obtained were dose-dependent and were in agreement with results from another 13-week toxicity study in monkeys and a study in humans (8).

A pharmacokinetic study in dogs has shown that after cefluprenam administration (5, 20, 80 or 320 mg/kg i.v.), respective mean plasma concentrations were 23.27 ± 0.59, 80.50 ± 4.30, 313.19 ± 29.68 and 1223.43 ± 4.11 μg/ml. The half-life of cefluprenam at all doses was 0.10-0.18 and 0.86- 1.00 h for α and β phases, respectively. In contrast to results obtained in another study using monkeys, mean clearance values for all doses were almost constant and mean AUC values were almost linear. Species-specific differences in the pharmacokinetic properties of the drug may be due to intrinsic differences in kidney clearance between monkeys and dogs (9).

The safety and efficacy of cefluprenam treatment (20-103 mg/kg i.v.) was demonstrated in a clinical study in 289 adult patients with various infections. A 73.6% rate of excellent responses to treatment was observed; efficacy rates for meningitis, sepsis and severe pneumonia were 100%, 60% and 100%, respectively, and bacteriological responses were also high with few adverse effects (10).

Administration of cefluprenam in 44 orthopedic patients with infections resulted in 66.7% and 73.3% efficacy rates for osteomyelitis and purulent arthritis, respectively. A high antibacteriological rate was also observed (88.9%). Side effects included skin rash in 2 patients and nausea and poor appetite in 2 patients (11).

A dose-finding study was carried out in 128 patients with urinary tract infections who were administered either cefluprenam (1 or 2 g/day i.v.) or ceftazidime (2 g i.v. for 5 days). Clinical efficacy rates of 84.8% , 92.1% and 85.3% were achieved in patients treated with 1 g and 2 g cefluprenam and ceftazidime, respectively; bacteriological responses and usefulness rates were also high. A 2 g dose of cefluprenam was the most effective treatment against polymicrobial infections and for eradication of Gram-positive bacteria (12).

In a clinical dose finding study, 106 patients with chronic respiratory tract infections received cefluprenam (2 g or 4 g q.i.d. i.v.) or ceftazidime (2 g q.i.d. i.v.) for 14 days. Clinical efficacy rates were higher for the group receiving 2 g cefluprenam as compared to those receiving 4 g cefluprenam or ceftazidime (90.9% *vs.* 82.4% and 87.5%, respectively); bacteriological responses were also higher for this group (95.5% *vs.* 71.4% and 82.4%, respectively). A low incidence of minor side effects was observed for all treatments and usefulness rates were 81.8%, 77.1%, and 84.4% for 2 g and 4 g cefluprenam and ceftazidime, respectively (13).

In a clinical study, 272 patients with bacterial pneumonia were administered 1 g b.i.d. (i.v.) cefluprenam or ceftazidime for 14 days. Similar clinical efficacy, usefulness and bacteriological rates were observed for both treatments. Cefluprenam was superior to ceftazidime against *Streptococcus pneumoniae*, *Enterobacter* and *Citrobacter*. More adverse reactions were observed in cefluprenam-treated patients (14).

A follow-up study evaluated the safety of 7-day cefluprenam therapy in 800 patients who received β-lactam or non-β-lactam antibiotics following cefluprenam treatment. No adverse drug interactions or allergic reac-

tions were detected in patients and treatment was considered highly safe in patients receiving subsequent antibiotic therapy (15).

The pharmacokinetics and clinical efficacy of cefluprenam have been assessed in patients with surgical infections. Good penetration into the gallbladder tissue and bile, abdominal skin, subcutaneous fat, parietal peritoneum, omentum, liver and stomach was observed at a dose of 1 g by i.v. drip infusion. Twenty patients, 8 with biliary tract infection, 6 with peritonitis and 6 with other infections, were administered doses of 0.5-1 g b.i.d. for 4-10 days and a clinical efficacy rate of 94.7% was obtained (16).

1. Izumi, K., Kawazoe, K., Mikamo, H., Sato, Y., Kai, J., Hachiya, S., Satoh, M., Munakata, K., Tamaya, T. *In vitro bactericidal activities and morphologic changes by cefluprenam (CFLP, E1077).* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-184.

2. Mikamo, H., Kawazoe, K., Izumi, K., Hachiya, S., Satoh, M., Munakata, K., Tamaya, T. *Therapeutic effects of cefluprenam (CFLP, E1077) against infections in the newly designed uterine endometrial cancer model.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst F-185.

3. Moriyama, M., Kimura, J., Watanabe, N., Toyosawa, T., Yamanishi, Y. *In vitro antibacterial activity of cefluprenam, a new cephem antibiotic.* Jpn Pharmacol Ther 1997, 25(Suppl. 6): 31.

4. Watanabe, N., Ohba, F., Moriyama, M., Kimura, J., Toyosawa, T., Sugihara, Y., Kai, J., Suzuki, T., Yamanishi, Y. *Antibacterial action of cefluprenam, a new cephem antibiotic.* Jpn Pharmacol Ther 1997, 25(Suppl. 6): 71.

5. Mikamo, H., Kawazoe, K., Izumi, K., Hachiya, S., Satoh, M., Munakata, K., Tamaya, T. *Therapeutic effects of cefluprenam (CFLP) on polymicrobial infections associated with Enterococcus faecalis in rat pyometra model.* Int J Antimicrob Agents 1997, 8(1): 7.

6. Toyosawa, T., Moriyama, M., Kimura, J., Watanabe, N., Ohba, F., Suzuki, T., Yamanishi, Y. *In vivo antibacterial activity of cefluprenam, a new cephem antibiotic.* Jpn Pharmacol Ther 1997, 25(Suppl. 6): 57.

7. Chiku, S., Mishima, M., Tadano, K. et al. *Pharmacokinetics of cefluprenam (3) - Blood concentration, distribution, metabolism and excretion following single intravenous administration of ^{14}C-cefluprenam in rats.* Jpn Pharmacol Ther 1997, 25(11): 233.

8. Chiku, S., Ishikawa, T., Nose, K., Kusano, K., Mishima, M., Tadano, K., Ida, S. *Pharmacokinetics of cefluprenam (1) - Plasma concentration of cefluprenam following single intravenous administration in monkeys.* Jpn Pharmacol Ther 1997, 25(11): 219.

9. Chiku, S., Mishima, M., Moriyama, M., Tadano, K., Nakata, H. *Pharmacokinetics of cefluprenam (2) - Plasma concentration of cefluprenam following single intravenous administration in dogs.* Jpn Pharmacol Ther 1997, 25(11): 227.

10. Fujii, R., Abe, T., Tajima, T. et al. *Pharmacokinetic and clinical studies with cefluprenam in the pediatric field.* Jpn J Antibiot 1997, 50(7): 19.

11. Hayashi, K., Sakurai, M., Shimazu, A. *Usefulness of cefluprenam for orthopedic infection.* Jpn Pharmacol Ther 1997, 25(Suppl. 6): 233.

12. Kamidono, S., Arakawa, S., Ban, Y., Kumon, H., Matsumoto, T., Ogawa, N., Ueno, K. *A dose finding study with cefluprenam in complicated urinary tract infections.* Jpn Pharmacol Ther 1997, 25(Suppl. 6): 243.

13. Shiba, K., Shimada, K., Kobayashi, H., Matsushima, T., Kohno, S., Saitoh, A., Ogawa, N., Yamaguchi, K. *A dose finding study with cefluprenam in chronic respiratory tract infections.* Jpn Pharmacol Ther 1997, 25(Suppl. 6): 263.

14. Shiba, K., Shimada, K., Kobayashi, H., Sekine, O., Matsushima, T., Kohno, S., Saito, A., Ogawa, N., Yamaguchi, K. *A comparative study of cefluprenam and ceftazidime in bacterial pneumonia.* Jpn Pharmacol Ther 1997, 25(Suppl. 6): 331.

15. Shimada, K. *The results of the follow-up search with safety after finishing the administration of cefluprenam, a newer injectable cephalosporin.* Jpn Pharmacol Ther 1997, 25(Suppl. 6): 353.

16. Uchiyama, K., Tanimura, H., Ishimoto, K., Ochiai, M. *Pharmacokinetics and clinical effects of cefluprenam on surgical infections.* 20th Int Cong Chemother (June 29-July 3, Sydney) 1997, Abst 4257.

Original monograph – Drugs Fut 1992, 17: 543.

Additional References

Takuma, K. et al. *Development of catheter related sepsis (CRS) and the preventive effects of cefluprenam (CFLP) in burned rats.* 20th Int Cong Chemother (June 29-July 3, Sydney) 1997, Abst 4272.

Tamaya, T. et al. *Effects of combination therapy with cefluprenam and clindamycin for polymicrobial infections caused by aerobes and anaerobes.* 20th Int Cong Chemother (June 29-July 3, Sydney) 1997, Abst 4276.

Shimada, K. *Overview of cefluprenam.* Jpn Pharmacol Ther 1997, 25(Suppl. 6): 5.

Okano, K. et al. *An assay method for determining cefluprenam concentrations in biological fluids.* Jpn Pharmacol Ther 1997, 25(Suppl. 6): 17.

Katsutani, N. et al. *Acute toxicity study of cefluprenam following intravenous administration in rats and beagle dogs.* Jpn Pharmacol Ther 1997, 25(Suppl. 6): 97.

Katoh, S. et al. *A 4-week repeated intravenous dose toxicity study with cefluprenam in rats.* Jpn Pharmacol Ther 1997, 25(Suppl. 6): 103.

Okasaki, K. et al. *A 4-week repeated intravenous dose toxicity study of cefluprenam followed by a 4-week recovery period in cynomolgus monkeys.* Jpn Pharmacol Ther 1997, 25(Suppl. 6): 121.

Chimoto, T. et al. *A 13-week repeated intravenous dose toxicity study with cefluprenam in rats.* Jpn Pharmacol Ther 1997, 25(Suppl. 6): 147.

Okasaki, K. et al. *A 13-week repeated intravenous dose toxicity study with cefluprenam followed by a 5-week recovery period in cynomolgus monkeys.* Jpn Pharmacol Ther 1997, 25(Suppl. 6): 171.

Matsubara, T. et al. *Teratology study of cefluprenam following intravenous injection in rats.* Jpn Pharmacol Ther 1997, 25(Suppl. 6): 197.

Chimoto, T. et al. *Nephrotoxicity study of cefluprenam by a single intravenous injection in rats.* Jpn Pharmacol Ther 1997, 25(Suppl. 6): 211.

Shimada, H., Aoki, N. *Efficacy of 7-day treatment with cefluprenam (E1077) on respiratory infections.* Jpn J Chemother 1997, 45(Suppl. A): Abst 100.

Sato, M. et al. *Eradication of E. coli and B. fragilis by cephem antibacterial agents (cefluprenam, ceftazidime, and cefotaxime).* Jpn J Chemother 1997, 45(5): Abst 139.

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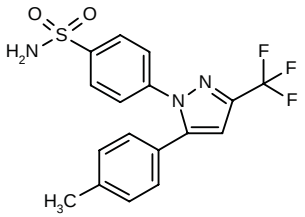
Cyclooxygenase-2 Inhibitor

EN: 228583



$C_{17}H_{14}F_3N_3O_2S$ **Searle; Yamanouchi; Pfizer**

In a mouse model of established hyperalgesia, SC-58635 administered orally reduced inflammatory hyperalgesia as efficiently as the nonselective COX inhibitor ketorolac (1).

Dietary administration of celecoxib (1500 ppm) in rats reduced the incidence and multiplicity of azoxymethane-induced colon tumors by 93% and 97%, respectively, while overall colon tumor burden was reduced by more than 87% as compared to saline-treated subjects (2).

Administration of celecoxib (3 mg/kg i.p.) completely abolished COX-2 activity in rats with endotoxemia, but had no effect on the degree of renal dysfunction or liver injury induced by E. coli lipopolysaccharide (3).

The gastrointestinal safety of celecoxib when given orally at supertherapeutic doses for 13 weeks has been compared to that of meloxicam and nabumetone at near-therapeutic doses for 2 weeks in dogs. Therapeutic plasma levels of nabumetone and plasma levels of meloxicam about 3-fold those considered therapeutic were associated with evidence of gastrointestinal and renal injury, whereas no GI injury was observed with celecoxib at plasma levels 16-fold greater than therapeutic levels. These results indicate that a high degree of COX-2 selectivity, such as with celecoxib, may be required for improved GI tolerance in man (4).

The COX-2 inhibitory effects of celecoxib were evaluated in 35 healthy volunteers receiving single doses of 100, 400 or 800 mg. The drug did not significantly inhibit arachidonic acid-induced TxA_2-dependent platelet aggregation, and no reductions in serum TxB_2 levels or urinary secretion of 11-dehydroTxB_2, the major thromboxane metabolite, were observed. However, the 800-mg dose suppressed COX-2 activity index, indicating selective inhibition of COX-2 isoform (5).

In a study in 200 molar extraction patients, SC-58635 (100 and 400 mg) was superior to placebo in pain relief, pain intensity difference and the two variables combined. Onset of pain relief was observed 0.75 h following administration of both doses of SC-58635 and was maintained for more than 4 h. At 1 h after administration, mean plasma concentrations of unmetabolized SC-58635 were 381 ± 319 ng/ml and 153 ± 115 ng/ml after the 400-mg and 100-mg doses, respectively (6).

A placebo-controlled pilot study has evaluated the efficacy and safety of celecoxib at doses of 40, 200 and 400 mg b.i.d. for 4 weeks in 330 patients with flaring rheumatoid arthritis. Of 37 patients withdrawing due to lack of efficacy, 15 received placebo, 14 celecoxib 40 mg, 3 celecoxib 200 mg and 5 celecoxib 400 mg, the difference between placebo and the two highest doses of celecoxib being statistically significant. A significant reduction in symptoms and the number of tender/painful joints was also observed on celecoxib 200 and 400 mg b.i.d. compared to placebo. Excellent tolerance was reported. The doses of 200 and 400 mg showed comparable efficacy and may represent the maximally effective doses (7).

The effects of celecoxib (40, 100 and 200 mg b.i.d. for 2 weeks) on health-related quality of life in patients with osteoarthritis have been assessed in a multicenter, double-blind, placebo-controlled trial enrolling 293 patients. The results indicated a significant benefit in regard to inflammation, pain and quality of life with the 200-mg dose (8).

A pilot endoscopic study compared the effects of celecoxib, naproxen and placebo on the gastroduodenal mucosa in 128 healthy subjects. Whereas patients receiving celecoxib (100 or 200 mg b.i.d. for 7 days) or placebo had no ulcers, 9 gastric ulcers developed in 6 of 32 patients administered naproxen (500 mg b.i.d. for 7 days) (9).

Healthy subjects were administered a single supratherapeutic dose of celecoxib (600 mg), naproxen (500 mg) or placebo, followed 48 h later by this dose given b.i.d. for 7 days and a morning dose on day 10. No significant differences were observed between placebo and celecoxib as regards effects on platelet aggregation, bleeding time or TxB_2 levels. In contrast, naproxen significantly reduced collagen- and arachidonate-induced platelet aggregation and TxB_2 levels, and significantly increased bleeding time. Thus, unlike naproxen, celecoxib appears to be devoid of inhibitory activity against platelet COX-1 activity (10).

Searle (Monsanto) and Pfizer have announced the expansion of their previous agreement to codevelop and copromote Searle's celecoxib (Celebra™). The agreement, which initially covered the U.S. only, has been extended to include all markets worldwide except Japan, where Searle already has an agreement in place with Yamanouchi (11).

1. Zhang, Y., Shaffer, A., Portanova, J., Seibert, K., Isakson, P.C. *Inhibition of cyclooxygenase-2 rapidly reverses inflammatory hyperalgesia and prostaglandin E_2 production.* J Pharmacol Exp Ther 1997, 283(3): 1069.

2. Kawamori, T., Rao, C.V., Seibert, K., Reddy, B.S. *Chemopreventive activity of celecoxib, a specific cyclooxygenase-2 inhibitor, against colon carcinogenesis.* Cancer Res 1998, 58(3): 409.

3. Leach, M., Wray, G., Thiemermann, C. *Effects of SC-58635, a selective inhibitor of cyclooxygenase 2 on haemodynamics and organ function of rats with endotoxaemia.* Brit J Pharmacol 1998, 123(Suppl.): Abst 311P.

4. Maziasz, T., Seibert, K., Khan, N., Paulson, S., Isakson, P. *Preclinical pharmacology of celecoxib and demonstration of superior GI safety compared with NSAIDs in dogs*. Arthritis Rheum 1997, 40(9, Suppl.): Abst 983.

5. McAdam, B.F., Kapoor, S., Catella-Lawson, F., FitzGerald, G.A. *Selective inhibition of monocyte COX-2 vs platelet COX-1 in humans.* Circulation 1997, 96(8, Suppl.): Abst 3117.

6. Mehlisch, D.R., Hubbard, R.C., Isakson, P., Karim, A., Weaver, M., Mills, S. *Analgesic efficacy and plasma levels of a highly selective inhibitor of COX-2 (SC-58635, SC) in patients with post-surgical dental pain.* J Clin Pharmacol 1997, 37(9): Abst 24.

7. Hubbard, R.C., Koepp, R., Yu, S.S., Talwalker, S., Geis,G.S. *Pilot efficacy of SC-58635, a COX-2-selective inhibitor, in rheumatoid arthritis.* Arthritis Rheum 1997, 40(9, Suppl.): Abst 125.

8. Zhao, S.Z., Hatoum, H.T., Hubbard, R.C., Koepp, R.J., Dedhiya, S.D., Geis, S.G., Bocanegra, T., Ware, J.E. Jr., Keller, S.D. *Effects of celecoxib, a novel COX-2 inhibitor, on health-related quality of life of patients with osteoarthritis of the knee.* Arthritis Rheum 1997, 40(9, Suppl.): Abst 348.

9. Lanza, F.L., Callison, D.A., Hubbard, R.C., Yu, S.S., Talwalker, S., Geis, G.S. *A pilot endoscopic study of the gastroduodenal effects of SC-58635, a COX-2-selective inhibitor.* Arthritis Rheum 1997, 40(9, Suppl.): Abst 373.

10. Mengle-Gaw, L., Hubbard, R.C., Karim, A., Yu, S.S., Talwalker, S., Isakson, P.C., Geis, G.S., Schwartz, B.D. *A study of the platelet effects of SC-58635, a novel COX-2-selective inhibitor.* Arthritis Rheum 1997, 40(9, Suppl.): Abst 374.

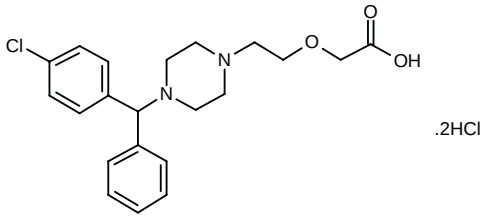
11. *Celecoxib copromotion agreement expanded.* Prous Science Daily Essentials March 26, 1998.

Original monograph – Drugs Fut 1997, 22: 711.

Cetirizine Hydrochloride *Antihistaminic*

Reactine®
Virlix®
Zyrtec®
Alerlisin®

EN: 136227



$C_{21}H_{25}ClN_2O_3.2HCl$ **UCB; Pfizer; Synthélabo; Sumitomo; Daiichi Pharm.; Menarini; Lacer**

The FDA has approved Pfizer's cetirizine hydrochloride (Zyrtec®) for the treatment of seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria in children as young as 2 years of age. Zyrtec® is the first and only once-daily prescription antihistamine indicated for use in pediatric patients under the age of 6 years. The product is available in an alcohol-free and dye-free fruity banana-grape flavor syrup (1 mg/ml), as well as 5-mg and 10-mg tablets (1).

1. *Zyrtec approved for use in children as young as two years.* Prous Science Daily Essentials June 5, 1998.

Original monograph – Drugs Fut 1987, 12: 624.

Additional References

Sannita, W.G. et al. *Histamine (H_1-selective) antagonist cetirizine and dose-related EEG concomitants of sedation in man.* Biol Psychiatry 1997, 42(1, Suppl.): Abst 65-9.

Didier, A., Melac, M. *Comparison of efficacy and safety of cetirizine and ebastine in patients with perennial allergic rhinitis.* J Allergy Clin Immunol 1997, 99(1, Part 2): Abst 1805.

Sedgwick, J.B., Busse, W.W. *Inhibitory effect of cetirizine on cytokine-enhanced in vitro eosinophil survival*. Ann Allergy Asthma Immunol 1997, 78(6): 581.

Ciprandi, G. et al. *Cetirizine treatment of allergic cough in children with pollen allergy.* Allergy 1997, 52(7): 752.

Day, J.H. et al. *Cetirizine, loratadine, or placebo in subjects with seasonal allergic rhinitis (SAR): Effects upon controlled ragweed pollen challenge in an environmental exposure unit (EEU).* Ann Allergy Asthma Immunol 1997, 78(1): Abst P93.

Horak, F. et al. *The comparison of cetirizine-pseudoephedrine (CTZ/PSE) and xylometazoline (XMZ) on nasal obstruction as objectivated by digital nasal airway imaging and patient symptom scores.* Ann Allergy Asthma Immunol 1997, 78(1): Abst P94.

Horak, F. et al. *The placebo (PLC) controlled effect of cetirizine 10 mg (CTZ) on rhinoconjunctivitis as objectivated by conjuncti-*

val digital imaging (CDI) and patient symptom scores. Ann Allergy Asthma Immunol 1997,78(1): Abst P95.

