Drugs of the Future 1999, 24(7): 789-830

CCC: 0377-8282/99

Information Update

Volume 1-23, Number 7

Estimated developmental phase for this month's updated products:

Phase I

C-1311 (antineoplastic; Tech. Univ. Gdansk, BTG)
Triptolide (immunosuppressant; Kunming Inst. Botany)

Phase II

1263W94 (antiviral; Glaxo Wellcome)
Acreozast (antiallergic/antiasthmatic, treatment of atopic dermatitis; Toyobo)
DMP-754 (platelet antiaggregatory, gpIIb/IIIa receptor antagonist; DuPont Pharm.)
Idoxifene (treatment of breast cancer, estrogen receptor modulator; SmithKline Beecham, BTG)
Moguisteine (antitussive; Roche)
Oltipraz (chemopreventive; Rhône-Poulenc Rorer)
Ramoplanin (glycopeptide antibiotic; Biosearch Italia, Hoechst Marion Roussel, IntraBiotics)
Saredutant (antiallergic/antiasthmatic, tachykinin NK_2 antagonist; Sanofi-Synthélabo)

Phase III

Bucindolol hydrochloride (treatment of CHF, β-adrenoceptor antagonist; Intercardia, Knoll)
Daptomycin (antibiotic; Lilly, Cubist)
Idoxuridine (antineoplastic; NeoPharm, Natl. Cancer Inst.)
Ipsapirone (anxiolytic, antidepressant, 5-HT_{1A} agonist; Troponwerke)
KE-298 (antiarthritic; Taisho)
Metazosin (treatment of BPH, treatment of heart failure, α_1-adrenoceptor antagonist; Res. Inst. Pharm. Biochem.)
MKC-442 (anti-HIV, reverse transcriptase inhibitor; Mitsubishi Chem., Triangle, Abbott)
Thrombopoietin (treatment of thrombocytopenia; Genentech, Novo Nordisk, Amgen, Kirin Brewery, Pharmacia & Upjohn)

Preregistered

Azelnidipine (antihypertensive; Sankyo, Ube)
Frovatriptan (antimigraine, 5-$HT_{1D/1B}$ agonist; Vanguard Medica, Elan, Draxis Health)
Vatanidipine hydrochloride (antihypertensive, calcium channel blocker; Yoshitomi)

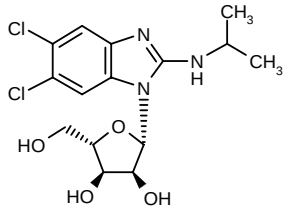
Launched/Year

Basiliximab (treatment of transplant rejection; Novartis)/1998
Celecoxib (antiarthritic, cognition enhancer, treatment of colon cancer, COX-2 inhibitor; Searle, Pfizer, Yamanouchi)/1999
Cetirizine hydrochloride (antihistaminic; UCB, Pfizer, Daiichi Pharm., Sumitomo)/1987
Ebastine (antihistaminic, treatment of allergic rhinitis; Almirall Prodesfarma, Rhône-Poulenc Rorer)/1990
Entacapone (antiparkinsonian, COMT inhibitor; Orion, Novartis)/1998
Fosphenytoin sodium (anticonvulsant; Parke-Davis, DuPont Pharm.)/1996
Imidapril hydrochloride (antihypertensive, ACE inhibitor; Nihon Schering, Tanabe, Trinity Pharm.)/1993
Levofloxacin (fluoroquinolone antibacterial; Daiichi Pharm., Ortho-McNeil, Glaxo Wellcome, Hoechst Marion Roussel)/1993
Nifedipine (antianginal, antihypertensive, calcium antagonist; Sanofi-Synthélabo, Pfizer, Bayer)/1975
Pentostatin (antineoplastic; Warner-Lambert, SuperGen)/1992
Phentolamine mesilate (treatment of erectile dysfunction, α-adrenoceptor antagonist; Zonagen, Schering-Plough)/1998
Raloxifene hydrochloride (treatment of postmenopausal syndrome, estrogen receptor modulator; Lilly, Gador, Chugai)/1998
Repaglinide (antidiabetic; Boehringer Ingelheim, Novo Nordisk)/1998
Risedronate sodium (bisphosphonate, treatment of osteoporosis, treatment of Paget's disease; Procter & Gamble, Takeda, Ajinomoto, Hoechst Marion Roussel)/1998
Ritonavir (anti-HIV, HIV protease inhibitor; Abbott, Dainippon, Triangle)/1996
Rivastigmine (cognition enhancer, acetylcholinesterase inhibitor; Novartis)/1997
Rizatriptan benzoate (antimigraine, 5-HT_{1D} agonist; Merck & Co.)/1998
Tolterodine (treatment of urinary incontinence, muscarinic M_3 antagonist; Pharmacia & Upjohn)/1997
Valaciclovir (antiviral; Glaxo Wellcome, Theraplix, Hoechst Marion Roussel)/1995
Zileuton (antiallergic/antiasthmatic, 5-lipoxygenase inhibitor; Abbott)/1997

1263W94
Benzimidavir
Maribavir

Antiviral

EN: 233414



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

In an open-label phase I/II study, the anti-CMV activity of 1263W94 (100, 200, 400 mg t.i.d. or 600 mg b.i.d. p.o.) was demonstrated in 24 male, HIV-infected subjects with asymptomatic CMV shedding treated for 28 days. A parallel quantitative decrease of CMV titer from saliva, semen and urine was observed on day 28 with 71, 80, 100 and 20% of subjects receiving the respective doses displaying semen titers below the limit of quantification (25 pfu/ml). No serious adverse events or laboratory abnormalities were reported. Side effects included taste disturbance, fatigue, headache and nausea (1).

Maribavir is the new proposed international nonproprietary name for 1263W94 (2).

1. Drew, W.L. et al. *In vivo anti-CMV activity and safety of oral 1263W94 in HIV-infected subjects with asymptomatic CMV shedding.* 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst H-25.

2. *Proposed international nonproprietary names (Prop. INN): List 80.* WHO Drug Inf 1998, 12(4): 268.

Original monograph - Drugs Fut 1997, 22: 707.

Additional References

McSharry, J. et al. *Comparison of phenotypic assays for determining susceptibility of human cytomegalovirus (HCMV) to 1263W94 and ganciclovir.* 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst H-107.

McSharry, J.J. et al. *Comparison of the in vitro antiviral activities of 1263W94, ganciclovir, foscarnet and cidofovir for human cytomegalovirus (HCMV) clinical isolates as determined by flow cytometry and plaque reduction assays.* Antivir Res 1999, 41(2): Abst 95.

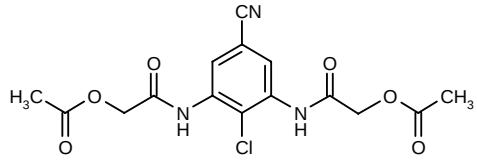
Talarico, C.L. et al. *Antiviral activity of the benzimidazole 1263W94 is mediated through the protein kinase activity of the HCMV UL97.* 38th Intersci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst H-90.

Tidwell, J.H. et al. *An efficient and scalable synthesis of the anti-HCMV agent 1263W94.* 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst ORGN 172.

Acreozast
TYB-2285

Antiallergic/Antiasthmatic
Treatment of Atopic Dermatitis

EN: 153417



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

The effects of TYB-2285 in a model of passive peritoneal anaphylaxis in rats were reported. When TYB-2285 (10 mg/kg i.p.) was administered to rats at 0.5, 1 and 2 min prior to antigen challenge, peritoneal anaphylactic histamine release was reduced by 36.2, 57.5 and 52.6%, respectively, and capillary permeability was also suppressed by 20.9, 51.6 and 49%, respectively. In comparison, disodium cromoglycate administered at a dose of 10 mg/kg i.p. 0.5 min prior to challenge inhibited antigen-induced histamine release and capillary permeability by 85.6 and 74.8, respectively. TC-1121 and TC-1122, metabolites of TYB-2285, were capable of inhibiting histamine release in a concentration-dependent manner at 0.1-10 μM. However, TYB-2285 and other metabolites such as TC-286 and TC-326 were ineffective even at 100 μM (1).