De Benedictis, F.M. et al. *Efficacy and safety of cetirizine and oxatomide in young children with perennial allergic rhinitis: A 10-day, multicenter, double-blinded, randomized, parallel-group study.* Pediat Asthma Allergy Immunol 1997, 11(2): 119.

Ciprandi, G. et al. *Cetirizine treatment of rhinitis in children with pollen allergy: Evidence of its antiallergic activity.* Clin Exp Allergy 1997, 27(10): 1160.

New insights in allergy mechanisms, and the antiinflammatory effects of cetirizine - Proceedings of a roundtable meeting, Vienna 1996. Clin Exp Allergy 1997, 27(Suppl. 2): whole issue.

Ciprandi, G. et al. *Continuous versus on demand treatment with cetirizine for allergic rhinitis.* Ann Allergy Asthma Immunol 1997, 79(6): 507.

Patel, P. et al. *A double-blind study of loratadine and cetirizine in atopic dermatitis.* J Dermatol Treat 1997, 8(4): 249.

Frossard, N. et al. *Comparative efficacy of cetirizine in the skin and nose in patients with allergic rhinitis.* J Allergy Clin Immunol 1998, 101(1, Part 2): Abst 1018.

Tosca, M. et al. *Cetirizine reduces conjunctival nonspecific hyperreactivity in children with mite allergy*. Invest Allergol Clin Immunol 1998, 8(1): 23.

Grob, J.J. et al. *Antiinflammatory properties of cetirizine in a human contact dermatitis model - Clinical evaluation of patch tests is not hampered by antihistamines.* Acta Dermato-Venereol 1998, 78(3): 194.

Daptomycin
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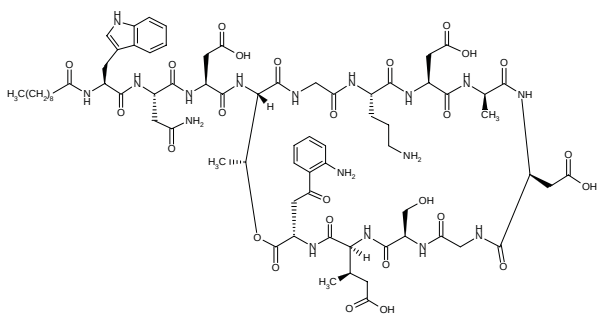


$C_{72}H_{101}N_{17}O_{26}$ **Lilly; Cubist**

Cubist Pharmaceuticals has acquired exclusive worldwide rights from Lilly to develop, manufacture and market daptomycin for the treatment of infectious diseases caused by *Staphylococcus aureus* and enterococci (1).

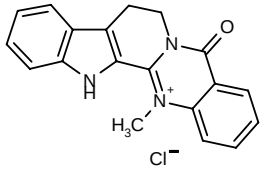
1. *Cubist acquires rights to daptomycin.* Prous Science Daily Essentials November 13, 1997.

Original monograph – Drugs Fut 1991, 16: 608.

Dehydroevodiamine Chloride

Antihypertensive

EN: 090958



$C_{19}H_{16}ClN_3O$ **Chinese Univ. Hong Kong**

The antiamnesic and antiischemic activities of dehydroevodiamine chloride (DHED have been described by investigators from Seoul National University. The compound was shown to inhibit acetylcholinesterase in a concentration-dependent, noncompetitive fashion. Administration of single doses of DHED to rats with memory impairments induced by scopolamine or mechanical lesioning effectively reversed amnesia in the passive avoidance task, and was in fact more potent than tacrine. Furthermore, pretreatment with DHED of rats subjected to occlusion of the middle cerebral artery resulted in a significant decrease in the infarcted area, which was attributed to cerebral vasorelaxation (1).

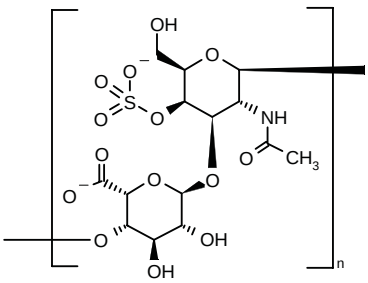
1. Park, C.H., Kim, S.H., Choi, W., Lee, Y.J., Lee, S.H., Kim, J.S., Kang, S.S., Suh, Y.H. *Novel anticholinesterase, antiamnesic and anti-ischemic activities of dehydroevodiamine, a constituent of Evodia rutaecarpa Bentham.* Soc Neurosci Abst 1997, 23(Part 2): Abst 536.5.

Original monograph – Drugs Fut 1985, 10: 556.

Desmin-370
D-370

Antithrombotic

EN: 210239



Alfa Wassermann; Opocrin

In a rat model of pulmonary embolism, desmin 370 (50 mg/kg i.v.) caused a significant increase in the rate of lysis at 30 min which persisted for 2 h. Furthermore, blood fibrinolytic activity was not enhanced and plasma levels and inhibitory activities of plasminogen activator were not changed by treatment (1).

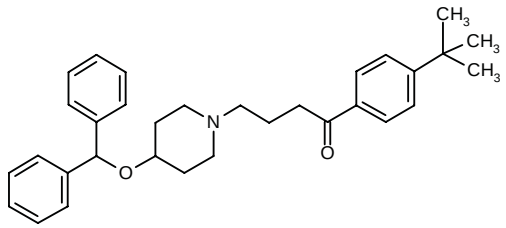
1. Colucci, M., Sardella, L., Barbanti, M., Calanni, F., Semeraro, N. *Thrombolysis enhancing activity of a low molecular weight dermatan sulfate (Desmin 370) in experimental pulmonary embolism in rats.* Thromb Res 1997, 87(5): 441.

Original monograph – Drugs Fut 1994, 19: 638

Ebastine *Antihistaminic*

Bastel®
Ebastel®
Kestine®
No-Sedat®
Evastel®

EN: 135187



$C_{32}H_{39}NO_2$ **Almirall Prodesfarma; Dainippon; Meiji Seika; Rhône-Poulenc Rorer; Merck KGaA; Boryung**

Rhône-Poulenc Rorer recently filed an NDA with the FDA for approval of ebastine tablets, a once-daily nonsedating antihistamine for the treatment of symptoms associated with seasonal and perennial allergic rhinitis. Ebastine is licensed for development and marketing to Rhône-Poulenc Rorer by Almirall Prodesfarma, who discovered, developed and launched ebastine in Spain under the name Ebastel™ (1).

1. *Rhône-Poulenc Rorer submits NDA for ebastine in U.S.* Prous Science Daily Essentials May 18, 1998.

Original monograph – Drugs Fut 1990, 15: 674.

Additional References

Didier, A., Melac, M. *Comparison of efficacy and safety of cetirizine and ebastine in patients with perennial allergic rhinitis.* J Allergy Clin Immunol 1997, 99(1, Part 2): Abst 1805.

Fujii, T. et al. *Studies on the first-pass metabolism of ebastine in rats.* Arzneim-Forsch-Drug Res 1997, 47(8): 949.

Comparison of ebastine with cetirizine. Ann Allergy Asthma Immunol 1997, 79(5): 465 (Letters to the Editor).

Gispert, J. et al. *Pharmacodynamic assessment of the efficacy of single and multiple doses of ebastine, cetirizine and loratadine against histamine-induced cutaneous challenge in healthy volunteers.* J Allergy Clin Immunol 1998, 101(1, Part 2): Abst 920.

Gras, J. et al. *Ebastine, in contrast to terbinafine, does not increase the QTc interval in guinea pigs pre-treated with ketoconazole.* J Allergy Clin Immunol 1998, 101(1, Part 2): Abst 1054.

Nakamura, R. et al. *Effects of ebastine, an antihistamine agent, on ventricular activation, effective refractory periods, programmed stimulation-induced ventricular arrhythmias and RT intervals in a canine myocardial infarction model.* Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-605.

Frossard, N. et al. *Consistency of the efficacy of cetirizine and ebastine on skin reactivity*. Ann Allergy Asthma Immunol 1998, 80(1): 61.

Roberts, D.J. III. *Histamine metabolism, receptors and anti-histamines. Towards the optimal antihistamine: Studies with ebastine.* Inflamm Res 1998, 47(Suppl. 1): S36.

Ecabapide *Antiulcerative*

Muralis® *Anti-Helicobacter pylori*

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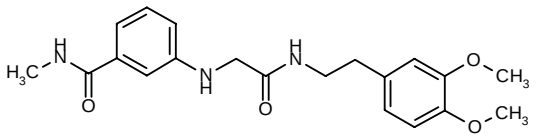

$C_{20}H_{25}N_3O_4$ **Daiichi Pharm.**

DQ-2511 has been evaluated for prokinetic effects in isolated guinea pig stomach smooth muscle. The results suggest that its prokinetic actions involve direct excitation of smooth muscle and indirect excitation of cholinergic transmission (1).

Results of studies in anesthetized rats indicate that ecabapide suppresses the activation of gastric vagal afferents via the nitric oxide-cGMP cascade (2).

1. Imaeda, K., Hashitani, H., Xue, L., Yamamoto, Y., Itoh, M., Suzuki, H. *Effects of DQ-2511, a novel prokinetic agent, on electrical activities of smooth muscle in the guinea pig stomach.* Pharmacology 1997, 55(3): 144.

2. Hatanaka, S., Niijima, A., Furuhama, K. *Possible mechanisms underlying the suppression of gastric vagal afferents due to ecabapide (DQ-2511), a gastroprokinetic agent, in rats.* Jpn J Pharmacol 1997, 74(1): 105.

Original monograph – Drugs Fut 1989, 14: 620.

Entacapone
Comtan™
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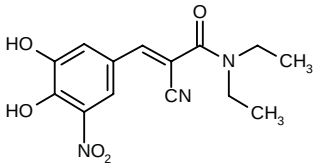
Antiparkinsonian
COMT Inhibitor

EN: 178077



$C_{14}H_{15}N_3O_5$ **Orion; Novartis**

Results from studies in cell culture, rat liver mitochondria and isolated guinea pig heart have shown that entacapone (5-40 μM) is safe for the treatment of Parkinson's disease, since it acts peripherally and does not interfere with mitochondrial energy metabolism at pharmacologically effective concentrations (1).

In a randomized, double-blind, placebo-controlled study in 21 patients with Parkinson's disease, a single dose of entacapone (200 mg) resulted in an improved clinical response to levodopa in terms of motor response and duration of dyskinesias, but had no effect on the magnitude of motor response (2).

Results from a randomized, double-blind, placebo-controlled, crossover study in 15 patients with Parkinson's disease indicated that both entacapone (200 mg/day) and selegiline (10 mg/day), administered alone or in combination, are safe adjuncts to levodopa/dopadecarboxylase inhibitor treatment. However, in some patients, dyskinesias and other levodopa-related side effects may be aggravated due to enhanced dopaminergic activity (3).

In a randomized, double-blind, crossover, comparative study in 15 Parkinson's disease patients without cardiovascular disease being treated with levodopa, the addition of entacapone (200 mg) did not affect dynamic work efficiency in patients with mild disease severity but did enhance the maximum exercise capacity in those patients who were clinically well-controlled (4).

The results of a pharmacokinetic study in 10 non-parkinsonian patients with impaired liver function due to alcoholic cirrhosis indicate that, although entacapone does not appear to affect liver function, the usual oral dose of 200 mg should be reduced by about 50% in patients with moderate liver function impairment (5).

The European Committee for Proprietary Medicinal Products has recommended approval of entacapone, developed by Orion and licensed to Novartis, as a new treatment for Parkinson's disease. The drug will be marketed as Comtan™ by Novartis and as Comtess® by Orion (6).

1. Nissinen, E., Kaheinen, P., Penttila, K.E., Kaivola, J.,Linden, I.B. *Entacapone, a novel catechol-O-methyltransferase inhibitor for Parkinson's disease, does not impair mitochondrial energy production.* Eur J Pharmacol 1997, 340(2-3): 287.

2. Ruottinen, H.M., Rinne, U.K., Kyyrä, T., Gordin, A. *Clinical response to entacapone in relation to plasma levodopa concentration and parkinsonian disability.* Mov Disord 1997, 12(Suppl. 1): Abst P462.

3. Lyytinen, J., Kaakkola, S., Teräväinen, H., Kultalahti, E.-R., Gordin, A. *Entacapone and selegiline as adjuncts to L-dopa in patients with Parkinson's disease (PD).* Mov Disord 1997, 12(Suppl. 1): Abst P383.

4. Lyytinen, J., Kaakkola, S., Sovijärvi, A., Reinikainen, K., Teräväinen, H. *Entacapone and cardiorespiratory capacity during exercise in patients with Parkinson's disease (PD).* J Neurol Sci 1997, 150(Suppl.): Abst 4-30-06.

5. Gordin, A., Parstikainen, P.P., Makimarti, M., Reinikainen, K. *Pharmacokinetics of the COMT inhibitor entacapone in liver failure and the effect of entacapone on liver function.* 50th Annu Meet Amer Assoc Neurol (April 25-May 2, Minneapolis) 1998, Abst P06.039.

6. *Entacapone receives favorable opinion from CPMP.* Prous Science Daily Essentials June 15, 1998.

Original monograph – Drugs Fut 1994, 19: 641.

Additional References

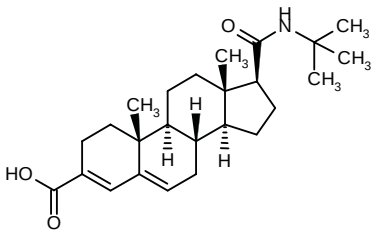
Haapalinna, A., Lindén, I.-B. *Synergism between partial peripheral inhibition of DOPA decarboxylase and COMT by low doses of carbidopa and entacapone in an animal model of Parkinson's disease.* J Neurol Sci 1997, 150(Suppl.): Abst 4-42-02.

Illi, A. et al. *COMT inhibition by entacapone: Interactions, haemodynamics and catecholamine metabolism.* J Neurol Sci 1997, 150(Suppl.): Abst 4-42-03.

Epristeride

5α-Reductase Inhibitor
Treatment of BPH

EN: 175166



$C_{25}H_{37}NO_3$ **SmithKline Beecham; Ono; Recordati**

Results of *in vitro* studies on cultured cells from benign hyperplastic adult prostates showed that epristeride (1 nM-0.3 μM) dose-dependently inhibited stromal cell proliferation in response to testosterone and down-regulated PSA secretion from epithelial cells (1).

Results of studies in rats demonstrated that ONO-9302 was approximately 80,000-fold more potent than allylestrenol in inhibiting the prostatic enzyme (IC_{50} = 11 nM). In addition, ONO-9302 significantly reduced ventral prostate growth (1-100 mg/kg/day) and ventral prostate weight (10-100 mg/kg/day) (2).

1. Robinson, E.J., Collins, A.T., Robson, C.N., Neal, D.E. *Effects of a new 5α reductase inhibitor (episteride) on human prostate cell cultures.* Prostate 1997, 32(4): 259.

2. Yasuda, N., Fujino, K., Shiraji, T., Nambu, F., Kondo, K. *Effects of steroid 5α-reductase inhibitor ONO-9302 and anti-androgen allylestrenol on the prostatic growth, and plasma and prostatic hormone levels in rats.* Jpn J Pharmacol 1997, 74(3): 243.

Original monograph – Drugs Fut 1994, 19: 646.

Fosphenytoin Sodium
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Anticonvulsant
Neuroprotectant

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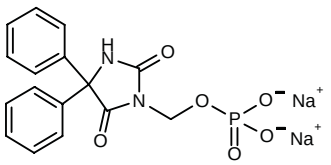


$C_{16}H_{13}N_2Na_2O_6P$ **DuPont Merck; Warner-Lambert**

Injection site tolerance and safety of intramuscular fosphenytoin (10 mg/kg) were evaluated in 60 patients receiving single or multiple site injections of 4-30 ml. Most patients experienced no irritation or discomfort after injection or at follow-up, although 67% reported transient side effects consisting of nystagmus, dizziness or ataxia. No serious adverse events were observed, indicating that intramuscular fosphenytoin is safe and well tolerated (1).

1. Ramsay, R.E., Wilder, B.J., Uthman, B.M., Garnett, W.R.,Pellock, J.M., Barkley, G.L., Leppik, I.E., Knapp, L.E. *Intramuscular fosphenytoin (Cerebyx®) in patients requiring a loading dose of phenytoin.* Epilepsy Res 1997, 28(3): 181.

Original monograph – Drugs Fut 1989, 14: 611.

Additional References

Roberge, R.J. *A new phenytoin prodrug, Cerebyx®.* Amer J Emerg Med 1997, 15(4): 444 (Letters to the Editor).

Paloucek, F.P. *Fosphenytoin safety and economics.* Amer J Health-Syst Pharm 1996, 53(22): 2702.

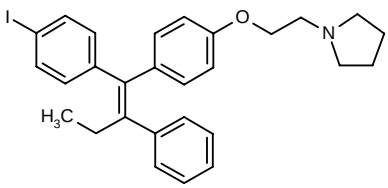
Fierro, L.S. et al. *Safety of fosphenytoin sodium.* Amer J Health-Syst Pharm 1996, 53(22): 2707.

Curry, W.J., Kulling, D.L. *Newer antiepileptic drugs: Gabapentin, lamotrigine, felbamate, topiramate and fosphenytoin.* Amer Fam Physician 1998, 57(3): 513.

Idoxifene

Antiestrogen
Antineoplastic
Treatment of Osteoporosis

EN: 143813



$C_{28}H_{30}INO$ **Natl. Res. Dev. Corp.; British Technol. Group; SmithKline Beecham; Cancer Res. Campaign Technol.**

SmithKline Beecham has initiated phase III clinical trials of idoxifene for the prevention of osteoporosis. The phase III osteoporosis prevention trials will take place at centers throughout Europe and the U.S. SmithKline Beecham is also continuing clinical studies of idoxifene in breast cancer (1).

1. *Idoxifene progresses to phase III for osteoporosis.* Prous Science Daily Essentials October 8, 1997.

Original monograph – Drugs Fut 1995, 20: 666.

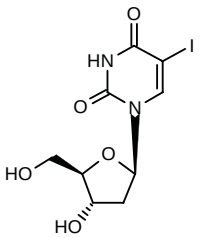
Additional Reference

Nuttall, M.E. et al. *Idoxifene, a tissue selective estrogen agonist/antagonist, has a mechanism of action in bone similar to estrogen and distinct from raloxifene.* J Bone Miner Res 1997, 12(Suppl. 1): Abst P273.

Idoxuridine

Antineoplastic

EN: 130013



$C_9H_{11}IN_2O_5$ **Natl. Cancer Inst. (US); Oncomed**

Encapsulated doxorubicin (50 μg i.v.) administered 16 h before irradiation and iododeoxyuridine (4 x 300 μg i.v. bolus) administered on alternate days for 8 days enhanced the effect of single fraction and fractionated radiotherapy in mice with head and neck squamous cell xenograft tumors (1).

In an attempt to increase the therapeutic index of iododeoxyuridine, nude mice bearing ME-180 human cervical carcinoma xenografts were pretreated with TNT-1 MAb or TNT-1/IL-2 immunoconjugate, followed by injec-

tions of iododeoxyuridine. Pretreatment with TNT-1/IL-2 produced a 3-fold increase in localization of iododeoxyuridine to tumor sites, without increasing drug uptake in normal tissues, indicating that pretreatment with vasoconjugates may improve the therapeutic index of chemotherapeutic drugs (2).

In a phase I trial, 16 patients with malignant gliomas were treated with continuous iododeoxyuridine infusion (100, 200, 300 or 400 mg/m^2 for 28 days) in combination with accelerated hyperfractionated external beam radiotherapy. The drug was well tolerated, with toxicities occurring in the 400-mg group and consisting of thrombocytopenia, elevated AST and diarrhea. Radiotherapy was also well tolerated with minimal toxicities (3).

Iododeoxyuridine (500 mg/m^2 initial dose, reduced to 250 or 125 mg/m^2) administered in combination with 5-FU (300 mg/m^2/day i.v. for 7 weeks), hydroxyurea (500 mg p.o. q12 h x 11) and radiation therapy was evaluated in 27 patients with malignant gliomas. Progression-free and cause-specific survivals during 3 years were 5.1% and 19.5%, respectively. Grade 3-4 toxicities included neutropenia (44%), thrombocytopenia (33%), stomatitis (30%) and infection (37%) (4).

1. Harrington, K.J., Rowlinson-Busza, G., Uster, P.S., Whittaker, J., Stewart, J.S.W. *Stealth® liposome encapsulated doxorubicin (SLED) and iododeoxyuridine (SLIUDR) as radiation sensitisers in head and neck squamous cell cancer xenograft tumours (HNSCCXT).* Proc Amer Soc Clin Oncol 1998, 17: Abst 881.

2. Hornick, J.L., Khawli, L.A., Sharifi, J., Epstein, A.L. *Improving the chemotherapeutic index of IUdR using a vasoactive immunoconjugate.* J Invest Med 1997, 45(1): 81A.

3. Schulz, C.A., Mehta, M.P., Robins, H.I., Badis, B., Arzoomanian, R., Simon, K., Alberti, D., Feierabend, C., Kinsella, T.J., Wilding, G. *A phase I study of iododeoxyuridine and accelerated hyperfractionated radiotherapy for malignant gliomas.* Proc Amer Soc Clin Oncol 1997, 16: Abst 882.

4. Sweeney, P.J., Mundt, A.J., Masters, G., Fasanmade, A., Dolan, M.E., Witt, M., Macdonald, R.L., Ratain, M., Vokes, E. *Phase I trial of iododeoxyuridine, 5-FU, hydroxyurea and concomitant RT for malignant gliomas: Clinical and pharmacologic analysis.* Proc Amer Soc Clin Oncol 1997, 16: Abst 1407.