TYB-2285 has been shown to effectively inhibit late asthmatic events and airways hyperresponsiveness in actively sensitized guinea pigs. Guinea pigs were pretreated with a dose of 300 mg/kg p.o. as a single dose or daily for 7 days. The late bronchial response at 4-7 h after antigen inhalation was inhibited by single and multiple doses of TYB-2285, but the immediate bronchial response at 1-10 min after antigen inhalation was inhibited only after multiple doses. The bronchoalveolar lavage fluid of TYB-2285-treated animals was found to have a reduced number of eosinophils, neutrophils and macrophages as compared to untreated animals. A single dose of TYB-2285 was capable of reversing airways hyperreactivity in response to histamine inhalation. It is suggested that TYB-2285 acts by inhibiting the accumulation and activation of eosinophils and other inflammatory cells (2).

The synthesis and pharmacology of TYB-2285 and related compounds, as previously described, have been reported. TYB-2285 is now under phase II evaluation in Japan for the treatment of asthma and atopic dermatitis (3).

1. Watanabe, A., Tominaga, T., Shutoh, H., Hayashi, H., Tsuji, J. *Effect of TYB-2285 on peritoneal anaphylaxis in passively sensitized rats.* Gen Pharmacol 1998, 31(2): 313.

2. Tohda, Y., Muraki, M., Kubo, H., Nakajima, S., Fukuoka, M., Watanabe, A. *Effect of TYB-2285 on early and late bronchial responses and airway hyperreactivity in actively sensitized guinea pigs.* Gen Pharmacol 1998, 31(2): 323.

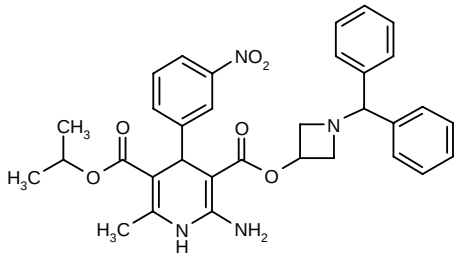
3. Ban, M., Taguchi, H., Katsushima, T., Takahashi, M., Shinoda, K., Watanabe, A., Tominaga, T. *Novel antiallergic and antiinflammatory agents. Part II: Synthesis and pharmacology of TYB-2285 and its related compounds.* Bioorg Med Chem 1998, 6(7): 1077.

Original monograph - Drugs Fut 1995, 20: 686.

Azelnidipine
Calblock®

Antihypertensive

EN: 141329



$C_{33}H_{34}N_4O_6$

Sankyo; Ube

Results from a study using Dahl salt-sensitive hypertensive rats showed that the renoprotection afforded by azelnidipine may be through effects on glycation involved in the pathogenesis of hypertensive renal damage. Systolic blood pressure (from 216 ± 11 to 132 ± 6 mmHg) and urinary albumin excretion (from 4.6 ± 2.6 to 2.1 ± 0.4 mg/day) were significantly reduced in rats treated with azelnidipine (3 mg/kg/day for 12 weeks); glomerular sclerosis index was also significantly improved (from 22.2 ± 28.1 to 3.2 ± 4.1) in treated animals. Anti-advanced glycation endproduct IgG staining of renal tubules, glomerulus and interlobular arteries was significantly decreased in azelnidipine-treated rats to levels observed in renal tissue from Dahl salt-resistant rats (1).

In a randomized, double-blind, placebo-controlled, crossover study, azelnidipine did not alter the hemodynamics or neurohumoral responses to exercise, indicating a potential use of the agent for patients with mild essential hypertension. After a 4-week placebo run-in period, 10 patients with mild essential hypertension received azelnidipine (8 mg/day x 4 weeks) or placebo and were exercised on an ergometer in a submaximal test. Decreases in systolic (from 158 ± 10 to 145 ± 14 mmHg) and diastolic (from 97 ± 7 to 90 ± 9 mmHg) blood pressure were observed at rest and significant decreases were noted during exercise in drug-treated patients. No changes in resting or exercise-enhanced heart rate, cardiac output and plasma norepinephrine were observed and resting plasma epinephrine levels were not affected by treatment (2).

Azelnidipine is awaiting regulatory approval in Japan for the oral treatment of hypertension (3).

1. Yamakado, M. et al. *Role for glycation in the mechanism of renoprotection of calcium antagonist in Dahl salt hypertensive rat.* Am J Hypertens 1999, 12(4, Part 2): 102A.

2. Arita, M. et al. *A new Ca-antagonist, azelnidipine, reduced blood pressure during exercise without augmentation of sympathetic nervous system in essential hypertension: A randomized, double-blind, placebo-controlled trial.* J Cardiovasc Pharmacol 1999, 33(2): 186.

3. *Focus on Sankyo's R&D activities at home and abroad.* DailyDrugNews.com (Daily Essentials) Oct 9, 1998.

Original monograph - Drugs Fut 1990, 15: 671.

Additional Reference

Sanmon, M. et al. *Relation of glycation-inhibitory effects of azelnidipine to renal protective mechanism of Ca antagonists.* 21st Annu Sci Meet Jpn Soc Hypertens (Sept 24-26, Hiroshima) 1998, Abst P54.

Basiliximab
CHI-621
chRFT5
SDZ-CHI-621
Simulect®

Treatment of Transplant Rejection

EN: 235373

Novartis

In a prospective, randomized, open-label study involving 24 recipients of primary cadaveric liver allografts receiving ciclosporin and steroids, the disposition and immunodynamics of basiliximab (40 mg i.v.) were examined. Treatment was well tolerated. The central distribution and steady-state volumes of the agent were 5.6 ± 1.7 l and 7.5 ± 2.5 l, respectively. Drained ascite fluid contained basiliximab and this route was responsible for 20% of the total clearance, although bleeding may be another route since total body clearance correlated with volume of postoperative blood loss. CD25 expression on T lymphocytes was related to serum basiliximab concentrations with complete saturation of IL-2 receptor alpha-chain lasting 23 ± 7 days posttransplantation and occurring with serum concentration above 0.1 μg/ml (1).

Basiliximab (Simulect®) was launched by Novartis in the U.K. and is indicated for use in conjunction with ciclosporin (Neoral) and corticosteroids for the prophylaxis of acute organ rejection in *de novo* allogeneic renal transplant recipients. The results of clinical trials indicate that basiliximab, administered 2 h prior to surgery and repeated 4 days thereafter in combination with baseline immunosuppression, significantly reduces the incidence of acute graft rejection both 6 and 12 months after transplant surgery. Basiliximab was granted E.U.-wide approval last October and is also marketed in the U.S. and Switzerland (2, 3).

A spokesperson from Novartis has informed Prous Science that basiliximab was introduced in Spain for use in conjunction with ciclosporin in preventing rejection in renal transplant recipients (4).

Novartis's basiliximab has been launched in Germany for the prevention of acute organ transplant rejection in combination with ciclosporin (Neoral) and corticosteroids. It is supplied as ampules, 20 mg (5).

1. Kovarik, J. et al. *Disposition and immunodynamics of basiliximab in liver allograft recipients.* Clin Pharmacol Ther 1998, 64(1): 66.

2. *Simulect gets the go-ahead from the European Commission.* DailyDrugNews.com (Daily Essentials) Oct 23, 1998.

3. *Another significant market introduction for basiliximab.* DailyDrugNews.com (Daily Essentials) Jan 25, 1999.

4. *Spanish market introduction announced for antirejection MAb.* DailyDrugNews.com (Daily Essentials) March 15, 1999.

5. *German launch announced for Novartis immunosuppressant.* DailyDrugNews.com (Daily Essentials) March 22, 1999.

Original monograph - Drugs Fut 1998, 23: 697.

Additional References

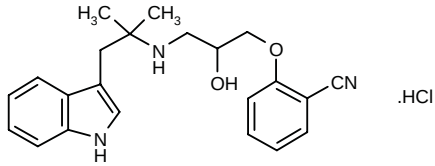
Breidenbach, T. et al. *Basiliximab (Simulect™) reduces acute rejections, CMV-infections and duration of hospital stay in renal allograft patients.* Transplantation 1998, 65(8, Suppl.): Abst 709.

Mulloy, L.L. et al. *Simulect (basiliximab) reduces acute cellular rejection in renal allografts from cadaveric and living donors.* Transplant Proc 1999, 31(1-2): 1210.

Schmidt, A.-G. et al. *Reduced acute rejection and superior one-year renal allograft survival with basiliximab (Simulect™) in patients with diabetes mellitus.* 17th World Cong Transplant Soc (July 12-17, Montréal) 1998, Abst 1629.