Original monograph – Drugs Fut 1995, 20: 670.

Additional References

Roelcke, U. et al. *^{124}I-Iodo-deoxyuridine imaging brain tumor proliferation.* J Neuro-Oncol 1996, 30(2): Abst O-12.

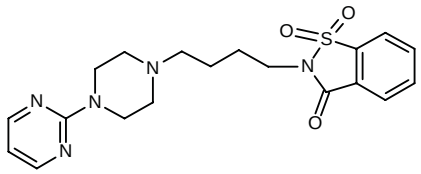
Neshastehriz, A. et al. *In vitro evaluation of radioiodinated iododeoxyuridine for glioma treatment.* J Neuro-Oncol 1996, 30(2): Abst P-38.

Galanis, E. et al. *Phase I trial of sequential administration of tomudex and 5-iodo-2'-deoxyuridine (IdUrd).* Proc Amer Assoc Cancer Res 1998, 39: Abst 2193.

Ipsapirone

Anxiolytic
Antidepressant
5-HT$_{1A}$ Agonist

EN: 127834



$C_{19}H_{23}N_5O_3S$

Troponwerke

In a double-blind, placebo-controlled study in 41 patients with moderate to severe panic disorder and 12 healthy volunteers, ipsapirone (0.3 mg/kg p.o.) as well as *m*-chlorophenylpiperazine (0.4 mg/kg p.o.), produced panic attacks in 55% of patients. Both compounds also resulted in significant increases in activation, feelings of altered-self, anxiety, depressive symptoms, dysphoria and functional deficits in the patient group, whereas control subjects did not experience significant anxiety. Divergent neuroendocrine responses to both drugs were also observed (1).

In a randomized, double-blind, placebo-controlled trial in 12 healthy men, ipsapirone (20 mg p.o) significantly increased the release of adrenocorticotrophin, cortisol, prolactin and growth hormone. Peak ipsapirone and hormone blood levels were reached 60 min after drug administration. Oxytocin release was also stimulated although with less potency and more baseline variation. A significant decrease in temperature was observed following ipsapirone administration compared to placebo (2).

The withdrawal effects of a 36-day treatment with ipsapirone (15 or 22.5 mg/day) were compared to those of lorazepam (3 mg/day) in a randomized, double-blind, placebo-controlled study in 65 healthy male volunteers experienced in the use of sedative-hypnotics and anxiolytics, and who did not meet DSM-III-R criteria for dependence or abuse. Assessment of outcome measures 3 days after discontinuation of treatment showed that ipsapirone and placebo produced fewer and less severe episodes of insomnia and fatigue than lorazepam. In addition, lorazepam-treated subjects reported longer sleep latency and poorer sleep quality than those treated with ipsapirone (3).

1. Broocks, A., George, A., Bartmann, U., Bandelow, B., Hajak, G., Rüther, E. *Increased psychological responses and divergent neuroendocrine responses to ipsapirone and m-CPP in patients with panic disorder.* Eur Neuropsychopharmacol 1998, 8(Suppl. 1): Abst B-59.

2. Cleare, A.J., Forsling, M., Bond, A.J. *Neuroendocrine and hypothermic effects of 5-HT$_{1A}$ receptor stimulation with ipsapirone in healthy men: A placebo-controlled study.* Int Clin Psychopharmacol 1998,13(1): 23.

3. Busto, U.E., Naranjo, C.A., Bremner, K.E., Peachey, J.E., Bologa, M. *Safety of ipsapirone treatment compared with lorazepam: Discontinuation effects.* J Psychiatry Neurosci 1998, 23(1): 35.

Original monograph – Drugs Fut 1986, 11: 565.

Additional References

Dong, J. et al. *Effect of repeated versus sustained administration of the 5-HT$_{1A}$ agonist ipsapirone: Electrophysiological studies in the rat hippocampus and dorsal raphe.* Soc Neurosci Abst 1996, 22(Part 2): Abst 525.4.

Dong, J. et al. *Effect of acute and repeated versus sustained administration of the 5-HT$_{1A}$ receptor agonist ipsapirone: Electrophysiological studies in the rat hippocampus and dorsal raphe.* Naunyn-Schmied Arch Pharmacol 1997, 356(3): 303.

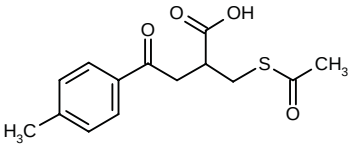
Tsutsui, M. et al. *Late phase II study of ipsapirone hydrochloride (BAY q 7821).* J New Rem Clin 1997, 46(8): 3.

Shiah, I.-S. et al. *Effects of divalproex sodium on 5-HT$_{1A}$ receptor function in healthy human males: Hypothermic, hormonal, and behavioral responses to ipsapirone.* Neuropsychopharmacology 1997, 17(6): 382.

KE-298

Antiarthritic

EN: 144187



$C_{14}H_{16}O_4S$ **Taisho**

An *in vitro* study has shown that KE-298 (10-100 μM with or without TNFα) inhibited proliferation, cytokine production and MMP-1 production through downmodulation of AP-1 transcription factor. KE-298 may therefore be a potential treatment for patients with rheumatoid arthritis (1).

KE-298 has been reported to concentration-dependently suppress the production of pro-MMP-1 and pro-MMP-3 in synovial membranes from patients with rheumatoid arthritis activated by tumor necrosis factor (2).

1. Sakane, T., Suzuki, N., Hirose, Y. et al. *Mechanisms of KE298, 2-acetylthiomethyl-3-(4-methylbenzoyl)propionic acid, to suppress abnormal synovial cell functions in patients with rheumatoid arthritis.* J Rheumatol 1997, 24(11): 2213.

2. Takahashi, S., Inoue, T., Higaki, M., Mizushima, Y. *Study on the suppressive effects of KE-298 on matrix metalloprotease and TIMP-1 production.* Ryumachi 1997, 37(2): Abst W 14-8.

Original monograph – Drugs Fut 1996, 21: 691.

Additional References

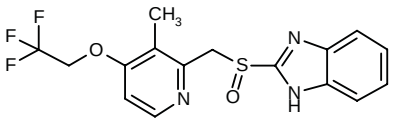
Daido, M. et al. *Pharmacokinetics of KE-298, a novel antirheumatic agent (6). Analysis of metabolites in plasma and in urine in humans.* Xenobiotic Metab Dispos 1997, 12(Suppl.): Abst 4D11-3.

Takahashi, S. et al. *Suppressive effect of a new anti-rheumatic drug KE-298 on TNF-α-induced matrix metalloproteinases production in RA synoviocytes.* Arthritis Rheum 1997, 40(9, Suppl.): Abst 299.

Lansoprazole
Prevacid®

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

EN: 123065



$C_{16}H_{14}F_3N_3O_2S$ **Takeda; TAP; Houdé; Almirall Prodesfarma; Tecnobio; Roussel-Uclaf; American Home Prod.**

TAP Holdings, a joint venture between Abbott and Takeda, has received FDA approval for Prevacid® (lansoprazole) delayed-release capsules for the short-term treatment of symptomatic gastroesophageal reflux disease (GERD) (1).

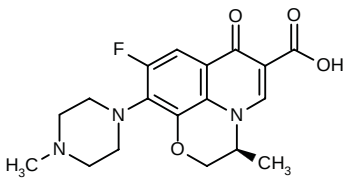
1. *FDA clears new indication for Prevacid.* Prous Science Daily Essentials April 17, 1998.

Original monograph – Drugs Fut 1989, 14: 625.

Levofloxacin
Tavanic®

Fluoroquinolone Antibacterial

EN: 134320



$C_{18}H_{20}FN_3O_4$ **Daiichi Pharm.; Johnson & Johnson; Glaxo Wellcome; Hoechst Marion Roussel**

Levofloxacin (Tavanic®) is now available from Hoechst Marion Roussel in the U.K. for the treatment of mild to moderate infections, including acute sinusitis, acute exacerbations of chronic bronchitis, community-acquired pneumonia, complicated urinary tract infections and skin and soft tissue infections. The drug is presented as tablets containing 250 and 500 mg levofloxacin, and as a solution for i.v. infusion containing 5 mg/ml (1).

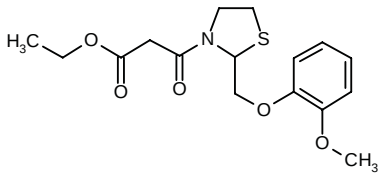
1. *Oral and parenteral formulations of levofloxacin now available in U.K.* Prous Science Daily Essentials April 30, 1998.

Original monograph – Drugs Fut 1992, 17: 559.

Moguisteine

Antitussive

EN: 147986



$C_{16}H_{21}NO_5S$ **Boehringer Mannheim**

The antitussive activity of moguisteine was assessed in guinea pig models of capsaicin-induced and allergic cough. At doses ranging from 3-30 mg/kg p.o., moguisteine suppressed capsaicin-induced cough in a dose-dependent fashion; dihydrocodeine suppressed coughing to a similar extent over the same dose range. In ovalbumin-sensitized guinea pigs, moguisteine (30 or 56 mg/kg p.o.) significantly suppressed ovalbumin aerosol-induced allergic coughing, again in a dose-dependent manner. Dihydrocodeine was effective, but not significantly so, in this model (1).

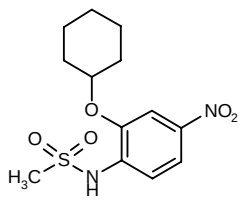
1. Kashiwazaki, T., Ohsawa, M., Morita, K., Kamei, J. *Antitussive effect of moguisteine on allergic cough in guinea pig.* Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-621.

Original monograph – Drugs Fut 1991, 16: 618.

NS-398

Antiinflammatory
Cyclooxygenase-2 Inhibitor

EN: 151658



$C_{13}H_{18}N_2O_5S$ **Taisho**

The effects of inhibitors of cyclooxygenase type 1 (COX-1) and type 2 (COX-2) on the growth of human colorectal carcinoma cells have been evaluated Neither indomethacin, a potent COX-1 inhibitor, nor L-745337 and NS-398, selective COX-2 inhibitors, had any effect on cell growth at concentrations of 30-100 μM. These results suggest that the anticarcinogenic effect of nonsteroidal antiinflammatory drugs against colorectal cancer is not mediated by inhibition of cyclooxygenase (1).

Results of studies in rats demonstrated that NS-398 (4 and 40 mg/kg) delayed the healing of hydrochloric acid-induced gastric injury via suppression of gastric epithelial replication *in vivo* (2).

NS-398 (0.04-1 mg/kg p.o.) was as effective as indomethacin (0.4-10 mg/kg p.o.) in inhibiting peptone-induced protection against mucosal damage in the rat stomach, indicating the involvement of prostaglandins generated by a COX-2 isoenzyme in gastric mucosa protection (3).

NS-398 (10 mg/kg), unlike indomethacin and aspirin, did not negatively affect the increase of acid secretion and hemorrhagic lesions caused by hypothermia stress in rat stomach. On the other hand, the drug significantly delayed the healing of gastric ulcers in mice (4).

In contrast to the results observed with indomethacin (10 mg/kg), acute mucosal ulcerogenic and functional responses mediated by prostaglandins following barrier disruption in rat stomach were not significantly affected by NS-398 (10 mg/kg), indicating that COX-1, but not COX-2, is a key enzyme in prostaglandin biosynthesis in the stomach under these conditions (5).

NS-398 (0.1-1 mg/kg) dose-dependently counteracted mild irritant-evoked gastroprotection in rats (ID_{50} 0.3 mg/kg), suggesting that prostaglandins derived from COX-2 may contribute to essential physiological functions involved in gastric homeostasis (6).

Angiogenesis in rat sponge implants was inhibited by oral administration of NS-398 (3 mg/kg q.i.d. for 14 days), suggesting the participation of COX-2 through prostaglandin synthesis in neovascularization (7).

Studies in rats have shown that indomethacin caused a significant decrease in duodenal bicarbonate secretion and dose-dependently potentiated duodenal lesion, whereas NS-398 had no effect (8).

Results of an *in vivo* study in rats with endotoxin shock demonstrated that NS-398 (0.3-100 mg/kg, p.o.) had preferential inhibitory effects on COX-2 activity (9).

1. Murphy, V.J., Yang, Z.Y., Rorison, K.A., Baldwin, G.S. *Cyclooxygenase-2-selective antagonists do not inhibit growth of colorectal carcinoma cell lines.* Cancer Lett 1998, 122(1-2): 25.

2. Tsuji, S., Sun, W.-H., Sawaoka, H., Tsujii, M., Gunawan,E.S., Murata, H., Nagano, K., Kawano, S. *A specific inhibitor for cyclooxygenase-2 delays gastric ulcer healing.* Dig Dis Week (May 10-16, Washington DC) 1997, Abst 389.

3. Ehrlich, K., Gretzer, B., Respondek, M., Peskar, B.M. *Selective inhibition of cyclooxygenase 2 counteracts the protective effect of peptone in the rat stomach.* Dig Dis Week (May 10-16, Washington DC) 1997, Abst 391.

4. Ukawa, H., Hirata, T., Kobayashi, H., Yamakuni, H., Takeuchi, K. *Effects of COX2-selective and no-releasing NSAIDs on mucosal ulcerogenic and healing responses in rat stomachs.* Dig Dis Week (May 10-16, Washington DC) 1997, Abst 397.

5. Hirata, T., Ukawa, H., Yamakuni, H., Kato, S., Takeuchi,K. *Cyclooxygenase isozymes (COX1 and COX2) in acute mucosal ulcerogenic and functional responses following barrier disruption in rat stomachs.* Dig Dis Week (May 10-16, Washington DC) 1997, Abst 398.

6. Gretzer, B., Lambrecht, N., Ehrlich, K., Chantrain, M., Peskar, B.M. *Prostaglandins involved in mild irritant-evoked gastropro-*

tection are derived via the cyclooxygenase 2 pathway. Dig Dis Week (May 10-16, Washington DC) 1997, Abst 4502.

7. Majima, M., Isono, M., Ikeda, Y., Hayashi, I., Hatanaka,K., Harada, Y., Katsumata, O., Yamashina, S., Katori, M., Yamamoto, S. *Significant roles of inducible cyclooxygenase (COX)-2 in angiogenesis in rat sponge implants.* Jpn J Pharmacol 1997, 75(2): 105.

8. Iwata, K., Murakami, N., Takase, H., Saito, T., Naruse, T. *Comparative study of the effects of indomethacin and NS-398, a selective cyclooxygenase 2 inhibitor, on duodenal bicarbonate secretion induced by luminal acidification in rats.* Jpn J Pharmacol 1997, 75(2): 191.

9. Futaki, N., Takahashi, S., Kitagawa, T., Yamakawa, Y., Tanaka, M., Higuchi, S. *Selective inhibition of cyclooxygenase-2 by NS-398 in endotoxin shock rats in vivo.* Inflamm Res 1997, 46(12): 496.

Original monograph – Drugs Fut 1993, 18: 603.

Additional References

Hara, A. et al. *Apoptosis induced by NS-398, a selective cyclooxygenase-2 inhibitor, in human colorectal cancer cell lines.* Jpn J Cancer Res 1997, 88(6): 600.

Hara, A. et al. *Apoptosis induced by NS-398, a selective cyclooxygenase-2 inhibitor, in human colorectal cancer cell lines.* 56th Annu Meet Jpn Soc Cancer Res (Sept 25-27, Kyoto) 1997, Abst VBP-060.

Gretzer, B. et al. *Selective cyclo-oxygenase-2 inhibitors and their influence on the protective effect of a mild irritant in the rat stomach.* Brit J Pharmacol 1998, 123(5): 927.

Ukawa, H. et al. *Effects of cyclooxygenase-2 (COX-2) selective and nitric oxide (NO)-releasing NSAIDs on mucosal ulcerogenic and healing responses of the stomach.* Jpn J Pharmacol 1998, 76(Suppl. 1): Abst O-313.

Shigeta, J. et al. *Role of cyclooxygenase (COX)-2 in healing of gastric ulcers in rats.* Jpn J Pharmacol 1998, 76(Suppl. 1): Abst O-315.

Niwa, M. et al. *Apoptosis induced by COX-2 inhibitor in human colorectal cancer cell lines.* Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-108.

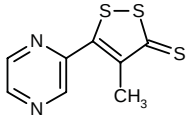
Patrignani, P. et al. *Differential inhibition of human prostaglandin endoperoxide synthase-1 and -2 by nonsteroidal anti-inflammatory drugs.* J Physiol Pharmacol 1997, 48(4): 623.

Perkins, D.J., Kniss, D.A. *Tumor necrosis factor-α promotes sustained cyclooxygenase-2 expression - Attenuation by dexamethasone and NSAIDs.* Prostaglandins 1997, 54(4): 727.

Oltipraz

Chemopreventive

EN: 090895



$C_8H_6N_2S_3$

Rhône-Poulenc Rorer

In a study in rat hepatocytes in primary culture, oltipraz produced a 2- to 3-fold increase in manganese superoxide dismutase gene expression which was associated with a 2- to 3-fold increase in free malondialdehyde and conjugated dienes, indicating oxidative stress. Copper/zinc superoxide dismutase and glutathione peroxidase genes were not affected (1).

Oltipraz (0.2 mmol/kg) administered on days 6, 4 and 2 prior to administration of aflatoxin B_1 in rats reduced DNA adduct levels by 74% and hepatic burden of foci by 92.8%, indicating that the drug has cancer chemopreventive properties (2).

In studies on DBP-induced DNA adducts in rats, oltipraz (500 mg/kg diet) inhibited adduct formation by 35-48% in mammary gland, lung and liver tissues, indicating that the drug may exert its anticarcinogenic properties during the preinitiation stages of carcinogenesis (3).

A review of oltipraz has shown that the compound inhibits chemically induced carcinogenesis in various animal models and has protective effects against carcinogens for several human target organs. Results from molecular and biochemical studies indicate that the protective effects of oltipraz are due to induction of phase II detoxification enzymes (4).

The biological effects and tolerability of oltipraz (200 mg twice weekly) were evaluated in a clinical trial involving 94 subjects at risk for lung cancer. Preliminary results demonstrated that 5/9 subjects (56%) evaluated after 6 months and 3/5 subjects (60%) evaluated after 12 months had no evidence of dysplasia or had a metaplasia index of less than 15%. Therapy-related symptoms were mainly gastrointestinal (5).

1. Antras Ferry, J., Maheo, K., Chevanne, M., Dubos, M.P., Morel, F., Guillouzo, A., Cillard, P., Cillard, J. *Oltipraz stimulates the transcription of the manganese superoxide dismutase gene in rat hepatocytes.* Carcinogenesis 1997, 18(11): 2113.

2. Roebuck, B.D., Maxuitenko, Y.Y., MacMillan, D.L., EGner,P.A., Baumgartner, K.J., Curphey, T.J., Kensler, T.W. *Inhibition of hepatic tumorigenesis in the rat by a natural analog of oltipraz.* Proc Amer Assoc Cancer Res 1998, 39: Abst 1820.

3. Smith, W.A., Arif, J.M., Gupta, R.C. *The effect of dietary oltipraz and genistein on DNA adducts induced by the potent mammary carcinogen dibenzo[a,l]pyrene in female Sprague-Dawley rats.* Proc Amer Assoc Cancer Res 1998, 39: Abst 2644.

4. Clapper, M.L. *Chemopreventive activity of oltipraz.* Pharmacol Ther 1998, 78(1): 17.

5. Szarka, C.E., Raskay, B.J., Garay, C.A. et al. *A phase II evaluation of oltipraz as a chemopreventive agent for lung cancer.* Proc Amer Soc Clin Oncol 1998, 17: Abst 1818.

Original monograph – Drugs Fut 1980, 5: 359.

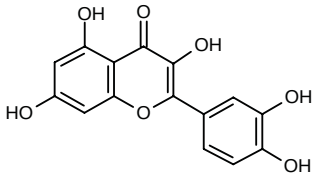
Additional Reference

Vargas, M. et al. *Phase II-selective induction of hepatic drug-metabolizing enzymes by oltipraz [5-(2-pyrazinyl)-4-methyl-1,2-dithiol-3-thione],1,7-phenanthroline, and 2,2'-dypyridyl in rats is not accompanied by induction of intestinal enzymes.* Drug Metab Dispos 1998, 26(2): 91.

Quercetin

Cardioprotectant
Antineoplastic
Antioxidant

EN: 131055



$C_{15}H_{10}O_7$ **Beijing Chem. Reagent Fact.; Taiyun Second Pharm. Fact.**

Quercetin (2.5-10 μM) and genistein (0.5-5.0 μM) were shown to produce synergistic cytotoxicity in human ovarian carcinoma cells, a finding which might be of interest in the treatment of relapsed inoperable ovarian carcinoma (1).

The antilipoperoxidative activity of quercetin was demonstrated in a membrane model of UV-radiation-induced peroxidation in phosphatidylcholine vesicles (IC_{50} = 6.24 μM). Furthermore, the degree of penetration through the skin during 24 h was very low (1.82%), indicating that topically applied quercetin may have protective activities in certain dermatological disorders associated with sunlight irradiation (2).

Quercetin (15-120 μmol/l) produced apoptosis-associated morphological changes in human leukemia HL-60 cells, including chromatin condensation, nuclear fragmentation and volume reduction, with a dose-dependent induction of DNA fragmentation and degradation. The compound also inhibited cell proliferation (IC_{50} = 43 μmol/l) (3).

1. Shen, F., Weber, G. *Quercetin and genistein reduced signal transduction activity and provided synergistic cytotoxicity in human ovarian carcinoma cells.* Proc Amer Assoc Cancer Res 1998, 39: Abst 3795.

2. Saija, A., Lanza, M., Montenegro, L., Smetiglio, P., Tomaino, A., Trombetta, D., Bonina, F. *Potential protective activity of flavonoids against photooxidative skin damage.* Pharmacol Res 1997, 35(Suppl.): 113.

3. Xiao, D., Zhu, S.-P., Gu, Z.-L. *Quercetin induced apoptosis in human leukemia HL-60 cells.* Acta Pharmacol Sin 1997, 18(3): 280.

Original monograph – Drugs Fut 1997, 22: 720.

Additional References

Sato, M. et al. *Quercetin, a bioflavonoid, inhibits the induction of interleukin 8 and monocyte chemoattractant protein-1 expression by tumor necrosis factor-α in cultured human synovial cells.* J Rheumatol 1997, 24(9): 1680.

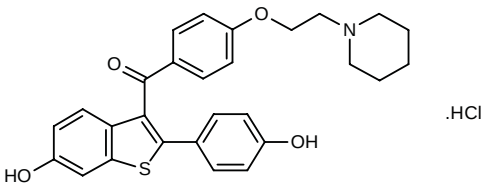
Kribben, A. et al. *Quercetin protects against hypoxia-induced injury in isolated rat proximal tubules.* J Amer Soc Nephrol 1997, 8: Abst A2749.

Motilva, V. et al. *Morphological, cytotoxic and nuclear degradation effects produced by quercetin and naringenin on neuroblastoma cells cultured in vitro.* Meth Find Exp Clin Pharmacol 1997, 19(Suppl. A): Abst PB-54.

Raloxifene Hydrochloride
Evista®

Antiestrogen
Treatment of Osteoporosis
Antineoplastic

EN: 090328



$C_{28}H_{27}NO_4S.HCl$ **Lilly; Chugai**

The two major metabolites of raloxifene, the glucuronide conjugates (VI) and (VIII) are synthesized as follows: The partial silylation of raloxifene (I) with *tert*-butyldimethylsilyl chloride (TBDMS-Cl) by means of dimethylaminopyridine (DMAP) in THF/DMF gives a mixture of the monosilylated compounds (II) and (III), which are separated by chromatography. Compounds (II) and (III) are independently condensed with methyl 1,2,3,4-tetra-*O*-acetyl-D-glucuronate (IV) by means of $BF_3.OEt_3$ in dichloromethane yielding protected glucuronides (V) and (VII), respectively. Finally, both compounds are deprotected by a treatment first with LiOH in dioxane to hydrolized the ester groups, and then with tetrabutylammonium fluoride in THF to eliminate the silyl groups, thus obtaining the desired metabolites (VI) and (VIII), respectively (1). Scheme 1.

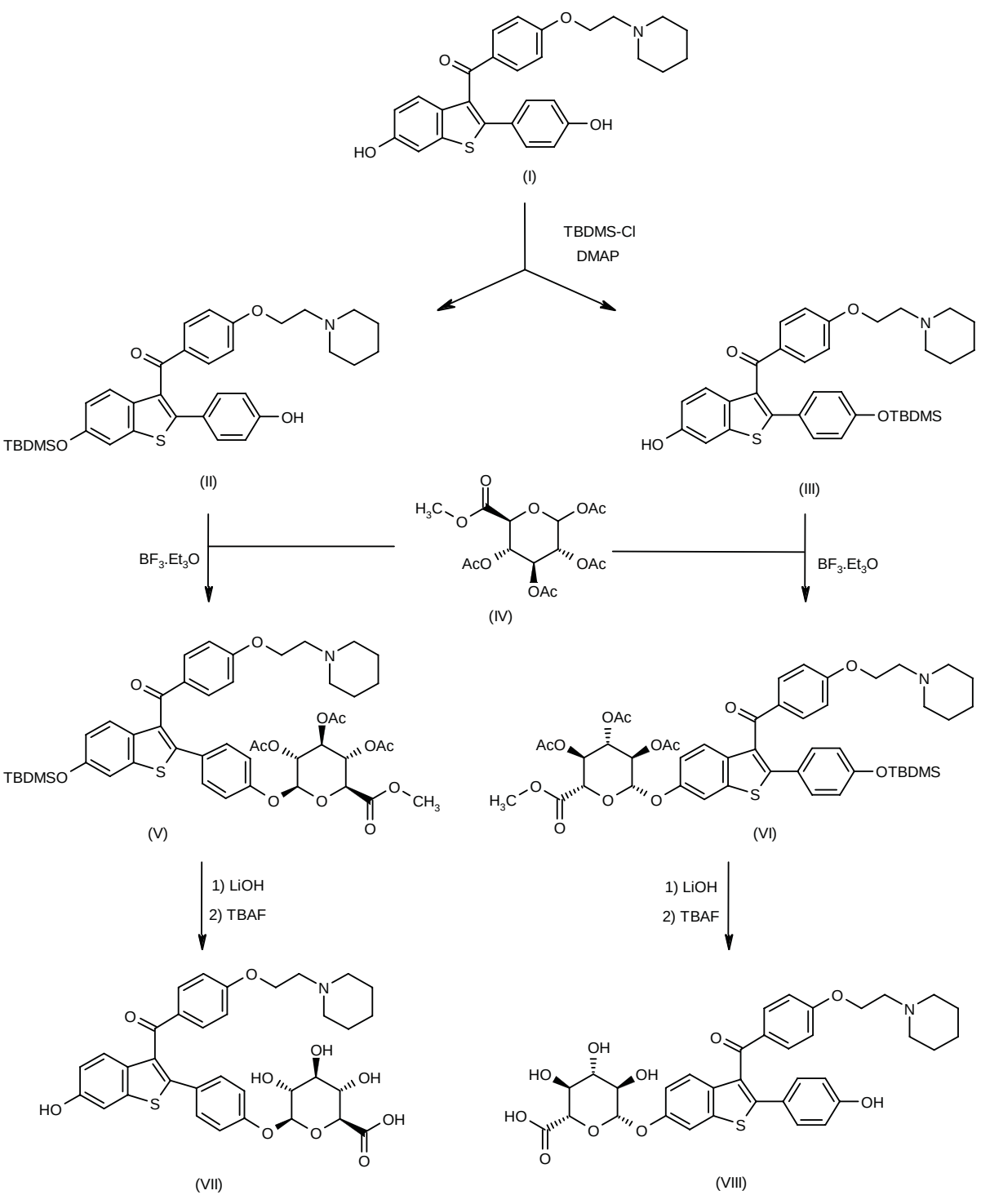
Transfection studies of mutant estrogen receptors in receptor-negative human breast cancer cells showed that an aspartate to tyrosine mutation at position 351 of the receptor changes the pharmacological activity of raloxifene from an antiestrogen to an estrogen, while a mutation at position 400 has no effect on the estrogen antagonistic activity of the drug (2).

In vivo studies in ovariectomized, cholesterol-fed rabbits demonstrated that raloxifene-treated animals had a significantly lower cholesterol content compared to placebo-treated animals (397 *vs.* 577nmol/mg protein), indicating the drug's potential antiatherogenic effect (3).

A regimen of raloxifene 1 or 5 mg/kg/day was evaluated in ovariectomized cynomolgus monkeys on a moderately atherogenic diet. The treatment reduced LDL-cholesterol levels but had no significant effect on HDL-cholesterol. Estrogen agonistic effects on coronary arteries were not observed. Animals in the 1-mg and 5-mg groups had 2 and 3 times more atherosclerosis than estrogen-treated animals (4).

The effects of raloxifene (60 and 120 mg/day) on serum lipids and coagulation factors were assessed in a double-blind, randomized, parallel trial in 390 healthy postmenopausal women. Drug treatment decreased LDL-cholesterol, fibrinogen and lipoprotein A, and increased

Scheme 1: Synthesis of Metabolites of Raloxifene



HDL_2-cholesterol without affecting triglycerides. No effects on HDL-cholesterol and PAI-1 were observed (5).

The 2-year findings from a randomized, double-blind trial evaluating raloxifene (60 or 120 mg/day) in 7704 postmenopausal women having osteoporosis with no history of breast or endometrial cancer have shown that the risk of newly diagnosed breast cancer was significantly decreased. Furthermore, raloxifene treatment may also

reduce the risk of newly diagnosed endometrial cancer during two years of use in this particular study population. The longer term effects of raloxifene are currently being investigated in this patient population (6).

An analysis of data from multicenter, double-blind, randomized trials in approximately 12,000 postmenopausal women has shown that raloxifene therapy produced a 58% reduction in the risk of developing breast cancer and a significant reduction in the incidence of estrogen receptor- and progesterone receptor-positive tumors (7).

Raloxifene was evaluated in a 1-year, prospective, double-blind, placebo-controlled study in 143 postmenopausal osteoporotic women with one or more vertebral fractures. Patients received raloxifene (60 or 120 mg/day) together with supplements of calcium (750 mg/day) and vitamin D (400 IU/day). Dose-related reductions in the incidence of vertebral fractures were statistically significant when using a more than 30% cutoff in the analysis of the data. The treatment was well tolerated, and no differences among groups in uterine bleeding, thrombophlebitis, breast abnormalities or endometrial thickness were observed (8).

In a double-blind, placebo-controlled, randomized phase III trial of raloxifene (30, 60 or 150 mg/day) in 601 healthy women aged 45-60 and within 2-8 years of menopause, the drug demonstrated a favorable profile in terms of endometrial thickness, serum lipids and bone mineral density. The incidence of adverse events and severity of hot flashes did not differ between the groups (9).

In a multicenter, open-label phase III study, the Nottingham Health Profile and SF-36 surveys were used to assess subject preference between raloxifene and hormone replacement therapy in 413 healthy postmenopausal women aged 45-60 with an intact uterus. No significant differences were observed between the treatment groups in terms of physical functioning, general health, vitality and mental health (10).

The effects of raloxifene (60 mg/day) on markers of cardiovascular risk were compared to those of hormone replacement therapy in 390 healthy postmenopausal women during a 6-month study. Raloxifene significantly reduced total and LDL-cholesterol, lipoprotein-A and fibrinogen levels, and significantly raised HDL-2, but not HDL, triglycerides or PAI-1. Hormone replacement therapy was more effective than raloxifene in lowering lipoprotein-A and PAI-1 and raising HDL, but less efficient in lowering fibrinogen (11).

Administration of raloxifene in 33 early postmenopausal women produced a significant calcium balance shift of +74 mg/day after 4 weeks and +60 mg/day after 31 weeks, while the calcium shift in subjects treated with estrogen was +60 and +91 mg/day at 4 and 31 weeks, respectively. Bone formation was reduced by estrogen but not with raloxifene, and remodeling suppression was greater for estrogen, although the remodeling balance was equal for the two agents (12).

Two groups of women with normal menstrual cycles received raloxifene in a regimen of 400 mg administered for 5 days in the follicular, periovulatory or luteal phase of the cycle (n=12) or a regimen of 100 or 200 mg for 28 days beginning on the third day of the cycle (n=19). Raloxifene had no effect on the length of the menstrual cycle or on the time of luteinizing hormone surge. The 400-mg regimen caused elevations in the AUC during the entire cycle for FSH and during the second half of the cycle for estradiol. Similar effects were seen with the 100-mg and 200-mg regimens (13).

Raloxifene (60 or 120 mg/day), in addition to preserving bone, produced beneficial changes in cardiovascular markers when evaluated in 390 healthy postmenopausal women for a period of 6 months (14).

The effects of long-term (24 months) treatment with raloxifene hydrochloride on bone mineral density, serum lipid concentrations and endometrial thickness were evaluated in 601 postmenopausal women. Subjects were randomly allocated to treatment with raloxifene (30, 60 or 150 mg/day) or placebo. Bone mineral density of the lumbar spine, hip and total body increased significantly from baseline values in all raloxifene treatment groups, whereas it decreased in patients administered placebo. Total cholesterol and LDL cholesterol concentrations in serum decreased in all active drug treatment groups, while HDL cholesterol and triglycerides remained constant. No difference in endometrial thickness was detected in raloxifene-treated women as compared to those in the placebo group, showing that the compound does not stimulate the endometrium. Likewise, the incidences of hot flashes and vaginal bleeding were similar in the active drug and placebo groups (15).

Lilly has initiated a large, prospective clinical trial denominated Raloxifene Use for The Heart (RUTH) to evaluate the efficacy of raloxifene hydrochloride (Evista®) in preventing heart attacks and heart-related deaths in postmenopausal women.The placebo-controlled worldwide trial is expected to enroll approximately 10,000 postmenopausal women at risk for heart attack and will last up to seven and a half years. The primary objective of the trial is to assess whether chronic treatment with Evista® reduces the incidence of coronary death and nonfatal myocardial infarction in postmenopausal women at risk for cardiovascular events. The trial will also assess the effect of the drug on a variety of other important parameters, including all-cause death, all-cause hospitalization, revascularization procedures, stroke and breast cancer (16).

According to a recent study, raloxifene is effective in lowering risk factors for cardiovascular disease in postmenopausal women, but is not as effective as hormone replacement therapy (HRT). In the study, 390 healthy postmenopausal women were randomized to receive 1 of 4 treatments: raloxifene 60 mg/day, raloxifene 120 mg/day, hormone replacement therapy (conjugated equine estrogen 0.625 mg/day and medroxyprogesterone acetate 2.5 mg/day) or placebo. Compared to the placebo group, both doses of raloxifene lowered markers that

are known risk factors for coronary artery disease, but did not lower them to the same degree as HRT treatment (17).

Raloxifene hydrochloride (Evista®) has been launched in the U.S. for the prevention of osteoporosis in postmenopausal women. The drug is available as 60-mg tablets (18-20).

1. Dodge, J.A., Lugar, C.W., Cho, S., Osborne, J.J., Phillips, D.L., Glasebrook, A.L., Frolik, C.A. *Synthesis and estrogen receptor binding affinities of the major human metabolites of raloxifene (LY139481).* Bioorg Med Chem Lett 1997, 7(8): 993.

2. Levenson, A.S., Jordan, V.C. *The key to the antiestrogenic mechanism of raloxifene is amino acid 351 (aspartate) in estrogen receptor.* Cancer Res 1998, 58(9): 1872.

3. Bjarnason, N.H., Haabo, J., Byrjalsen, I., Kauffman, R.F., Christiansen, C. *Raloxifene inhibits aortic accumulation of cholesterol in ovariectomized, cholesterol-fed rabbits.* Circulation 1997, 96(6): 1964.

4. Clarkson, T.B., Anthony, M.S., Jerome, C.P. *Lack of effect of raloxifene on coronary artery atherosclerosis of postmenopausal monkeys.* J Clin Endocrinol Metab 1998,83(3): 721.

5. Walsh, B.W., Kuller, L.H., Wild, R.A., Paul, S., Farmer,M., Lawrence, J.B., Shah, A.A., Anderson, P.W. *Effects of raloxifene on serum lipids and coagulation factors in healthy postmenopausal women.* JAMA-J Amer Med Assoc 1998, 279(18): 1445.

6. Cummings, S.R., Norton, L., Eckert, S., Grady, D., Cauley, J., Knickerbocker, R., Black, D.M., Nickelsen, T., Glusman, J., Krueger, K. *Raloxifene reduces the risk of breast cancer and may decrease the risk of endometrial cancer in post-menopausal women. Two-year findings from the multiple outcomes of raloxifene evaluation (MORE) trial*. Proc Amer Soc Clin Oncol 1998, 17: Abst 3.

7. Jordan, V.C., Glusman, J.E., Eckert, S., Lippman, M., Powles, T., Costa, A., Morrow, M., Norton, L. *Incident primary breast cancers are reduced by raloxifene: Integrated data from multicenter, double-blind, randomized trials in approx. 12,000 postmenopausal women.* Proc Amer Soc Clin Oncol 1998, 17: Abst 466.

8. Lufkin, E.G., Whitaker, M.D., Argueta, R., Caplan, R.H.,Nickelsen, T., Riggs, B.L. *Raloxifene treatment of postmenopausal osteoporosis.* J Bone Miner Res 1997, 12(Suppl. 1): Abst 191.

9. Bjarnason, N.H., Delmas, P.D., Mitlak, B., Shah, A., Huster, W., Draper, M.W., Christiansen, C. *Raloxifene HCl: Long term efficacy and safety profile.* Acta Obstet Gynecol Scand 1997, 76(Suppl. 167, 4): Abst FC715.4.

10. Houpt, L.S., Minshall, M.E., Shen, W., Kopetsky, M.G., Huster, W.J., Agnusdei, D., Muchmore, D.B. *Quality of life results: Randomized clinical trial of a selective estrogen receptor modulator, raloxifene, & hormone replacement therapy*. Acta Obstet Gynecol Scand 1997, 76(Suppl. 167, 4): Abst FC801.1.

11. Walsh, B.W., Kuller, L.H., Wild, R.A., Paul, S., Shah, A., Anderson, P.W. *The effect of raloxifene on markers of cardiovascular risk in healthy, post-menopausal women.* Atherosclerosis 1997, 134(1-2): Abst 2.P.313.

12. Heaney, R.P., Draper, M.W. *Raloxifene and estrogen: Comparative bone-remodeling kinetics.* J Clin Endocrinol Metab 1997, 82(10): 3425.

13. Baker, V.L., Draper, M., Paul, S., Allerheiligen, S., Glant, M., Shifren, J., Jaffe, R.B. *Reproductive endocrine and endometrial effects of raloxifene hydrochloride, a selective estrogen receptor modulator, in women with regular menstrual cycles.* J Clin Endocrinol Metab 1998, 83(1): 6.

14. Walsh, B.W., Kuller, L.H., Wild, R.A., Paul, S., Farmer,M., Lawrence, J.B., Shah, A.S., Anderson, P.W. *Raloxifene and hormone replacement therapy: Comparative effects on serum lipids and coagulation factors in postmenopausal women.* J Amer Coll Cardiol 1998, 31(5,Suppl. C): Abst 2135.

15. Delmas, P.D., Bjarnason, N.H., Mitlak, B.H., Ravoux, A.-C., Shah, A.S., Huster, W.J., Draper, M., Christiansen, C. *Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women.* New Engl J Med 1997, 337(23): 1641.

16. *Lilly evaluates cardiovascular effects of Evista in RUTH trial.* Prous Science Daily Essentials March 27, 1998.

17. *HRT more effective than raloxifene in improving heart disease risk factors*. Prous Science Daily Essentials May 13, 1998.

18. *FDA grants raloxifene NDA priority review status.* Prous Science Daily Essentials July 24, 1997.

19. *FDA approves SERM for preventing postmenopausal osteoporosis.* Prous Science Daily Essentials December 11, 1997.

20. *Raloxifene launched in U.S*. Prous Science Daily Essentials January 19, 1998.

Original monograph – Drugs Fut 1984, 9: 516.

Additional References

Glasebrook, A.L. et al. *The effect of a selective estrogen receptor modulator on the progression of spontaneous autoimmune disease in MRL lpr/lpr mice.* J Allergy Clin Immunol 1997, 99(1, Part 2): Abst 744.

Nuttall, M.E. et al. *Idoxifene, a tissue selective estrogen agonist/antagonist, has a mechanism of action in bone similar to estrogen and distinct from raloxifene.* J Bone Miner Res 1997, 12(Suppl. 1): Abst P273.

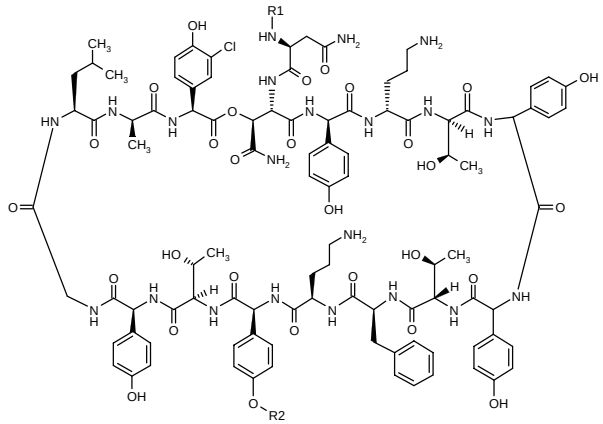
Sato, M. *Raloxifene efficacy in nonreproductive and reproductive tissues.* IBC Conf Emerg Ther Osteoporos (April 28-29, Boston) 1997.

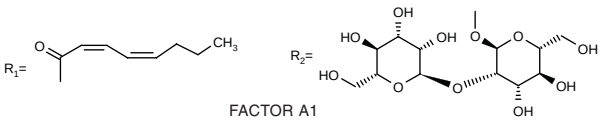
Fuleihan, G.E.-H. *Tissue-specific estrogens - The promise for the future.* New Engl J Med 1997, 337(23): 1686.