Bucindolol Hydrochloride *Treatment of CHF*
Bextra® *β-Adrenoceptor Antagonist*

EN: 090305



$C_{22}H_{25}N_3O_2.HCl$ **Intercardia; Knoll**

Intercardia initiated a randomized, double-blind, placebo-controlled trial, the BEAT study (Bucindolol Evaluation in Acute myocardial infarction Trial), to evaluate the ability of bucindolol hydrochloride to prolong survival in patients who have reduced left ventricular systolic function within 7 days following an acute myocardial infarction (AMI). The trial, conducted by BASF/Knoll, is designed to enroll 2000 patients at several sites in Denmark and the U.K. Patients will be randomized 2-7 days after an AMI and must be hemodynamically stable for entry into the trial. Eligible patients must not have had an AMI within 6 months prior to enrollment and they must have moderate to severe signs or symptoms of congestive heart failure (CHF). So far, approximately 2400 CHF patients have enrolled in North America (1).

Intercardia and Astra Pharmaceuticals have terminated their agreement for the U.S. development and commercialization of bucindolol hydrochloride (Bextra®), presently under investigation for the treatment of CHF. Due to a noncompete clause in the original agreement between the two companies, Intercardia will now assume responsibility for the U.S. development and commercialization of Bextra®. Astra will be returning to Intercardia all rights, material and information relating to bucindolol, as well as a termination fee (2).

Intercardia has been informed that the data and safety monitoring board for the Beta-blocker Evaluation of Survival Trial (BEST) has met to review interim study data and has recommended that BEST be continued. BEST is being conducted by the Department of Veterans Affairs and the National Heart, Lung and Blood Institute of the NIH. The study is designed to test the hypothesis that the addition of bucindolol hydrochloride to standard therapy will reduce mortality in patients with moderate to severe CHF (3).

1. *European trial of Bextra initiated.* DailyDrugNews.com (Daily Essentials) June 30, 1998.

2. *Intercardia and Astra end Bextra collaboration.* DailyDrugNews.com (Daily Essentials) Oct 2, 1998.

3. *DSMB recommends continuation of Bextra study.* DailyDrugNews.com (Daily Essentials) March 1, 1999.

Original monograph - Drugs Fut 1981, 6: 405.

Additional References

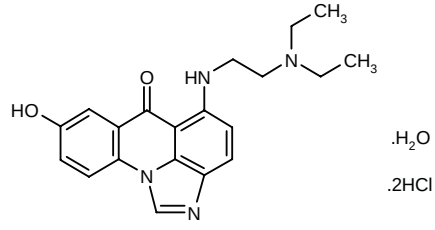
Fink, G.D. et al. *Interaction of the β receptor adrenergic antagonist bucindolol with serotonergic receptors.* FASEB J 1999, 13(5, Part 2): Abst 826.4.

Hjalmarson, A. *The role of β-blocker therapy in heart failure based on the results of mega trials – Focus on MERIT-HF and CIBIS II.* 63rd Annu Sci Meet Jpn Circ Soc (March 27-Macrh 29, Tokyo) 1999, 73.

Tackett, R.L. et al. *α Receptor antagonism of bucindolol and two of its metabolites in human saphenous veins.* FASEB J 1999, 13(4, Part 1): Abst 123.17.

C-1311 *Antineoplastic*
NSC-645809
Imidacrine

EN: 227463



$C_{20}H_{22}N_4O_2.2HCl.H_2O$ **Tech. Univ. Gdansk (PL); BTG**

A series of substituted imidazoacridone compounds has been prepared and the lead compound C-1311 (imidacrine) has been identified. The compounds are readily synthesized and their salts are freely soluble. Encouraging data are available showing the activity of C-1311 against the National Cancer Institute's screening panel, as well as against other cell lines and human tumor xenografts. C-1311 appears to be particularly effective in models of slow-growing tumors, such as colorectal cancer, that are normally difficult to treat. The compound is orally active and maintains its efficacy in various models of acquired resistance. The compound is available for licensing from BTG (1).

1. *Antitumor imidazoacridone available for licensing from BTG.* DailyDrugNews.com (Daily Essentials) Sept 3, 1998.

Original monograph - Drugs Fut 1998, 23: 702.

Additional References

Dziegielewski, J. et al. *Characterization of covalent binding to DNA of antitumor imidazoacridinone C-1311, after metabolic activation.* 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 525.

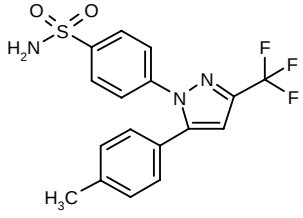
Phillips, R.M. et al. *Temporal characterisation of blood vessel development to hollow fibres: Implications for drug delivery and drug evaluation.* 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 272.