Ramoplanin

Glycopeptide Antibiotic
Antiacne

EN: 091144





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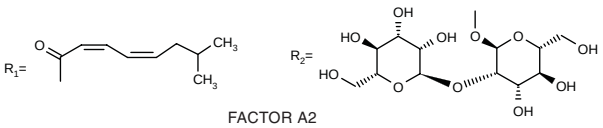

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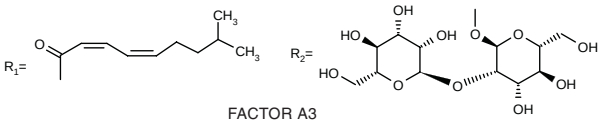

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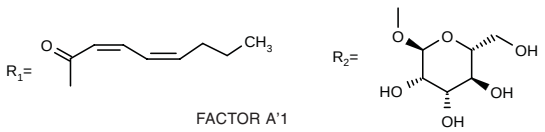

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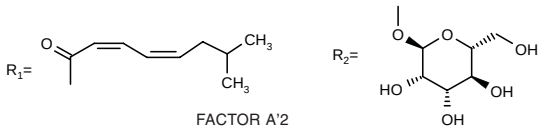

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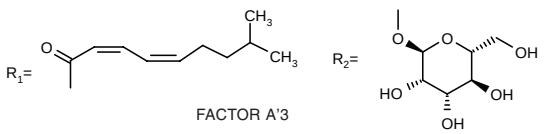


FACTOR A'3

Hoechst Marion Roussel; Lepetit; Intrabiotics

IntraBiotics has entered into a licensing and supply agreement with Biosearch Italia for ramoplanin. IntraBiotics intends to conduct U.S. phase II trials with ramoplanin in the second half of 1998. The agreement grants IntraBiotics the right to develop and commercialize ramoplanin for the prevention and treatment of infectious diseases in the U.S. and Canada. In exchange, Biosearch will receive a licensing fee, clinical milestone payments, royalties and bulk supply payments and will be responsible for manufacturing the drug substance (1).

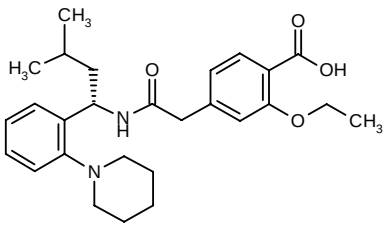
1. *IntraBiotics obtains certain rights to ramoplanin*. Prous Science Daily Essentials May 14, 1998.

Original monograph – Drugs Fut 1990, 15: 689.

Repaglinide
NovoNorm®
Prandin®
Actulin®

Antidiabetic

EN: 178930



$C_{27}H_{36}N_2O_4$

Boehringer Ingelheim; Novo Nordisk; Schering Plough

In vitro evaluation of repaglinide in pancreatic islet B-cells indicated that the drug primarily affects cationic flux and has favorable insulinotropic effects. Furthermore, it has no effect on nutrient metabolism or biosynthetic activity, has a low insulin-releasing threshold concentration (0.1-1.0 μmol/l) and is capable of stimulating insulin release in the presence of high glucose-D concentrations (1)

Pharmacokinetic interactions between repaglinide and digoxin were evaluated in 14 healthy male volunteers. The 9-day regimens consisted of either digoxin monotherapy (0.5 mg/day on day 1 and 0.25 mg/day on days 2-9) followed by repaglinide (2 mg t.i.d.) or a combination therapy of the two drugs followed by digoxin monotherapy. AUC, $C_{max,}$ C_{ssmin} and t_{max} values did not differ significantly between digoxin monotherapy and combination therapy. The combination therapy was well tolerated without notable effects on the safety profile of digoxin (2).

Pharmacokinetic interactions between repaglinide and cimetidine were evaluated in 14 healthy nonsmoking volunteers receiving either repaglinide alone (2 mg t.i.d. on days 1-3 and 2 mg once on day 4), followed by repaglinide in combination with cimetidine (400 mg b.i.d. on days 1-4 and 400 mg once on day 5), or repaglinide in combination with cimetidine followed by repaglinide alone. No significant differences in AUC, C_{max}, t_{max}, λ_z and $t_{1/2}$ values were observed following repaglinide monotherapy compared to the two drugs together. Combination

therapy had no effects on the safety profile of repaglinide, indicating that the pharmacokinetics of repaglinide are not affected by coadministration of cimetidine (3).

The pharmacokinetics and mean residence time of repaglinide were evaluated in 24 healthy males following administration of 4 single doses of 2 mg, either in tablet formulation or as an oral solution. Both formulations of the drug were rapidly absorbed to a similar extent, without significant differences in AUCs. Relative bioavailability was 110% and elimination half-life was approximately 32 min. The rate of absorption was 57% lower for the tablet formulation, resulting in a 10% lower C_{max} and 35% longer mean residence time (4).

Evaluation of single-dose repaglinide, administered either as a 2-mg tablet or as a 15-min i.v. infusion, in 12 healthy male volunteers demonstrated a low volume of distribution and rapid elimination of the drug from the blood stream, as well as a rapid absorption of the compound from the gastrointestinal tract, indicating high first-pass metabolism (5).

Repaglinide was evaluated in 24 healthy male volunteers receiving single doses of 2 mg under fasting and fed conditions. AUC and C_{max} decreased slightly after administration of the drug under fed conditions. Absorption of the compound under both fasting and fed conditions was rapid with a tmax of 0.6 h, indicating that administration of repaglinide preprandially does not affect absorption (6).

A regimen of repaglinide (0.5-4 mg t.i.d.) in combination with metformin (1-3 g/day) was compared to monotherapy with either drug in 83 patients with noninsulin dependent diabetes mellitus. Fasting insulin, C-peptide levels and lipid profiles were similar in all three regimens. Metformin alone or in combination with repaglinide produced more gastrointestinal side effects than repaglinide monotherapy. No severe hypoglycemia or adverse events were observed. Thus repaglinide produces the same hypoglycemic control as metformin but with fewer gastrointestinal side effects (7).

The efficacy of repaglinide was compared to glibenclamide in 195 patients with noninsulin-dependent diabetes mellitus. Repaglinide was administered preprandially at doses of 0.5, 1.0, 2.0 or 4.0 mg and glibenclamide was administered at doses of 1.75, 3.5, 7.0 or 10.5 mg. Both drugs produced a similar decrease in HbAlc and FBG. Fructosamine levels, lipid profiles and fasting levels of C-peptide, insulin and proinsulin did not change significantly between the groups. Both treatments were well tolerated and the frequency of low-insulin episodes was low (8).

In a 4-week study in 18 patients with noninsulin-dependent diabetes mellitus, 3 times daily dosing with repaglinide (0.25 mg) given prior to meals was compared to a twice-daily regimen of the same dosage. The doses were doubled during the last 2 weeks of the study. Blood glucose levels decreased significantly in both groups, while glycemic control was better in the group receiving 3 daily doses of repaglinide, as were the AUCs. The group receiving repaglinide 3 times daily demonstrated significantly decreased HbA1c levels, while the decrease in the twice daily group was nonsignificant. Plasma insulin levels in both regimens decreased to pretreatment levels before the next meal and did not increase during the night (9).

Results of an open-label, single/multiple-dose pharmacokinetic study in three study groups consisting of sulfonylurea-treated elderly patients with noninsulin-dependent diabetes mellitus, elderly healthy subjects and young healthy subjects showed that the pharmacokinetics did not differ significantly between healthy young and elderly subjects, while mean diurnal serum values were consistently higher in diabetic patients as compared to healthy subjects. Serum log AUC values in diabetic patients were significantly higher following day 7 of treatment, indicating reduced serum clearance of repaglinide in elderly diabetic patients (10).

In a single-center, double-blind, placebo-controlled study, 20 sulfonylurea-treated patients with noninsulin-dependent diabetes mellitus were administered escalating multiple doses of repaglinide (4, 8, 12, 16 and 20 mg q.i.d.). Serum glucose levels were reduced in all treatment groups with the most prominent effect in the 16-mg group. Repaglinide serum levels increased dose-dependently reaching C_{max} after 30-60 min. Adverse effects on liver enzymes and cardiac function were not observed; adverse events included mild headache, loose stools and dizziness (11).

Novo Nordisk and Schering-Plough have signed an agreement to jointly launch and promote repaglinide (Prandin™) in the U.S. (12)

Novo Nordisk has introduced repaglinide (Prandin™) in the U.S., where it is indicated as an adjunct to diet and exercise to lower blood glucose in patients with type II diabetes whose hyperglycemia cannot be controlled sufficiently on diet and exercise alone, and for use in combination with metformin to lower blood glucose in patients whose hyperglycemia cannot be controlled by exercise, diet and either repaglinide or metformin alone. It is supplied as tablets, 0.5, 1.0 and 2.0 mg (13-15).

1. Louchami, K., Jijakli, H., Sener, A., Malaisse, W.J. *Effect of repaglinide upon nutrient metabolism, biosynthetic activity, cationic fluxes and insulin release in rat pancreatic islets.* Res Commun Mol Pathol Pharmacol 1998, 99(2): 155.

2. Schwietert, R., Wemer, J., Jonkman, J.H., Thomsen, M.S., Hatorp, V. *Co-administration of repaglinide does not affect digoxin pharmacokinetics.* Eur J Clin Pharmacol 1997, 52(Suppl.): Abst 430.

3. Schwiertert, R., Wemer, J., Jonkman, J.H.G., Hatorp, V.,Thomsen, M.S. *No change in repaglinide pharmacokinetics with cimetidine coadministration.* Eur J Clin Pharmacol 1997, 52(Suppl.): Abst 431.

4. Oliver, S., Windfeld, K., Hatorp, V. *Pharmacokinetics and bioavailability of repaglinide, a new OHA for patients with NIDDM.* Diabetes 1997, 46(Suppl. 1): Abst 1263.

5. Hatorp, V., Nielsen, K.K., Rathgen, K. *Bioavailability of repaglinide after administration as either 2 mg tablet or 2 mg i.v. infusion.* J Clin Pharmacol 1997, 37(9): Abst 70.

6. Hatorp, V., Bayer, T. *Repaglinide bioavailability in the fed or fasting state.* J Clin Pharmacol 1997, 37(9): Abst 72.

7. Moses, R., Slobodniuk, R., Donnelly, T., Moffitt, P., Boyages, S., Colagiuri, S., Kidson, W., Carter, J. *Additional treatment with repaglinide provides significant improvement in glycaemic control in NIDDM patients poorly controlled on metformin.* Diabetes 1997, 46(Suppl. 1): Abst 0365.

8. Landgraf, R., Bilo, H. *Repaglinide vs glibenclamide: A 14-week efficacy and safety comparison.* Diabetes 1997, 46(Suppl. 1): Abst 0626.

9. Damsbo, P., Andersen, P.H., Lund, S., Pørksen, N. *Improved glycaemic control with repaglinide in NIDDM with 3 times daily meal related dosing.* Diabetes 1997, 46(Suppl. 1): Abst 0132.

10. Hatorp, V., Perentesis, G., Nielsen, K.K., Wu, F.F. *Pharmacokinetics of repaglinide, a comparison between young and elderly healthy subjects and elderly NIDDM patients.* J Clin Pharmacol 1997, 37(9): Abst 69.

11. Damsbo, P., Perentesis, G., Müller, P.G., Hatorp, V. *Favorable tolerability profile of repaglinide in NIDDM after multiple ascending doses.* J Clin Pharmacol 1997, 37(9): Abst 71.

12. *Schering-Plough to copromote Novo Nordisk's Prandin.* Prous Science Daily Essentials January 30, 1998.

13. *Repaglinide gets expedited review status in U.S.* Prous Science Daily Essentials August 20, 1997.

14. *FDA approval obtained for Prandin.* Prous Science Daily Essentials December 29, 1997.

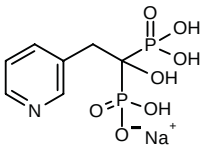
15. *Prandin introduced for treatment of type II diabetes in U.S.* Prous Science Daily Essentials June 3,1998.

Original monograph – Drugs Fut 1996, 21: 694.

Risedronate Sodium
Actonel®

Bisphosphonate
Treatment of Osteoporosis

EN: 196922



$C_7H_{10}NNaO_7P_2$

Procter & Gamble; Takeda; Ajinomoto; Hoechst Marion Roussel

In ovariectomized rats previously administered high-dose parathyroid hormone, treatment with risedronate (3 mcg/kg/day, 3 days/week) was found to reduce marrow area without affecting cortical area (1).

In 6-month old ovariectomized rats, combination treatment with intermittent on/off PGE_2 (6 mg/kg/d) and risedronate (5 μg/kg/twice weekly) resulted in increases in trabecular bone mineral density, cortical bone density and cortical thickness, and was as effective as daily PGE_2 treatment alone (2).

Results of studies in ovariectomized rats demonstrated that cotreatment with PGE_2 (6 mg/kg/day) and risedronate (5 μg/kg/twice weekly) was as anabolic as treatment with PGE_2 alone on tibial shaft. Furthermore, coadministration of risedronate modulated bone resorption without abrogating the true anabolic effects of PGE_2 (3).

In ovariectomized minipigs, oral risedronate (0.1, 0.5 or 2.5 mg/kg/day) resulted in significant reductions in bone turnover and dose-dependent decreases in trabecular separation and osteoid thickness. None of the doses studied caused deleterious effects on bone mineralization (4).

Results of a study in ovariectomized rats on the skeletal effects of withdrawing risedronate suggest that a treatment regimen of 60 days on/90 days off would be sufficient to prevent the development of osteopenia in postmenopausal and oophorectomized women (5).

Results of a study in ovariectomized rats showed that treatment with risedronate (5 μg/kg s.c. twice weekly) for 60 days on then 90 days off prevented the development of osteoporosis (6).

Results of a multicenter, randomized, double-blind, placebo-controlled trial in postmenopausal women with low lumbar spine bone mass showed that oral risedronate (2.5 or 5 mg/day) dose-dependently increased bone mass at the spine, hip and radius, and was well tolerated (7).

The results of a 1-year multicenter, double-blind, randomized study in 123 patients with Paget's disease showed that oral risedronate (30 mg/day x 2 months) produced a rapid, durable remission (normalization of alkaline phosphatase) in the majority of patients and was more effective than etidronate (400 mg/day x 6 months). Furthermore, risedronate was better tolerated (8).

Results from a 1-year multicenter, double-blind, randomized, parallel-group study in 123 patients with Paget's disease have shown that risedronate (30 mg/day p.o. for 2 months), compared to etidronate (400 mg/day for 6 months), produced significant improvement in pain which was sustained for at least 10 months after discontinuation of treatment (9).

In patients with Paget's disease of bone, risedronate (30 mg/day p.o. for 34 days) was shown to be highly effective in improving lesions across all skeletal sites, including tibia, femur, humerus, forearm, pelvis, spine and skull, and had no deleterious effect on osteolytic lesions in tibia and femur (10).

Results from an open-label, single-dose (30 mg) study of risedronate in patients with varying degrees of renal impairment have shown that dosage adjustment with clinical monitoring may be necessary in patients with severe renal impairment (creatinine clearance less than 20 ml/min) but not in patients with mild or moderate renal impairment (creatinine clearance more than 20 ml/min) (11).

In a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study in both early and late postmenopausal women, risedronate (2.5 or 5 mg/day for 12-18 months) dose-dependently increased lumbar spine bone mass, irrespective of postmenopausal period.

Patients within 5 years postmenopausal appeared to be more resistant to calcium supplementation than those more than 5 years postmenopausal (12).

Results from an open-label, single-center study in 20 patients with severe Paget's disease showed that treatment with oral risedronate (30 mg/day for 3 months) significantly reduced the biochemical indices of disease activity, resulting in normalization of serum alkaline phosphatase in 13 patients and a progressive decline and elimination of bone pain in 14 patients. Risedronate was well-tolerated and no drug- related adverse events were reported (13).

In a double-blind, placebo-controlled trial in 111early postmenopausal patients with normal bone mass, treatment with oral risedronate (5 mg daily or cyclic) for 2 years followed by 1 year off treatment increased bone mass of the lumbar spine and trochanteric bone mass at the hip and maintained bone mass at the femoral neck (14).

The results of two single-dose, crossover studies evaluating the gastrointestinal absorption of risedronate in 16 healthy male volunteers indicated that the rate and extent of absorption are independent of the site of administration, and that the rate of administration does not affect the extent of absorption (15).

The long-term effects of risedronate on bone mass, fracture rate and biochemical markers have been evaluated in a multicenter, double-masked, randomized, placebo-controlled phase II trial in 132 patients with posmtenopausal osteoporosis and at least 1 vertebral fracture. Patients received continuous risedronate 2.5 mg, cyclical risedronate 2.5 mg or placebo for 2 years in addition to daily calcium supplementation, with 1-year follow-up on calcium supplementation only. Statistically significant differences among groups were not observed for femoral and spinal bone mineral density at 2 years, but the placebo and cyclical risedronate groups showed a significant increase in bone mineral density in the femoral neck after 3 years. Markers of bone turnover showed only minor changes and no differences were observed among groups in the incidence and rate of new vertebral fractures. Side effects also showed a similar distribution among groups. It is suggested that the lack of efficacy in this trial may have been due to insufficient doses and/or impaired oral absorption (16).

Procter & Gamble and Hoechst Marion Roussel have formed a global alliance to commercialize Procter & Gamble's risedronate sodium (Actonel™).The companies will work together to complete clinical studies, obtain regulatory approvals and develop sales and marketing plans to launch the drug as a treatment for osteoporosis in all countries except Japan (17).

The U.S. FDA has approved risedronate sodium (Actonel™) for marketing in the treatment of Paget's disease of bone. Actonel™ tablets, containing 30 mg of the active ingredient, will be launched by Procter & Gamble and copromoted by Hoechst Marion Roussel. An application for marketing approval has also been filed in Canada, and the companies continue to evaluate the compound in clinical trials for other indications such as osteoporosis (18).

1. Uwaniec, U., Samnegard, E., Howard, T., Bare, S., Matula, J., Kimmel, D.B. *Long-term effect of low dose PTH, estrogen, or risedronate on cortical bone in ovariectomized osteopenic rats.* J Bone Miner Res 1997, 12(Suppl. 1): Abst T526.

2. Zhou, H., Ma, Y.F., Jee, W.S.S., Setterberg, R., Pun, S.W., Chen, H.K. *Intermittent on/off prostaglandin E_2 (PGE_2) with risedronate (RIS) is equally effective as daily PGE_2 alone in maintaining added bone in ovariectomized (OVX) rats.* J Bone Miner Res 1997, 12(Suppl. 1): Abst T471.

3. Ma, Y.F., Chen, H.K., Lee, W.S.S., Setterberg, R. *Co-treatment of prostaglandin E_2 (PGE_2) and risedronate (RIS) is equally anabolic as PGE_2 alone on tibial shaft in ovariectomized rats.* J Bone Miner Res 1997, 12(Suppl. 1): Abst S472.

4. Gropp, K.E., Bouchard, G.F., Phipps, R.J., Smith, P.N. *Risedronate dose-dependently decreases bone turnover in ovariectomized minipigs.* J Bone Miner Res 1997, 12(Suppl. 1): Abst S473.

5. Li, Q.N., Liang, N.C., Huang, L.F., Wu, T., Hu, B., Mo, L.E. *Skeletal effects of withdrawal of bisphosphonate-risedronate in ovariectomized rats.* 15th Meet Jpn Soc Bone Metab Res (July 24-26, Ohmiya) 1997, 177.

6. Li, Q.-N., Liang, N.-C., Huang, L.-F., Wu, T., Hu, B., Mo, L.-E. *Skeletal effects of constant and terminated use of sodium risedronate in ovariectomized rats.* Acta Pharmacol Sin 1998, 19(2): 160.

7. McClung, M.R., Bensen, W., Bolognese, M.A. et al. *Risedronate increases BMD at the hip, spine and radius in postmenopausal women with low bone mass.* J Bone Miner Res 1997, 12(Suppl. 1): Abst P269.

8, Miller, P.D., Adachi, J.D., Brown, J.P. et al. *Risedronate vs. etidronate Paget's study: Durable remission with only two months of 30 mg risedronate.* J Bone Miner Res 1997, 12(Suppl. 1): Abst T670.

9. Bekker, P.J., Miller, P.D., Adachi, J.D. et al. *Risedronate treatment improves pain status in patients with Paget's disease of bone.* J Bone Miner Res 1997, 12(Suppl. 1): Abst T673.

10. Chines, A., Bekker, P., Ritter-Hmcirik, C., Brown, J., Hayes, C. *Improvement of pagetic bone lesions with risedronate treatment: A radiographic study.* J Bone Miner Res 1997, 12(Suppl. 1): Abst T674.

11. Mitchell, D.Y., St. Peter, J.V., Eusebio, R.A., Pallone,K.A., Kelly, S.C., Nesbitt, J.D., Russell, D.A., Powell, J.H. *The effect of renal impairment on risedronate pharmacokinetics.* J Bone Miner Res 1997, 12(Suppl. 1): Abst F472.

12. Bekker, P.J., McClung, M.R., Bensen, W. et al. *Risedronate is effective in increasing BMD in both early and late postmenopausal women with low bone mass.* J Bone Miner Res 1997, 12(Suppl. 1): Abst S474.

13. Hosking, D.J., Eusebio, R.A., Chines, A.A. *Paget's disease of bone: Reduction of disease activity with oral risedronate.* Bone 1998, 22(1): 51.

14. Mortensen, L., Charles, P., Bekker, P.J., Digennaro, J., Johnston, C.C. *Risedronate increases bone mass in an early postmenopausal population: Two years of treatment plus one year of follow-up.* J Clin Endocrinol Metab 1998, 83(2): 396.

15. Mitchell, D.Y., Eusebio, R.A., Dunlap, L.E., Pallone, K.A., Nesbitt, J.D., Russell, D.A., Clay, M.E., Bekker, P.J. *Risedronate gastrointestinal absorption is independent of site and rate of administration.* Pharm Res 1998, 15(2): 228.

16. Clemmesen, B., Ravn, P., Zegels, B., Taquet, A.N., Christiansen, C., Reginster, J.Y. *A 2-year phase II study with 1-year of follow-up of risedronate (NE-58095) in postmenopausal osteoporosis.* Osteoporosis Int 1997, 7(5): 488.

17. *Procter & Gamble and Hoechst Marion Roussel to comarket Actonel.* Prous Science Daily Essentials May 12,1997.

18. *FDA approves Actonel for Paget's disease.* Prous Science Daily Essentials April 3, 1998.

Original monograph – Drugs Fut 1993, 18: 605.

Additional References

Study results highlight the promise of risedronate in treating postmenopausal women with low bone mass. The Procter & Gamble Co. Press Release 1997, September 11.

Ma, Y.F. et al. *Intermittent on/off prostaglandin E-2 and risedronate are equally anabolic as daily PGE_2 alone treatment in cortical bone of ovariectomized rats.* J Bone Miner Res 1997, 12(12): 2108.

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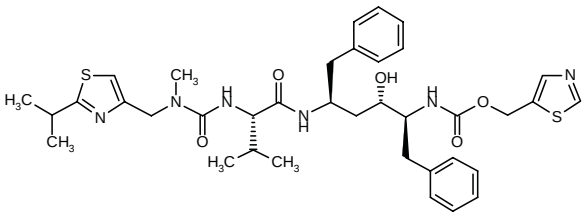

$C_{37}H_{48}N_6O_5S_2$

Abbott; Dainippon

The multiple-dose pharmacokinetics of ritonavir (200, 400 or 500 mg q12h x 2 weeks) were investigated in 64 HIV-positive males under nonfasting conditions. Results showed that the pharmacokinetics were moderately dose-dependent, with concentration-dependent autoinduction being the most likely mechanism for the time-dependent pharmacokinetics. Less than 2% of the dose was eliminated unchanged in the urine (1).

Results of a study in 6 HIV-positive male patients with advanced disease demonstrated that combination therapy with saquinavir (600 mg q.i.d.) and ritonavir (300 mg b.i.d.) resulted in a significant drug interaction mediated by enzyme inhibition which exposed patients to potential toxicity. Therefore, the dose of saquinavir should be greatly reduced if used in combination with ritonavir (2).

Results of a retrospective evaluation in patients with detectable plasma HIV-1 RNA showed that the addition of saquinavir (400-600 mg b.i.d.) to ritonavir-nucleoside combination therapy was well tolerated and associated with a modest improvement in plasma HIV-RNA response and CD4 counts. Adverse effects included mild to moderate increases in liver function tests, fasting serum triglycerides, loose stool/diarrhea and intermittent paresthesias, although none required drug discontinuation (3).

Results of a placebo-controlled, rising single-dose study in 16 healthy volunteers demonstrated that the pharmacokinetics of ritonavir in combination with ABT-378 were not significantly different under fasting and nonfasting conditions. The drug combination was well tolerated and resulted in concentrations that are expected to be highly suppressive for HIV-1 (4).

In a phase I/II clinical trial in 44 HIV-infected children with advanced disease who were naive to protease inhibitor treatment, combination therapy with zidovudine, didanosine and ritonavir resulted in considerable improvement in thymic-derived $CD4^+$ T-cell numbers and minimal decrease in viral burden (5).

Data from a retrospective study in 34 children with high viral load and/or advanced immunologic decline and prior nucleoside therapy demonstrated that triple therapy including ritonavir was effective in reducing viral load and increasing CD4 number, CD4 percent and CD4/CD8 ratio in the majority of patients at week 26 (6).

Results of a controlled, open-label study of ritonavir in 12 HIV-infected patients with underlying hepatic disease demonstrated that ritonavir exposure (AUC) increased by 40% and peak concentration (C_{max}) increased by 27% as compared to controls. Consequently, dose reduction of ritonavir is recommended in these patients (7).

Results of a pilot study evaluating combination therapy with ritonavir and one or two nucleoside reverse transcriptase inhibitors in children and adolescents over 8 years of age with perinatally acquired HIV infection showed that 78% (18/23) of the long-term survivors had an antiviral response to ritonavir, defined as a decrease in viral load of equal to or more than 0.5 log (8).

The results of a study in 141 AIDS patients with a high incidence of HIV-HCV coinfection treated with ritonavir showed that acute hepatitis occurred in a significant proportion of patients (7%) during the first 3 months of treatment (9).

Results of a prospective study of ritonavir treatment in 99 patients with advanced AIDS suggested that oral *Candida* colonization does not improve significantly during the first 16 weeks of antiretroviral treatment. However, control of opportunistic pathogens such as *Candida* may occur later than the virological response seen after 16 weeks of treatment (10).

Combination therapy of ritonavir (50 or 100 mg b.i.d.) and ABT-378 (200-600 mg b.i.d.) was found to be well tolerated at all doses evaluated in a placebo-controlled, multiple-dose study in healthy volunteers under nonfasting conditions. The ABT-378 levels achieved should be highly suppressive for HIV patients (11).

Maculopapular eruption and fever were reported in 2 HIV-infected patients on day 2 of ritonavir treatment, demonstrating that the drug induces adverse cutaneous reactions (12).

A pharmacokinetic study of multiple oral doses of ritonavir (500 mg q12h x 10 days) administered in combination with oral ketoconazole (200 mg/day x 7 days) in 12 healthy volunteers showed that no dosage adjustment of ritonavir is necessary, although high-dose ketoconazole should be used with caution during coadministration. Adverse events were nausea, vomiting, circumoral paresthesia and vasodilatation (13).

In a phase I/II study in 48 HIV-infected children between 6 months and 18 years of age, oral ritonavir (250, 300, 350 and 400 mg/m^2 q12h) had potent antiretroviral activity when administered alone and was relatively well tolerated when administered alone or in combination with zidovudine or didanosine (14).

The safety and clinical efficacy of ritonavir was demonstrated in 1090 HIV-infected patients with baseline CD4 lymphocyte counts of 100/µl or less. Patients were randomized to twice-daily treatment with oral ritonavir (600 mg) or placebo, while continuing on treatment with up to two marketed nucleosides. Open-label ritonavir was given to any patient manifesting an AIDS-defining event following 16 weeks of double-blind treatment. In this large study, which involved subjects who are considered to be representative of many HIV-infected patients with advanced disease, ritonavir reduced the risk of AIDS complications and prolonged survival as compared to placebo. However, significantly more patients on ritonavir discontinued treatment due to drug-related adverse effects, which may have influenced the final outcome. At 51 weeks, 87 patients in the ritonavir group had died of any cause *versus* 126 in the placebo group. This data appears to indicate that in patients with advanced HIV disease and extensive prior treatment with antiretroviral drugs, ritonavir is safe and effective in prolonging survival and lowering the risk of AIDS complications (15).

A review describing the details of the discovery and preclinical development of ritonavir has recently been published (16).

1. Hsu, A., Granneman, G.R., Witt, G. et al. *Multiple-dose pharmacokinetics of ritonavir in human immunodeficiency virus-infected subjects.* Antimicrob Agents Chemother 1997, 41(5): 898.

2. Barry, M., Merry, C., Mulcahy, F., Heavey, J., Tjia, J., Gibbons, S., Back, D. *Saquinavir pharmacokinetics alone and in combination with ritonavir.* Brit J Clin Pharmacol 1997, 43(5): 531P.

3. Hellinger, J., Canniff, J., Jackson-Pope, L., Cohen, C. *A retrospective evaluation of the plasma HIV-RNA and CD4 cell response to the addition of saquinavir to ritonavir-nucleoside therapy.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst I-80.

4. Lal, R., Hsu, A., Chen, P., Dennis, S., El-Shourbagy, T., Locke, C., Lam, W., Japour, A., Leonard, J., Granneman, G.R., Sun, E. *Single dose pharmacokinetics of ABT-378 in combination with ritonavir.* 37th Intersci Conf Antimicrob Agents Chemother (Sept 28-Oct 1, Toronto) 1997, Abst I-194.

5. Sleasman, J., Goodenow, M., Nelson, R., Wilfert, D., Hutson, A., Heath-Chiozzi, M., Pizzo, P., Mueller, B. *Reconstitution of memory (CD450RO) and naive (CD450RA) CD4$^+$ T cells following ritonavir therapy in HIV-infected children with advanced disease.* 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 158.

6. Pelton, S.I., Yogev, R., Johnson, D. *Changes in viral load and immunologic markers in children treated with triple therapy including ritonavir.* 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 234.

7. Hsu, A., Cameron, D.W., Valdes, J., Garber, G., Seguin, I., Carothers, L., Dennis, S., Granneman, R., Sun, E. *Ritonavir pharmacokinetics in HIV-infected patients underlying hepatic disease.* 5th Conf Retroviruse Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 359.

8. Febo, I., Chantry, C., Lugo, L. *Use of ritonavir in combination with nucleoside reverse transcriptase inhibitor agents in children and adolescents with perinatally acquired HIV infection.* 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 366.

9. Arribas, J.R., Gonzalez-Garcia, J., Ibañez, C., Ruiz, B., Peña, J.M., Esteban, C., Frias, J., Vazquez, J.J. *Acute hepatitis in AIDS patients during ritonavir treatment.* 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 417.

10. Arribas, J.R., Hernadez-Albujar, S., Gonzalez-Garcia, J., Gonzalez, A., Cañedo, T., Peña, J.M., Vazquez, J.J., Powderly, W.G. *Prospective study of oral Candida colonization in advanced AIDS patients treated with ritonavir.* 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 485.

11. Lal, R., Hsu, A., Granneman, G.R., El-Shourbagy, T., Johnson, M., Lam, W., Manning, L., Japour, A., Sun, E. *Multiple dose safety, tolerability and pharmacokinetics of ABT-378 in combination with ritonavir.* 5th Conf Retroviruses Opportunistic Infect (Feb 1-5, Chicago) 1998, Abst 647.

12. Bachmeyer, C., Blum, L., Cordier, F., Launay, E., Danne,O., Aractingi, S., Mougeot Martin, M. *Early ritonavir-induced maculopapular eruption.* Dermatology 1997, 195(3): 301.

13. Bertz, R., Wong, C., CArothers, L., Lauva, I., Dennis, S., Valdes, J. *Evaluation of the pharmacokinetics of multiple dose ritonavir and ketoconazole in combination.* Clin Pharmacol Ther 1998, 63(2): Abst PIII-94.

14. Mueller, B.U., Nelson, R.P., Sleasman, J. et al. *A phase I/II study of the protease inhibitor ritonavir in children with human immunodeficiency virus infection.* Pediatrics 1998, 101(3): 335.

15. Cameron, R.W., Heath-Chiozzi, M., Danner, S. et al. *Randomised placebo-controlled trial of ritonavir in advanced HIV-1 disease*. Lancet 1998, 351(9102): 543.

16. Kempf, D.J., Sham, H.L., Marsh, K.C. et al. *Discovery of ritonavir, a potent inhibitor of HIV protease with high oral bioavailability and clinical efficacy.* J Med Chem 1998, 41(4): 602.

Original monograph – Drugs Fut 1996, 21: 700.

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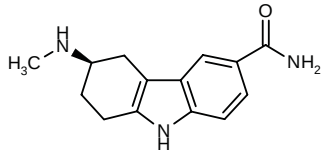

$C_{14}H_{17}N_3O$ **SmithKline Beecham; Vanguard Medica**

Vanguard Medica and SmithKline Beecham have terminated their collaboration for frovatriptan as a result of SmithKline Beecham's decision not to commit the level of resources needed to commercialize the product. Under the terms of the original agreement, Vanguard now has an exclusive worldwide license to commercialize frovatriptan in return for a royalty to SmithKline Beecham on net sales. Vanguard will be free to negotiate commercial terms with a new partner or partners (1).

1. *Vanguard Medica and SmithKline Beecham terminate frovatriptan collaboration.* Prous Science Daily Essentials May 20, 1998.

Original monograph – Drugs Fut 1997, 22: 725.

Additional Reference

Parsons, A.A. et al. *Comparison of the cardiovascular effects of the novel 5-HT$_{1B/1D}$ receptor agonist, SB 209509 (VML251), and sumatriptan in dogs.* J Cardiovasc Pharmacol 1997, 30(1): 136.

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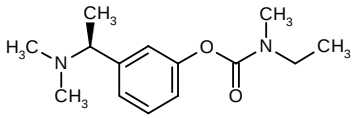

$C_{14}H_{22}N_2O_2$ **Novartis**

The neuroprotective effects of ENA-713 treatment (1, 2 or 5 mg/kg) on brain injury in rats were examined in a study in young and aged animals 2 h following closed head injury. A 40-85% dose-dependent inhibition of acetylcholine(ACh) was observed and significantly decreased motor and neurological deficits and a faster recovery was noted in treated aged rats. A 50% decrease in edema (24 h postinjury) and disruption of the blood-brain barrier (4 h after injury) was observed in aged rats treated with 2 and 5 mg/kg. Results suggest that the neuroprotective actions of ENA-713 are due to the suppression of cholinergic activity in the brain (1).

The neuroprotective effects of rivastigmine were studied in a murine model of closed-head injury. Rivastigmine 2 mg/kg s.c. given 5 min following severe injury to the left hemisphere reduced brain edema by at least 50% at 24 h and accelerated recovery of motor function at 7 and 14 days postinjury. The compound also reversed the impairment in spatial memory in a Morris water maze by day 3. These effects could be completely antagonized by concomitant scopolamine or mecamylamine, indicating that the ameliorating effects of rivastigmine on both immediate and long-term sequelae of brain injury are mediated by enhanced cholinergic activity at both muscarinic and nicotinic receptors (2).

An *in vivo* study in which young and aged rats were administered SDZ-ENA-713 (0.1 or 0.2 mg/kg) examined the ameliorating effects of treatment on age-related learning deficits and cholinergic dysfunction. Spatial learning was significantly increased in aged rats receiving 0.2 mg/kg SDZ- ENA -13 and both doses inhibited frontal cortex choline acetyltransferase activity (3).

A randomized, open-label, dose-escalation study in 82 patients with Alzheimer's disease investigated the efficacy of 4 antiemetic treatments against nausea and vomiting caused by SDZ-ENA-713 (3-12 mg/day). Treatment prevented symptoms in 33, 50, 89 and 90% of patients administered glycopyrrolate (1 mg), ondansetron (4 mg), trimethobenzamide (250 mg) or trihexyphenidyl (2 mg) for 4 weeks, respectively, indicating central mediation of the adverse effects of SNZ-ENA-713 (4).

Rivastigmine is the new proposed nonproprietary name for SDZ-ENA-713 (5).

Novartis has received approval from the European Commission to market rivastigmine (Exelon®) as a treatment for mild to moderately severe Alzheimer's disease (6).

Novartis has launched rivastigmine (Exelon®) in the U.K. for the treatment of Alzheimer's disease (7).

Rivastigmine (Exelon®) has been launched by Novartis in Switzerland for the treatment of mild to moderate Alzheimer's disease. It is supplied as capsules, 1.0, 1.5, 3.0, 4.5 and 6.0 mg (8).

1. Chen, Y., Shohami, E., Bass, R., Weinstock, M. *Cerebro-protective effects of ENA713, a novel acetylcholinesterase inhibitor, in closed head injury in the rat.* Brain Res 1998, 784(1-2): 18.

2. Chen, Y., Shohami, E., Constantini, S., Weinstock, M. *Rivastigmine, a brain-selective acetylcholinesterase inhibitor, ameliorates cognitive and motor deficits induced by closed-head injury in the mouse.* J Neurotrauma 1998, 15(4): 231.

3. Ohara, T., Fukaya, H., Tanaka, K., Seno, N. *Ameliorating effects of SDZ ENA 713 on age-associated decreases in learning performance and brain choline acetyltransferase activity in rats.* Brain Res Bull 1997,43(1): 39.

4. Cutler, N.R., Anand, R., Hartman, R.D., Messina, J.C. Jr., Jhee, S.S. *Antiemetic therapy for Alzheimer's patients receiving the cholinesterase inhibitor SDZ ENA 713.* Clin Pharmacol Ther 1998, 63(2): Abst PII-62.

5. *Proposed international nonproprietary names (Prop. INN): List 77.* WHO Drug Inform 1997, 11(2): 99.

6. *European Commission approves Novartis' Exelon.* Prous Science Daily Essentials May 18, 1998.

7. *Alzheimer's disease treatment launched in U.K.* Prous Science Daily Essentials June 1, 1998.

8. *New product intros.* Drugs News Pespect 1997, 10(7): 416.

Original monograph – Drugs Fut 1994, 19: 656.

Additional References

Imminent launch of Novartis' Alzheimer's disease therapy. Prous Science Daily Essentials August 12, 1997.

Ciszewska, G. et al. *Synthesis of tritium, deuterium, and carbon-14 labeled (S)-N-ethyl-N-methyl-3-[1(dimethylamino)ethyl]carbamic acid,phenyl ester, (L)-2,3-dihydroxybutanedioic acid salt (SDZ ENA 713 hta), an investigational drug for the treatment of Alzheimer's disease.* J Label Compound Radiopharm 1997, 39(8): 651.

Novartis launches Exelon. Prous Science Daily Essentials September 11, 1997.

Anand, R. *Global development of Exelon™ in the absence of international harmonized anti-dementia drugs development guidelines.* IBC Conf Alzheimer's Dis. Exploiting Mech Drug Dev Diagn (May 1-2, San Francisco) 1997.

Rizatriptan Benzoate
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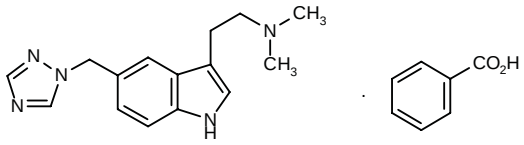


$C_{15}H_{19}N_5.C_7H_6O_2$

Merck & Co.

The *in vitro* pharmacological profile of rizatriptan has been reported. The compound displayed high and selective affinity for human cloned 5-HT$_{1D}$ and 5-HT$_{1B}$ receptors *versus* other receptors and ion channel binding sites. Full agonist activity at these receptors was demonstrated in functional assays. Only one minor metabolite of rizatriptan displayed activity similar to the parent compound in binding (1).

To evaluate the potential for coronary side effects of the 5-HT$_{1B/1D}$ receptor agonists rizatriptan and sumatriptan, their contractile effects on human isolated middle meningeal and coronary arteries have been assessed and compared. Both compounds showed a 10-fold greater selectivity for cranial vessels over coronary artery. The maximal contraction in the middle meningeal artery was significantly greater for rizatriptan compared to sumatriptan, whereas the maximal contraction in coronary artery was significantly lower for rizatriptan than for sumatriptan. These results suggest that rizatriptan has greater selectivity than sumatriptan for cranial vessels (2).

A 3 mg/kg i.v. dose of rizatriptan in anesthetized rats was shown to inhibit the action potential induced by electrical stimulation of the dura mater by up to 63%, as evaluated by extracellular recording of single neurons in the trigeminal nucleus caudalis (3).

In anesthetized rats, rizatriptan significantly reduced the electrically stimulated dural vasodilation, while increases in dural vessel diameter produced by substance P or calcitonin-gene related peptide were unaffected. Dural plasma protein extravasation was also significantly reduced (4).

Evaluation of the sympatholytic potential of rizatriptan (10 or 15 mg p.o.) in a double-blind, randomized trial in 10 healthy male subjects demonstrated that the drug had no effect on forearm blood flow during lower body negative pressure maneuvers. Effects on the responses to cold pressor test or the mid-frequency component of resting heart rate variability were also absent (5).

The therapeutic effects of rizatriptan (2.5, 5 or 10 mg) on quality of life during an acute migraine attack were evaluated in 247 patients. Drug doses of 5 and 10 mg were significantly more effective than placebo in relieving pain and improving functional disability. The 10-mg dose significantly improved social functioning, migraine symptoms and feelings/concerns as compard to placebo (6).

Results of a study evaluating the dose proportionality of rizatriptan in 8 healthy females administered doses of 0.5, 1.0, 2.5 and 5.0 mg i.v. yielded mean $AUC_{(0-\infty)}$ values of 9, 19, 49 and 105 ng/h/ml, respectively, with mean plasma clearance values of 941, 900, 859 and 797 ml/min, respectively. Half-lives and apparent volumes of distribution were 1.5-2.2 h and 91-106 l, respectively. It appears that in healthy females, rizatriptan produces slightly nonlinear pharmacokinetics at doses above 2.5 mg (7).

Oral rizatriptan administered to 12 male and 12 female subjects at doses of 2.5, 5, 10 and 15 mg produced mean AUCs of 16, 33, 72 and 127 ng/h/ml in males and 19, 42, 97 and 161 ngúh/ml in females. The higher plasma concentrations in females than in males resulted in lower plasma clearance (821ml/min *vs.* 1042 ml/min). Mean t_{max} and $t_{1/2}$ were similar in both sexes, as was oral availability (40-45%) within the linear dose range (8).

In a double-blind, placebo-controlled crossover trial in 20 patients with controlled hypertension, rizatriptan 10 mg produced no appreciable difference in pressor response from that observed in healthy subjects, indicating that the drug can be safely used in the treatment of hypertension (9).

Interactions between rizatriptan (10 mg on day 14) and paroxetine (20 mg/day) were evaluated in a placebo-controlled, crossover trial in 12 healthy subjects. Plasma concentrations of rizatriptan and its active metabolite, *N*-monodesmethyl rizatriptan, were unaffected by coadministration of paroxetine. Clinically, the combination was well tolerated; the frequency of adverse events and

changes in blood pressure, heart rate and temperature did not differ between drug and placebo groups (10).

Evaluation of rizatriptan 5 mg p.o. in 10 patients with mild to moderate hepatic insufficiency due to alcoholic cirrhosis showed that pharmacokinetic differences were minor between this group of patients and healthy young subjects. Results indicate that dose adjustment of rizatriptan is not required in patients with mild hepatic insufficiency (11).