Skladanowski, A. et al. *Abrogation of transient S phase arrest induced by a new drug imidacrine decreases its cytotoxic activity toward HT-29 colon carcinoma cells.* Proc Amer Assoc Cancer Res 1998, 39: Abst 466.

Celecoxib
Celebra®
Celebrex®

Antiarthritic
Cognition Enhancer
Treatment of Colon Cancer
COX-2 Inhibitor

EN: 228583



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

Dramatic chemopreventive activity was seen with celecoxib in a hairless mouse model of UV light-induced skin cancer (1).

In the azoxymethane-induced colon carcinogenesis model, celecoxib reduced the incidence, multiplicity and burden of colon cancer by 93, 97 and 89%, respectively. It also dose-dependently inhibited the growth of Lewis lung and HT-29 human colon carcinoma tumors by up to 86% (2).

The safety and efficacy of celecoxib have been demonstrated in 4 phase II clinical trials: a 2-week efficacy trial in osteoarthritis and a 4-week efficacy study in rheumatoid arthritis, a 1-week endoscopy study evaluating gastrointestinal (GI) side effects and a 1-week study evaluating potential effects on platelet function. The compound was statistically superior to placebo in the efficacy studies in treating the signs and symptoms of arthritis, as measured by standard arthritis scales. No ulcers developed in celecoxib-treated patients in the endoscopy study, while 6 of 32 subjects administered naproxen developed gastric ulcers. In the platelet function study, the compound did not have any significant effects on platelet aggregation or on thromboxane B_2 levels, in contrast to aspirin which affected both parameters. The tolerability and safety of celecoxib were excellent in all 4 studies (3).

In 4 randomized, double-blind, parallel group, placebo-controlled studies, 40 healthy subjects on a low sodium diet received celecoxib (200 and 400 mg b.i.d.), naproxen (500 mg b.i.d.) or placebo for 8 days. Selective inhibition of COX-2 with celecoxib (400 mg) slightly decreased glomerular filtration rate (–18.8 ± 7.7 *vs.* –7.4 ± 4.6 with placebo) and renal plasma flow (–98 ± 53 *vs.* –33 ± 18 with placebo) and significantly reduced sodium and potassium excretion as compared to placebo (0.08 ± 0.05 to –0.22 ± 0.07 and –2.2 ± 1.4 to –9.8 ± 3.0, respectively). Decreased proximal sodium reabsorption was responsible for the effect of the agent on sodium excretion, suggesting that during salt restriction, COX-2 is involved in sodium balance and renovascular tone (4).

A total of 1000 patients with rheumatoid arthritis participated in a double-blind, placebo-controlled study of the efficacy and safety of celecoxib. Subjects were administered celecoxib at 100, 200 or 400 mg b.i.d., naproxen 500 mg b.i.d. or placebo for 12 weeks. All doses of celecoxib showed comparable efficacy, and were at least as efficacious as naproxen and superior to placebo. The safety profile of celecoxib was similar to that of placebo and superior to that of naproxen. Gastroduodenal ulcers were reported in 27% of naproxen patients, 6% of those on celecoxib 400 mg, 5% on celecoxib 200 mg, 6% on celecoxib 100 mg and 4% on placebo. At supratherapeutic doses, celecoxib did not affect platelet aggregation or thromboxane production. Adverse event profiles for celecoxib and placebo were similar (5).

Results from a multicenter, double-blind, placebo-controlled 12-week trial in 1148 patients with symptomatic rheumatoid arthritis showed that celecoxib significantly improved the ability to perform daily activities. Patients randomly received either celecoxib (100, 200 or 400 mg b.i.d.) naproxen (500 mg b.i.d.) or placebo. Significant improvements in ability to perform daily activities were observed with the 200 and 400 mg celecoxib groups at 2, 6 and 12 weeks as compared to placebo. Percentage of reduction in the Health Assessment Questionnaire for 20 items in categories 2 (perform with much difficulty) and 3 (unable to do) at week 12 were 10.9, 23.8, 19.9% for celecoxib (100, 200 and 400 mg, respectively), 14.5% for

naproxen and 1.8% in the placebo group; reductions with 200 mg celecoxib for some items were significantly higher than naproxen and placebo groups (6).

Results from a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in 686 patients with symptomatic osteoarthritis of the knee demonstrated the efficacy and tolerability of celecoxib given once (100 mg) or twice daily (200 mg). Similar efficacy, which was significantly better than with placebo, was observed for both celecoxib regimens at 2 and 6 weeks. Withdrawals due to lack of efficacy (8-9%) and adverse events (4-5%) were also similar for both celecoxib groups, with rates lower than with placebo (24 and 9%, respectively) (7).

The profile of significant upper GI events associated with celecoxib (25-400 mg b.i.d.) as found in 14 double-blind, placebo-controlled trials enrolling 11,007 patients with osteoarthritis or rheumatoid arthritis was compared to those profiles found with naproxen (500 mg b.i.d.), diclofenac (50-75 mg b.i.d.) and ibuprofen (800 mg t.i.d.) administered for 2-24 weeks. Significant upper GI events were defined as perforation, bleeding and gastric outlet obstruction. An excess risk of 1.48% was associated with NSAIDs as compared to celecoxib. No excess risk was found between celecoxib and placebo. Of 11 events, 9 were a bleeding episode (2, 3, 3 and 1 on celecoxib, naproxen, diclofenac, and ibuprofen, respectively) and 2 events were gastric outlet obstructions associated with naproxen (8).

Results from a multicenter, randomized, double-blind, placebo-controlled, 12-week trial in 1003 patients with symptomatic osteoarthritis of the knee showed that celecoxib significantly reduced pain and improved functioning as assessed by the WOMAC index. Significant improvements were observed with 100 and 200 mg celecoxib and naproxen (500 g b.i.d.) over placebo and with 50 mg celecoxib at 2 and 12 weeks (9).

A randomized, double-blind, placebo-controlled study in 37 healthy volunteers examined the effects of celecoxib (100, 400 or 800 mg) on platelet function as compared to ibuprofen (800 mg) and placebo. All doses of celecoxib were well tolerated with no side effects observed. The effects of celecoxib on collagen- and arachidonate-induced platelet aggregation were similar to placebo at 3, 8 and 12 h postdosing. Ibuprofen groups exhibited significantly moderate and marked inhibition of collagen- and arachidonate-induced aggregation, respectively, at 3 h postdosing with aggregation returning to normal (similar to placebo) at 24 h. Thromboxane B_2 levels were significantly decreased 3- to 4-fold in the ibuprofen group as compared to celecoxib and placebo groups (10).

Results from a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in 1061 patients with symptomatic osteoarthritis of the hip demonstrated the efficacy and tolerability of celecoxib (50, 100 or 200 mg b.i.d.) for 12 weeks as compared to naproxen (500 mg b.i.d.) and placebo. Patient and physician arthritis assessments showed that celecoxib doses of 100 and 200 mg and naproxen were similar and significantly more effective than placebo at 2, 6 and 12 weeks; 50 mg celecoxib was also significantly better than placebo but less effective than the other doses. Serious adverse events were similar in all groups and no significant alterations in laboratory analyses for celecoxib groups were observed (11).

In a key multinational, double-blind, double-dummy, parallel-group, 24-week study involving 655 patients in 21 countries, celecoxib was as effective as diclofenac SR in treating signs and symptoms of rheumatoid arthritis. However, celecoxib was associated with a significant reduction in GI complaints (36% *vs.* 48%) and with a 4-fold reduction in ulcers as compared to diclofenac (2% *vs.* 7%). Over the course of the treatment period, celecoxib (200 mg b.i.d.) was as effective as diclofenac (75 mg b.i.d.) in treating pain and swelling associated with rheumatoid arthritis. Withdrawals due to treatment failure were comparable in the two groups, but those due to side effects were significantly more frequent with diclofenac (12).

Results from a multicenter, randomized, double-blind, placebo-controlled study in 1103 patients with symptomatic rheumatoid arthritis demonstrated the efficacy and tolerability of celecoxib (100, 200 or 400 mg b.i.d.) for 12 weeks as compared to naproxen (500 mg b.i.d.) and placebo. Patient and physician assessments, number of tender/painful joints and swollen joints were similar at all time points for all doses of celecoxib and were significantly better than the placebo; naproxen showed efficacy similar to celecoxib. Functional disability indices were found to be improved and significantly better than placebo for celecoxib and naproxen groups at 12 weeks. Incidence of side effects was similar in all groups (13).