Preliminary results from a multicenter, placebo-controlled, double-blind study in 1538 patients with moderate or severe migraine showed that rizatriptan (5 and 10 mg) was as well tolerated as sumatriptan (25 and 50 mg) and had an excellent efficacy profile at both doses. No serious drug-related adverse events were reported (12).

The effects of rizatriptan (5 and 10 mg) and sumatriptan (100 mg) on nausea, photophobia and phonophobia were compared in 1095 migraine patients. In patients with nausea at baseline, both doses of rizatriptan were more effective than sumatriptan in providing relief of nausea and other migraine-associated symptoms. Furthermore, sumatriptan induced nausea in significantly more patients than either dose of rizatriptan (13).

The FDA has cleared for marketing Merck & Co.'s Maxalt® (rizatriptan benzoate), for the acute treatment of migraine attacks with or without aura in adults. The product is available as tablets and orally disintegrating tablets of 5 and 10 mg, corresponding to 7.265 and 14.53 mg of the benzoate salt, respectively. Maxalt® has also been approved by regulatory authorities in Mexico and The Netherlands (14).

1. Beer, M., Middlemiss, D., Stanton, J., Heald, M., Handford, E., Stagg, A., Street, L., Hargreaves, R., Ragan, I. *An in vitro pharmacological profile of rizatriptan.* Cephalalgia 1997, 17(3): 390.

2. Longmore, J., Razzaque, Z., Hargreaves, R., Schofield, W., Pickard, J., Boulanger, C., Brown, M., Ferro, A., Taylor, A., Hill, R.G. *Rizatriptan selectively contracts human middle meningeal over coronary artery: Comparison with sumatriptan*. Cephalalgia 1997, 17(3): 388.

3. Cumberbatch, M.J., Hill, R.G., Hargreaves, R.J. *Rizatriptan has central antinociceptive effects against durally evoked responses.* Eur J Pharmacol 1997, 328(1): 37.

4. Williamson, D.J., Shepheard, S.L., Hill, R.G., Hargreaves, R.J. *The novel anti-migraine agent rizatriptan inhibits neurogenic dural vasodilation and extravasation.* Eur J Pharmacol 1997, 328(1): 61.

5. Sciberras, D.G., Majmudar, N., Bowman, A.J., Massey, A.,Bradstreet, T., Clayton, R., Reed, J., Shadle, C., Goldberg,M.R., Ford, G.A. *A study of the effects of MK-462 (rizatriptan), clonidine and sumatriptan on autonomic function.* Brit J Clin Pharmacol 1997, 43(5): 535P.

6.Santanello, N.C., Polis, A.B., Hartmaier, S.L., Kramer, M.S., Block, G.A., Silberstein, S.D. *Improvement in migraine-specific quality of life in a clinical trial of rizatriptan.* Cephalalgia 1997, 17(8): 867.

7. Rogers, J.D., Lee, Y., Goldberg, M.R., Ermlich, S., Brucker, M.J., McLoughlin, D.A., Olah, T.V. *Pharmacokinetics (PK) of intravenous (IV) rizatriptan (R) in healthy females.* Clin Pharmacol Ther 1998, 63(2): Abst PI-22.

8. Lee, Y., Rogers, J.D., Mendel, C., Conroy, J.A., Stepanavage, M., McLoughlin, D.A., Olah, T.V. *Pharmacokinetics (PK) of oral rizatriptan (R) in healthy males and females.* Clin Pharmacol Ther 1998, 63(2): Abst PI-23.

9. Noveck, R.J., Bialy, G.P., Bradstreet, T.E., Gagliano, K.D., Goldberg, M.R. *Effects of rizatriptan on blood pressure in hypertensive patients.* Clin Pharmacol Ther 1998, 63(2): Abst PII-48.

10. Goldberg, M.R., Lowry, R., Musson, D.G., Birk, K.L., Fisher, A., DePuy, M.E., Shadle, C.R. *Lack of pharmacokinetic and pharmacodynamic interaction between rizatriptan and paroxetine.* Clin Pharmacol Ther 1998, 63(2): Abst PII-54.

11. Goldberg, M.R., Lee, Y., Panebianco, D., Noveck, R.J., Brucker, M.J., McLoughlin, D.A., Olah, T.V., Shadle, C.R. *Pharmacokinetics of rizatriptan in patients with mild-moderate hepatic insufficiency.* Clin Pharmacol Ther 1998, 63(2): Abst PII-55.

12. Norman, B.A., Block, G.A., Jiang, K. et al. *Two-period crossover comparison of rizatriptan 5 mg and 10 mg to sumatriptan 25 mg and 50 mg for the acute treatment of migraine.* 50th Annu Meet Amer Assoc Neurol (April 25-May 2, Minneapolis) 1998, Abst S46.005.

13. Visser, W.H., Jiang, K. *Effect of rizatriptan versus sumatriptan on migraine associated symptoms.* 50th Annu Meet Amer Assoc Neurol (April 25-May 2, Minneapolis) 1998, Abst P06.001.

14. *U.S. approval for Maxalt.* Prous Science Daily Essentials July 2, 1998.

Original monograph – Drugs Fut 1995, 70: 676.

Additional References

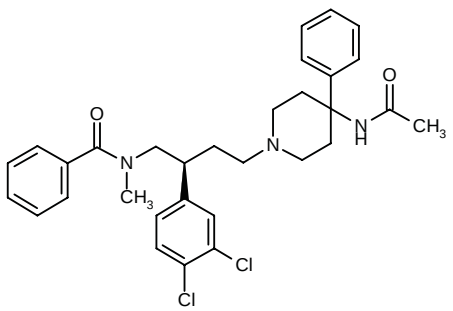
Valentin, J.P. et al. *Modulation by the endothelium of contractile responses evoked by 5-HT$_{1B/D}$ receptor agonists in the rabbit isolated saphenous vein.* Brit J Pharmacol 1997, 122(Suppl.): Abst 206P.

Pagniez, F. et al. *Analysis of the haemodynamic effects of 5-HT$_{1B/D}$ receptor agonists in the rat.* Brit J Pharmacol 1997, 122(Suppl.): Abst 244P.

Saredutant
SR-48968

Antiinflammatory
Tachykinin Antagonist

EN: 183412



$C_{31}H_{35}Cl_2N_3O_2$

Sanofi

In TNBS-induced colonic inflammation in rats, SR-48968 (5 mg/kg i.p.) reduced myeloperoxidase activity by 20% and colonic mucosal injury by 58%, compared with vehicle. Moreover, the TNBS-induced increase in gut permeability was suppressed by SR-48968 (1).

Results from a study of the antitussive activity and site of action of SR-48968 in cats and guinea pigs have shown that the compound dose-dependently inhibited cough in both species by a central site of action. In the cat, the antitussive action appeared to be solely by a central site (2).

1. Mazelin, L., Theodorou, V., Fioramonti, J., Bueno, L. *Involvement of NK_1 and NK_2 receptors in inflammatory reaction during experimental colitis in rats.* Dig Dis Week (May 10-16, Washington DC) 1997, Abst 4447.

2. Bolser, D.C., DeGennaro, F.C., O'Reilly, S., McLeod, R.L., Hey, J.A. *Central antitussive activity of the NK_1 and NK_2 tachykinin receptor antagonists, CP-99,994 and SR 48968, in the guinea-pig and cat.* Brit J Pharmacol 1997, 121(2): 165.

Original monograph – Drugs Fut (Rev Art) 1995, 20: 701.

Additional References

Snider, R.M., Lowe, J.A. III. *Nonpeptide substance P and other tachykinin receptor, antagonists as a novel pharmacologic and therapeutic class.* Biol Psychiatry 1997, 42(1, Suppl.): Abst 96-3.

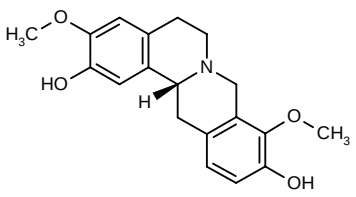
Ricciardolo, F.L.M. et al. *Differential activation of the epithelial and smooth muscle NK_1 receptors by synthetic tachykinin agonists in guinea-pig trachea.* Annu Cong Eur Respir Soc (Sept 20-24, Berlin) 1997, Abst P2574.

Steinberg, R. et al. *NK_2 receptor antagonists SR 48968 and SR 144190 reveal that endogenous NKA/SP modulates striatal and septo-hippocampal cholinergic neurotransmission.* Int Tachykinin Conf: Tachikinins Health Dis (Sept 7-11, Cairns) 1997, 50.

l-Stepholidine

Analgesic
Antidyskinetic

EN: 121569



$C_{19}H_{21}NO_4$ **Yunnan Inst. Drug Control; Shanghai Inst. Materia Med.**

In studies on cultured bovine aortic smooth muscle cells, stepholidine had no effect on resting Ca^{2+}_i but did inhibit KCl-induced elevation of Ca^{2+}_i in a dose-dependent manner (1).

Results from studies using rat striatal synaptosomes demonstrated that stepholidine enhanced potassium depolarization-induced activation of tyrosine 3-monooxygenase, but had no effect on protein kinase activation (2).

Stepholidine was shown to induce differentiation of laryngeal and nasopharyngeal carcinoma cell lines by inhibiting oncogene expression and improving carcinoma suppressor gene expression (3).

1. Li, X.T., Wang, Y.L. *Effects of stepholidine on cytosolic free calcium in cultured bovine aortic smooth muscle cells.* Chin Pharmacol Bull 1997, 13(4): 358.

2. Hu, G., Wu, Y.M., Jin, G.Z. *(–)-Stepholidine enhances K^+ depolarization-induced activation of synaptosomal tyrosine 3-monooxygenase from rat striatum.* Acta Pharmacol Sin 1997, 18(1): 49.

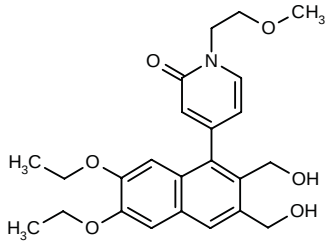
3. Wang, J., Zhao, L.S., Lin, D.C., Tang, H., Liang, C.Y., Liu, C. *Study of stepholidine and retinoic acid induced differentiation of cell lines of laryngeal and nasopharyngeal carcinoma.* Acta Acad Med Militaris Tertiae 1997, 19(1): 7.

Original monograph – Drugs Fut 1991, 16: 624.

T-440

Antiasthmatic
Phosphodiesterase IV Inhibitor

EN: 237395



$C_{24}H_{29}NO_6$ **Tanabe Seiyaku**

In vitro, T-440 inhibited phosphodiesterase 4 activity in tissue preparations from guinea pigs (IC_{50} = 0.071 μM) and dogs (IC_{50} = 0.13 μM); the IC_{50}s for isozymes 1, 2, 3 and 5 were > 20 μM. In anesthetized dogs, the compound blocked histamine-induced bronchoconstriction (ED_{50} = of 0.029 mg/kg) and increased left ventricular pressure (ED_{50} = 3.6 mg/kg),indicating potent and selective bronchial antispasmogenic effects (1).

In an *in vitro* study, T-440 suppressed cAMP-phosphodiesterase activities in cytosolic and membrane fractions of Jurkat cells. PGE_2 and forskolin elevated intracellular cAMP concentrations, whereas T-440 did not. However, the PGE_2-induced elevation of cAMP was significantly augmented by T-440 (2).

The potent activity of T-440 has been demonstrated in a series of *in vitro* studies. The compound was several times more potent than rolipram in inhibiting PDE IV extracted from isolated human bronchial smooth muscle (IC_{50} = 0.08 and 2.0 μM, respectively). The activity of T-440 in reversing aminophylline-induced contractions was similar to that of aminophylline; both compounds also significantly reversed acetylcholine-induced contractions in isolated bronchial smooth muscle, although in this case the activity of T-440 was weaker than in the model of his-

tamine-induced contractions. In passively sensitized bronchi, T-440 significantly reversed allergen-induced contractions with more potent activity than aminophylline. Pretreatment with either aminophylline or T-440 prevented allergen-induced bronchial contractions, indicating that the PDE IV inhibitor inhibits the release of chemical mediators, most likely from bronchial mast cells, in the allergic response (3).

1. Yamagata, S., Wada, K., Sugaya, T., Oka, K., Kaminuma, O., Kikkawa, H., Ikezawa, K. *Bronchial anti-spasmogenic effects and selectivity of T-440, phosphodiesterase type 4 inhibitor, in the dog.* Biol Pharm Bull 1997, 20(12): 1261.

2. Kaminuma, O., Mori, A., Wada, K., Kikkawa, H., Ikezawa, K., Suko, M., Okudaira, H. *A selective type 4 phosphodiesterase inhibitor, T-440, modulates intracellular cyclic AMP level and interleukin-2 production of Jurkat cells.* Immunopharmacology 1998, 38(3): 247.

3. Fujii, K., Kohrogi, H., Iwagoe, H., Hamamoto, J., Hirata, N., Goto, E., Kawano, O., Wada, K., Yamagata, S., Ando, M. *Novel phosphodiesterase 4 inhibitor T-440 reverses and prevents human bronchial contraction induced by allergen.* J Pharmacol Exp Ther 1998, 284(1): 162.

Original monograph – Drugs Fut 1997, 22: 729.

Thrombopoietin *Treatment of Thrombocytopenia*

EN: 213238

Genentech; Novo Nordisk; Zymogenetics; Amgen; Kirin Brewery; Pharmacia & Upjohn

Results of *in vitro* studies have shown that TPO in the presence of IL-3 and Flt3 produced a 10-fold increase in progenitor cells in an expansion culture of 20% cord blood donation in comparison to an untreated donation (1).

In experiments using serum-free cell cultures, thrombopoietin was found to have very little direct stimulatory effect on erythroid progenitor cells, although it did indirectly enhance erythropoiesis by preventing erythroid progenitor cells from undergoing apoptosis (2).

Results of experimental studies using serum-free cultures indicated that thrombopoietin alone stimulated the early proliferation and survival of human erythroid, myeloid and multipotential progenitors (3).

Studies using lineage-negative, Sca-1+, c-kit+ marrow cells from 5-FU-treated mice demonstrated that thrombopoietin alone and the combination of interleukin-6 and FLT3/FLK-2 ligand promoted the survival of hematopoietic long-term reconstituting cells without stimulating their active cell proliferation (4).

Stimulation of TF-1/TPO cells with thrombopoietin resulted in tyrosine phosphorylation of the common beta-subunit of GM-CSF/IL-3 receptor complex as well as the TPO receptor (5).

In vitro studies have shown that thrombopoietin induces a cytokine inducible SH2-containing protein, CIS, which binds to the activated thrombopoietin receptor, Mpl. These results indicate that CIS may regulate the proliferation and differentiation of hematopoietic cells via its function as a signaling component (6).

In vitro studies on myelodysplastic bone marrow progenitor cells have shown that megakaryocyte growth and development factor behaves as a pleiotropic cytokine by expanding megakaryocytic, erythroid and myeloid compartment in normal subjects and in patients with myelodysplastic syndrome (7).

Results of *in vivo* studies in mice following carboplatin/irradiation-induced myelosuppression have demonstrated that thrombopoietin and IL-11 synergize to stimulate megakaryocytopoiesis and thrombopoiesis, thus preventing severe thrombocytopenia (8).

The tolerance and biological effects of rhTPO monotherapy and combination therapy with carboplatin were evaluated in a phase I-II study in 22 patients with gynecologic malignancy. Patients received a single dose (0.6, 1.2, 2.4 or 3.6 mcg/kg s.c.) prior to carboplatin administration and 4 doses following a second cycle of carboplatin in the dose-escalation phase, and an optimal biological dose of rhTPO as a secondary prophylaxis for severe thrombocytopenia in the dose-expansion phase. rhTPO administered prior to carboplatin increased platelet count and bone marrow karyocytes and erythroid elements; in patients receiving rhTPO at optimal biological dose, transfusion was not required in 71% of the subjects (9).

Results from a study in patients with responding metastatic and high-risk primary breast cancer indicated that treatment with recombinant human thrombopoietin (0.6, 1.2 or 2.4 mg/kg i.v.) followed by G-CSF (5 mg/kg b.i.d. s.c.) may improve both mobilization of peripheral blood progenitor cells and hematologic recovery (10).

In a phase I trial in 8 patients with advanced breast cancer, treatment with recombinant human thrombopoietin (0.6-2.4 μg/kg i.v.) and G-CSF (6 μg/kg q12h) appeared to be well tolerated and enhanced the mobilization of peripheral blood progenitor cells for autologous transplantation. No major drug-related toxicity was observed (11).

The preliminary results of a multicenter, open-label, phase I/II trial in patients with stage III/IV breast cancer indicated that recombinant human thrombopoietin (0.3, 0.6, 1.2 or 2.4 μg/kg i.v.) was safe and potentially active in reducing the time to platelet transfusion indepencence following autologous bone marrow transplant (12).

Results from a study in 8 children with hepatoblastoma suggested that hepatoblastoma cells could produce considerable levels of thrombopoietin and might utilize this substance as in paracrine/autocrine system (13).

An overview of preclinical and clinical data for rHuMGDF has shown that administration of the com-

pound in normal mice produces a dose-dependent increase in platelet count within 1 week after administration, without affecting other cell lineages. In murine models of myelosuppression, it ameliorates the decrease and duration of platelet count reduction. Administration of rHuMGDF prior to chemotherapy in patients with solid tumors induces a dose-dependent rise in platelet count similar to that observed in animal models. In addition, an increased proportion of megakaryocytes in the bone marrow is observed. Currently, studies are evaluating rHuMGDF following myelosuppressive chemotherapy in disorders such as acute myeloid leukemia, lymphoma, breast cancer and mixed solid tumors. So far, it appears to be well tolerated and shows biological activity during these trials (14).

Pharmacia & Upjohn and Genentech have signed an agreement providing exclusive worldwide rights to Pharmacia & Upjohn for Genentech's thrombopoietin (15).

1. Denning-Kendall, P.A., Chapman, M., Bradley, B., Hows, J. *Effect of Flt-3 ligand and thrombopoietin on in-vitro expansion of cord blood hemopoietic cells.* Blood 1997, 90(10, Suppl. 1, Part 2): Abst 4281.

2. Ratajczak, M.Z., Ratajczak, J., Marlicz, W., Pletcher, C.H., Machalinski, B., Moore, J., Hung, H.L., Gewirtz, A.M. *Recombinant human thrombopoietin (TPO) stimulates erythropoiesis by inhibiting erythroid progenitor cell apoptosis.* Brit J Haematol 1997, 98(1): 8.

3. Yoshida, M., Tsuji, K., Ebihara, Y., Muraoka, K., Tanaka, R., Miyazaki, H., Nakahata, T. *Thrombopoietin alone stimulates the early proliferation and survival of human erythroid, myeloid and multipotential progenitors in serum-free culture*. Brit J Haematol 1997, 98(2): 254.

4. Matsunaga, T., Kato, T., Miyazaki, H., Ogawa, M. *Thrombopoietin (TPO) promotes the survival of murine hematopoietic long-term reconstituting cells: Comparison with the effects of FLT3/FLK-2 ligand (FL) and interleukin-6 (IL-6).* Blood 1997, 90(10, Suppl. 1, Part 1): Abst 717.

5. Ooi, J., Tojo, A., Oka, Y., Asano, S. *Thrombopoietin induces tyrosine phosphorylation of a common β subunit of GM-CSF receptor and its association with Stat5 in TF-1/TPO cells.* Blood 1997, 90(10, Suppl. 1, Part 1): Abst 731.

6. Okabe, S., Tauchi, T., Ohyashiki, K., Morita, H., *Ohashi, H., Yoshimura, A., Toyama, K. Thrombopoietin induces a cytokine inducible SH2 protein, CIS, that binds to activated MPL.* Blood 1997, 90(10, Suppl. 1, Part 1): Abst 732.

7. Sarina, B., Cortelezzi, A., Cristiani, S., Cattaneo, C.,Silvestris, I., Carrabba, M., Della Volpe, A., Maiolo, A.T. *In vitro effect of c-mpl ligand on normal and myelodysplastic hemopoiesis.* Blood 1997, 90(10, Suppl. 1, Part 1): Abst 897.

8. Collins, M., Quinto, C., Goldman, S.J. *rhIL-11 and thrombopoietin synergize to improve platelet recovery in mice treated with a combined modality regimen of carboplatin and irradiation.* Blood 1997, 90(10, Suppl. 1, Part 1): Abst 758.

9. Vadhan-Raj, S., Verschraegen, C., McGarry, L. et al. *Recombinant human thrombopoietin (rhTPO) attenuates high-dose carboplatin (C)-induced thrombocytopenia in patients with gynecologic malignancy.* Blood 1997, 90(10,Suppl. 1, Part 1): Abst 2581.

10. Somlo, G., Doroshow, J.H., Jones, D. et al. *Recombinant human thrombopoietin (rhTPO) with G-CSF enhances mobilization of peripheral blood progenitor cells (PBPC).* Proc Amer Soc Clin Oncol 1997, 16: Abst 307.

11. Champlin, R., Korbling, M., Donato, M. et al. *Recombinant human thrombopoietin (rhTPO) for mobilization of peripheral blood progenitor cells (PBPC) for autologous transplantation in breast cancer: Preliminary results of a phase I trial.* Proc Amer Soc Clin Oncol 1997, 16: Abst 352.

12. Wolff, S., Lynch, J., Herzig, R., Ashby, M., Rose, D., Tremblay, T., Jones, D., Fay, J. *Safety and activity of recombinant human thrombopoietin (rhTPO) in patients (pts) receiving autologous bone marrow transplant (ABMT): Preliminary results of a phase I/II trial.* Proc Amer Soc Clin Oncol 1997, 16: Abst 382.

13. Naitoh-Komura, E., Matsumura, T., Sawada, T., Tamai, M.,Iehara, T., Arimoto-Suehiro, A., Kato, T., Tahara, T. *Thrombopoietin in patients with hepatoblastoma.* Proc Amer Soc Clin Oncol 1997, 16: Abst 401.

14. Barge, A.J. *Recombinant megakaryocyte growth and development factor - Biology and potential clinical applications.* Platelets 1997, 8(6): 446.

15. *Genentech licenses TPO to Pharmacia & Upjohn.* Prous Science Daily Essentials January 9, 1998.

Original monograph – Drugs Fut 1996, 21: 711.

Additional References

Stefanich, E. et al. *Metabolism of thrombopoietin (TPO) in vivo: Determination of the binding dynamics for TPO in mice.* Blood 1997, 89(11): 4063.

Akahori, H. et al. *The optimal administration protocol of rhTPO on thrombocytopenia in myelosuppressed mice.* Int J Hematol 1997, 65(Suppl. 1): Abst 578.

Kuwaki, T. et al. *Analysis of thrombopoietion (TPO) receptors on human platelets and megakaryocytic cells.* Int J Hematol 1997, 65(Suppl. 1): Abst 579.

Kirin's TPO enters phase II in several Asian countries. Prous Science Daily Essentials September 15, 1997.

Kubota, Y. et al. *Response of platelets from patients with myeloproliferative disorders of thrombopoietin.* 56th Annu Meet Jpn Soc Cancer Res (Sept 25-27, Kyoto) 1997, Abst WAP-030.

Tokunaga, Y. et al. *Effect of thrombopoietin on proliferation of CD7-positive blasts from acute myelogenous leukemia.* Blood 1997, 90(10, Suppl. 1, Part 1): Abst 298.

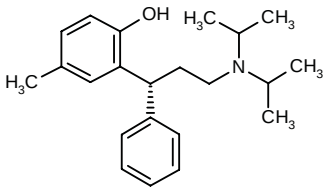
Maruyama, M. et al. *Ex vivo expansion of pro-megakaryocytes ($CD61^+$ cells) from $CD34^+$ cells in cord blood with a combination of SCF, TPO and Flt-3 ligand.* Blood 1997, 90(10, Suppl. 1, Part 1): Abst 2389.

Miyazaki, M. et al. *The relationship between carboplatin (CBDCA) AUC and serum thrombopoietin (TPO) kinetics in patients with lung cancer.* Proc Amer Soc Clin Oncol 1998, 17: Abst 874.

Tolterodine
PNU-200583
Detrusitol™
Detrol®

Agent for Urinary Incontinence
Muscarinic Receptor Antagonist

EN: 154881



$C_{22}H_{31}NO$ **Pharmacia & Upjohn**

The pharmacokinetics and pharmacodynamics of single oral (0.2-12.5 mg) and intravenous (0.64 and 1.28 mg) doses of tolterodine were evaluated in 17 healthy volunteers. Results revealed rapid absorption after oral administration and a highly variable absolute boavailability (10-70%). Values for steady-state volume of distribution and systemic clearance were 0.9-1.6 l/kg and 0.23-0.52 l/h/kg, respectively, resulting in a terminal half-life of 2-3 h. Tolterodine showed high first-pass metabolism and oxidation and dealkylation were identified as hepatic metabolic pathways. Urinary excretion accounted for less than 1% of the parent compound (1).

Results of a study in 9 evaluable psychiatric patients with symptoms of urinary incontinence demonstrated that the metabolism of oral tolterodine (2 mg b.i.d. for 3 days) was significantly inhibited during coadministration with fluoxetine (20 mg/day for 3 weeks) (2).

Results of a phase III randomized, double-blind, placebo-controlled study in 316 male and female patients with detrusor instability showed that tolterodine (1 and 2 mg b.i.d.) resulted in significantly greater decreases in number of micturitions and increases in voided volume/micturition as compared to placebo. The drug was safe and well tolerated, with a compliance rate of approximaely 90% (3).

In a randomized, double-blind, placebo-controlled study in 277 patients with unstable bladder, tolterodine (2 mg b.i.d.) significantly decreased the frequency of micturitions/24 h, was as effective as oxybutynin (5 mg t.i.d.) in reducing micturitions and incontinence episodes/24 h, and was significantly more effective than placebo in increasing mean volume voided. The tolerability profile of tolterodine was significantly better than that of oxybutynin, especially in regard to incidence of dry mouth (30% *vs.* 69% of patients) (4).

Results from a double-blind, placebo-controlled, dose-ranging study of tolterodine (0.5-4 mg b.i.d. for 2 weeks) in 64 patients with detrusor instability have indicated a good safety and efficacy profile for the drug. A dose of 1-2 mg twice daily appears to be the optimum dosage (5).

Tolterodine (Detrusitol®) has been introduced in Sweden by Pharmacia & Upjohn for the treatment of unstable bladder. The product is available as tablets of 1 and 2 mg (6-8).

Pharmacia & Upjohn's tolterodine tartrate tablets (Detrol®) have been approved by the FDA for the treatment of overactive bladder. Tolterodine tartrate is the first new medication approved by the FDA for a bladder control problem in more than 20 years (9).

1. Brynne, N., Stahl, M.M.S., Hallen, B., Edlund, P.O., Palmer, L., Hoglund, P., Gabrielsson, J. *Pharmacokinetics and pharmacodynamics of tolterodine in man: A new drug for the treatment of urinary bladder overactivity.* Int J Clin Pharmacol Ther 1997, 35(7): 287.

2. Brynne, N., Apéria, B., Aberg-Wistedt, A., Hallén, B., Bertilsson, L. *Inhibition of tolterodine metabolism by fluoxetine with minor change in antimuscarinic activity.* Eur J Clin Pharmacol 1997, 52(Suppl.): Abst 390.

3. Rosamilia, A., Dwyer, P.L., Clarke, B., Moore, K., Millard, R.P., Tuttle, J. *The clinical efficacy and safety of two doses of tolterodine in detrusor instability (DI).* Acta Obstet Gynecol Scand 1997, 76(Suppl. 167, 5): Abst FC811.3.

4. Drutz, H., Appell, R.A. *Clinical efficacy of tolterodine vs. oxybutynin and placebo in patients with unstable bladder.* Acta Obstet Gynecol Scand 1997, 76(Suppl. 167, 5): Abst FC811.4.

5. Rentzhog, L., Stanton, S.L., Cardozo, L., Nelson, E., Fall, M., Abrams, P. *Efficacy and safety of tolterodine in patients with detrusor instability: A dose-ranging study.* Brit J Urol 1998, 81(1): 42.

6. *Pharmacia & Upjohn's urinary incontinence treatment approved in Sweden.* Prous Science Daily Essentials September 9, 1997.

7. *First launch for Detrusitol.* Prous Science Daily Essentials November 21, 1997.

8. *New product intros.* Drug News Perspect 1997, 10(10): 621.

9. *Detrol approved by FDA for overactive bladder.* Prous Science Daily Essentials March 30, 1998.

Original monograph – Drugs Fut 1997, 22: 733.

Additional References

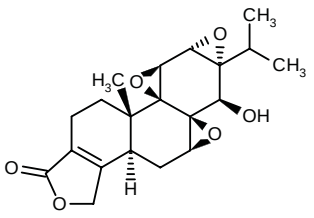
Gozzi, P., Pahlman, I. *Serum protein binding of tolterodine and its 5-hydroxymethyl metabolite in different species.* 6th Eur ISSX Meet (June 30-July 3, Gothenburg) 1997, Abst 227.

Nilvebrant, L. et al. *Antimuscarinic potency and bladder selectivity of PNU-200577, a major metabolite of tolterodine.* Pharmacol Toxicol 1997, 81(4): 169.

Triptolide

Immunosuppressant

EN: 090968



$C_{20}H_{24}O_6$ **Kunming Inst. (CN)**

The contraceptive potential of triptolide was evaluated in rats given oral doses of 50 or 100 μg/kg/day for 35 or

70 days. The higher dose produced sterility in all 6 animals during the second mating trial (days 63-70), while the lower dose produced intermediate results. The compound produced no detectable adverse effects on spermatogenesis and exerted its activity mainly on epididymal sperm (1).

1. Lue, Y.H., Hikin, A.P.S., Leung, A., Baravarian, S., Wang, C., Swerdloff, R.S. *Triptolide: A potential male contraceptive.* J Invest Med 1997, 45(1): 94A.

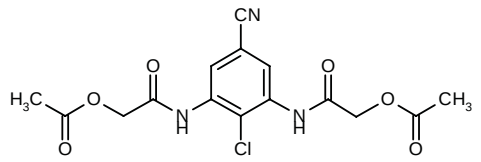
Original monograph – Drugs Fut 1985, 10: 575.

Additional Reference

Yang, J.W. et al. *Triptolide: A new immunosuppressant arresting homo T cells proliferation and inducing homo T lymphocytes apoptosis.* J Amer Soc Nephrol 1997, 8: Abst A3123.

TYB-2285 *Antiallergy*
Acreozast

EN: 153417



$C_{15}H_{14}ClN_3O_6$ **Toyobo**

In vitro studies have shown that TYB-2285 and its metabolites TC-286 and TC-326 dose-dependently inhibited antigen-induced lymphocyte proliferation and allogeneic mixed lymphocyte reaction. Unlike ciclosporin, TYB-2285 and its metabolites did not affect concanavalin A-induced lymphocyte proliferation (1).

Acreozast is the new proposed nonproprietary name for TYB-2285 (2).

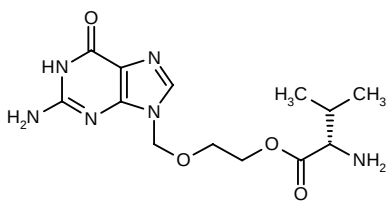
1. Tominaga, T., Watanabe, A., Tsuji, J., Koda, A., Nagai, H., Kumazawa, Y., Shimada, H. *The effects of TYB-2285 and its metabolites on lymphocyte response in vitro.* Gen Pharmacol 1997, 29(3): 473.

2. *Proposed international nonproprietary names (Prop. INN): List 77.* WHO Drug Inform 1997, 11(2): 87.

Original monograph – Drugs Fut 1995, 20: 686.

Valaciclovir *Antiviral*
Valtrex®

EN: 149658



$C_{13}H_{20}N_6O_4$ **Glaxo Wellcome; Hoechst; Theraplix**

The efficacy and safety of twice-daily valaciclovir and aciclovir given 5 times daily have been compared in a double-bind, randomized trial in which 739 immunocompetent patients with a history of recurrent genital herpes simplex virus (HSV) infection initiated therapy with valaciclovir (500 mg b.i.d.) or aciclovir (200 mg 5 times daily) upon the appearance of the first signs or symptoms of HSV recurrence. The treatments were found to be equivalent both clinically and microbiologically, and their safety profiles were also comparable, side effects being infrequent and generally mild. The results demonstrate that valaciclovir provides the clinical efficacy and safety of aciclovir for the treatment of HSV infection on a much more convenient dosing schedule (1).

Valaciclovir was shown to be safe and effective in reducing the incidence of CMV disease in allogeneic bone marrow transplant patients. In an international, double-blind, randomized clinical trial involving 746 patients, treatment with valaciclovir (2 g p.o. 4 times daily) was shown to reduce the incidence of CMV infection in both the blood and the urine by approximately 50% as compared to aciclovir (80 mg p.o. 4 times daily). The incidence of CMV disease was low in both valaciclovir- and aciclovir-treated patients (4.2% and 6.4%, respectively) due to the use of preemptive therapy, and survival was the same in both groups (2).

The safety and efficacy of valaciclovir for preventing cytomegalovirus (CMV) disease has been demonstrated in CMV-seronegative recipients of renal allografts obtained from seropositive donors. In a placebo-controlled, randomized, double-blind, multinational study enrolling 208 transplant recipients, treatment with valaciclovir (2 g p.o.) 4 times daily for 90 days beginning 72 h posttransplant was effective in preventing CMV disease; only 3 of 167 patients on valaciclovir developed CMV disease during the treatment period, in contrast to all 41 patients receiving placebo (3).

In a placebo-controlled, randomized, double-blind, multinational study in 208 cytomegalovirus-seronegative renal transplant recipients, treatment with valaciclovir (2 g p.o.) 4 times daily for 90 days beginning 72 h posttransplant was effective in preventing CMV disease; only 3 of 167 patients on valaciclovir developed CMV disease during the treatment period,in contrast to all 41 patients receiving placebo. Valaciclovir also prevented VZV and HSV disease, as well as other opportunistic infections such as *Candida spp.*, with good tolerability (4).

1. Bodsworth, N.J., Crooks, R.J., Borelli, S. et al. *Valaciclovir versus aciclovir in patient initiated treatment of recurrent genital herpes: A randomised, double blind clinical trial.* Genitourin Med 1997, 73(2): 110.

2. Ljungman, P., Camara, R., Milpied, N., Volin, L., Reilly, L., Crisp, A. *Valaciclovir reduces the incidence of cytomegalovirus infection in allogeneic bone marrow transplant patients.* 8th Int Cong Infect Dis (May 15-18, Boston) 1998, Abst 21.012.

3. Keating, M.R., Fauchald, P., Grant, D.M., Coggon, G.L., Lee, I.C. *Impact of valaciclovir for cytomegalovirus prophylaxis on*

medical resource use in renal allograft recipients. 8th Int Cong Infect Dis (May 15-18, Boston) 1998, Abst 21.013.

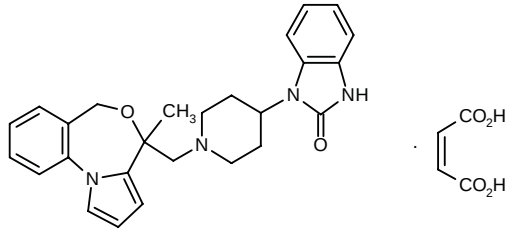
4. Keating, M.R., Kovarik, J., Salmela, K., First, M.R., Lee, I.C., Coggon, G.L., Crisp, A. *Valaciclovir reduces the incidence of cytomegalovirus (CMV) disease and other opportunistic infections in CMV-seronegative recipients of a seropositive cadaveric renal allograft.* 8th Int Cong Infect Dis (May 15-18, Boston) 1998, Abst 21.014.

Original monograph – Drugs Fut (Rev Art) 1993, 18: 619.

Zaldaride Maleate
CGS-9343B
Zy-17617B

Calmodulin Inhibitor
Antidiarrheal

EN: 135879



$C_{26}H_{28}N_4O_2.C_4H_4O_4$ **Novartis; Zyma; Kyowa Hakko**

In studies in rats, zaldaride maleate (3, 30 and 100 mg/kg p.o.) was as effective as loperamide in delaying the onset of diarrhea, but in contrast to loperamide, did not inhibit gastrointestinal propulsion (1).

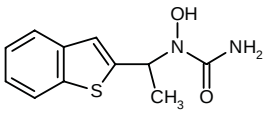
1. Aikawa, N., Karasawa, A. *Effects of KW-5617 (zaldaride maleate), a potent and selective calmodulin inhibitor, on secretory diarrhea and on gastrointestinal propulsion in rats.* Jpn J Pharmacol 1998, 76(2): 199.

Original monograph – Drugs Fut 1996, 21: 719.

Zileuton
Leutrol®
Zyflo®

Antiallergic/Antiasthmatic
5-Lipoxygenase Inhibitor

EN: 145060



$C_{11}H_{12}N_2O_2S$ **Abbott**

The effects of zileuton have been studied in a canine model of hypothermic intestinal organ ischemia-reperfusion (I/R) injury (transplant preservation injury). Results of the study indicated that the metabolism of arachidonic acid via the 5-LO pathway plays a significant role in the pathophysiology of hypothermic I/R injury to the intestine. In this respect, the use of a 5-LO inhibitor such as zileuton may impart favorable pharmacological and biological responses in intestinal injury, and should be considered in the clinical amelioration of intestinal transplant preservation injury (1).

Zileuton was found to be well tolerated in a clinical study in 5 healthy subjects and 25 patients with mild to severe renal failure. The pharmacokinetics were similar in all groups and only a small percentage of zileuton was eliminated (less than 0.5%) in those patients requiring hemodialysis, indicating that dosage of zileuton does not have to be adjusted in these patients (2).

Results from a randomized, crossover pharmacokinetic study, in which 12 healthy subjects received either a single (600 mg) dose of zileuton in the morning or evening or multiple doses (600 mg q.i.d. for 5 days), demonstrated that there was little or no diurnal variation in the pharmacokinetics of the drug (3).

In a double-blind, randomized, placebo-controlled study, the pharmacokinetic interaction of zileuton on terfenadine treatment was examined. Sixteen healthy subjects received terfenadine (60 mg every 12 h) on days 1-7 and zileuton or a placebo (600 mg every 6 h) on days 1 and 10. The combination of therapies was well tolerated with a minimal, clinically insignificant, effect of zileuton on terfenadine metabolism (4).

In a randomized, step-down study, 278 asthmatic patients showing improvements in FEV_1 after previous zileuton treatment (600 mg q.i.d. for 2 months), received either 600 or 800 mg (t.i.d); subsequently, frequency of dosing was further decreased to b.i.d. Results showed that zileuton treatment was well tolerated and FEV_1 values were 25-39% above pretreatment levels in all groups. β-Agonist treatment was significantly reduced (123.7%) in the group receiving 600 mg t.i.d. It was concluded that control of asthmatic symptoms could be maintained with lower dose/frequency regimens of zileuton (5).

A randomized, double-blind, placebo-controlled, crossover study involving 7 asthmatic patients receiving maintenance corticosteroid therapy with bronchial hyperresponsiveness to histamine and ultrasonically nebulized distilled water, received either 400 mg zileuton or a placebo and were challenged 3 h following dosing. Results demonstrated that baseline airway caliber was unchanged by treatment and bronchial hyperresponsiveness to histamine was reduced in zileuton-treated patients (6).

In a randomized, parallel, placebo-controlled trial, patients with moderate asthma received either 1200 mg controlled release zileuton b.i.d.,600 mg immediate release zilueton/day or placebo. Controlled release zileuton was found to be well tolerated and side effects included infection in 14.2% and headache in 11.7% of the patients. Similar safety profiles were obtained for both immediate release and controlled release regimens (7).

A double-blind, placebo-controlled, crossover trial examined the potential benefits of incorporating zileuton in existing glucocorticosteroid treatment in 40 aspirin-

intolerant asthmatics. In addition to glucocorticosteroids, patients received either zileuton (600 mg 4 times/day) or a placebo for 6 weeks. Improvement in acute and chronic pulmonary function (FEV_1, peak expiratory flow rate), decrease in stuffiness, increase in nasal inspiratory flow, return of smell, reduction in rhinorrhea, inhibition of aspirin-induced bronchoconstriction, and decrease in nasal dysfunction were observed in drug-treated patients, and increased and more stable control of asthma was observed (8).

1. Mangino, M.J., Mangino, J.E., Kotadia, B., Sielczak, M. *Effects of the 5-lipoxygenase inhibitor A-64077 on intestinal hypothermic organ preservation injury.* J Pharmacol Exp Ther 1997, 281(2): 950.

2. Awni, W.M., Wong, S., Chu, S.Y., Patterson, K., Hansen, R., Machinist, J.M., Drajesk, J., Keane, W.F., Halstenson, C.E. *Pharmacokinetics of zileuton and its metabolites in patients with renal impairment.* J Clin Pharmacol 1997, 37(5): 395.

3. Awni, W.M., Locke, C., Dube, L.M., Cavanaugh, J.H. *Evaluation of the diurnal variation in the pharmacokinetics of zileuton in healthy volunteers.* J Clin Pharmacol 1997, 37(5): 388.

4. Awni, W.M., Cavanaugh, J.H., Leese, P., Kasier, J., Cao,G.L., Locke, C.S., Dube, L.M. *The pharmacokinetic and pharmacodynamic interaction between zileuton and terfenadine.* Eur J Clin Pharmacol 1997, 52(1): 49.

5. Grossman, J., Du Buske, L.M., Dubé, L.M., Nabulsi, A., Swanson, L.J. *Maintenance of asthma control with zileuton, 600 or 800 mg, in a TID or BID regimen, in patients whose FEV-1 values improved with 600 mg QID for two months.* Annu Cong Eur Respir Soc (Sept 20-24, Berlin) 1997, Abst P2807.

6. Dekhuijzen, P.N.R., Bootsma, G.P., Wielders, P.L.M.L., van den Berg, L.R.M., Festen, J., van Herwaarden, C.L.A. *Effects of single-dose zileuton on bronchial hyperresponsiveness in asthmatic patients treated with inhaled corticosteroids.* Eur Respir J 1997, 10(12): 2749.

7. Lee, T., Grossman, J., Swanson, L.J. et al. *Safety of zileuton, 1200 mg BID, controlled release and 600 mg QID, immediate release, in patients with moderate asthma.* Amer J Respir Crit Care Med 1998, 157(3): A409.

8. Dahlen, B., Nizankowska, E., Szczeklik, A. et al. *Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics.* Amer J Respir Crit Care Med 1998, 157(4): 1187.

Original monograph – Drugs Fut 1993, 18: 616.

Additional Reference

Pasha, M.A. et al. *The role of neuropeptides and zileuton on activation and mediator synthesis and release.* J Allergy Clin Immunol 1998, 101(1, Part 2): Abst 163.