A 15-day, multiple-dose, randomized, parallel study in 24 healthy young adults receiving a loading dose of racemic warfarin (10 mg/day on days 1 and 2) followed by maintenance dosing from days 3-15 and celecoxib (200 mg b.i.d.) or a placebo from days 8-15 showed that celecoxib did not affect the pharmacokinetics of warfarin. Mean prothrombin times and C_{min}, C_{max} and AUC values for S-warfarin on day 15 predosing were 15.6 and 15.5 s, 84.2 and 81.7 ng/ml, 152 and 138 ng/ml and 2475 and 2485 ng/ml.h, respectively, for treated and placebo groups (14).

A 12-week study was conducted in 1004 patients with osteoarthritis of the knee. This trial demonstrated that celecoxib (100 or 200 mg b.i.d.) was as good as naproxen (500 mg b.i.d.) and superior to placebo for reducing disease symptoms. Both doses of celecoxib were associated with a rate of GI-related adverse events and withdrawals similar to that for placebo (15).

In phase III trials comparing celecoxib to naproxen in rheumatoid arthritis and osteoarthritis, celecoxib demonstrated an efficacy profile similar to that of naproxen but had a superior GI safety profile. In a 12-week trial involving 1149 patients with active rheumatoid arthritis, celecoxib (100, 200 or 400 mg b.i.d.) and naproxen (500 mg b.i.d.) were equally effective in reducing joint tenderness, pain and swelling, and both were superior to placebo. The upper GI safety profile of celecoxib, however, was

superior to that of naproxen and statistically equivalent to that of placebo. Endoscopically documented ulcers developed in 26, 4-6 and 4% of the patients treated with naproxen, celecoxib and placebo, respectively (16).

Celecoxib was compared to ibuprofen and placebo for antipyretic activity in a double-blind, randomized trial in 180 male volunteers. Subjects received celecoxib 25, 100, 200 or 400 mg, ibuprofen 400 mg or placebo followed at 30 min by *E. coli* endotoxin to induce fever. Body temperature and symptoms were evaluated for 8 h after administration of the drugs. Celecoxib doses of 100-400 mg and ibuprofen were superior to placebo regardimg the adjusted temperature AUC (AAUC) and the maximum change from baseline temperature; the lowest dose of celecoxib was significantly superior to placebo for AAUC but not for maximum temperature change. Comparable effects were noted for celecoxib 200 and 400 mg and ibuprofen for AAUC and for the highest dose of celecoxib and ibuprofen for maximum temperature change. Chills, myalgia and headache were reported more frequently on placebo and celecoxib 25 and 100 mg. The results from this study indicate that celecoxib is an effective antipyretic agent with a minimally effective dose between 25 and 100 mg (17).

Celecoxib (Celebrex™) has been launched in the U.S., its first market. The drug was approved by the FDA for the treatment of rheumatoid arthritis and osteoarthritis, and is supplied as capsules containing 100 and 200 mg of the active ingredient. Celecoxib is the first COX-2 inhibitor to reach the market and is comarketed in the U.S. by Searle and Pfizer (18-23).

The Brazilian Ministry of Health approved celecoxib (Celebra™) for the treatment of arthritis. This marks the first government approval of celecoxib outside of the U.S. (24).

The Mexican Health Secretariat has approved celecoxib (Celebrex™) for the treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis and for the management of pain (25).

Searle and Pfizer have announced the Swiss approval of celecoxib (Celebrex™) for the treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis. Switzerland marks the drug's first European approval. Searle and Pfizer will promote the drug in all world markets except Japan (26).

Celecoxib (Celebrex™) has been approved in Canada for acute and chronic use in the relief of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA) in adults. Celebrex™ is available in 100-mg and 200-mg strengths. For OA, the recommended dose is 200 mg/day administered as a single dose or 100 mg b.i.d. For RA, the recommended dose is 100-200 mg b.i.d. (27, 28).

Following reports of several patient deaths attributed to treatment with celecoxib, Searle issued a statement stating that the company's first interest is patient safety and that adverse reaction reports are always taken seriously, reviewed and discussed with the FDA. The company's medical review of the 10 individual reports to the FDA indicates that no direct causality can be associated between use of celecoxib and any of the reported deaths. Celecoxib is currently being used by more than two million patients, and experience shows that the drug is safe and effective when used as prescribed within the approved label (29).

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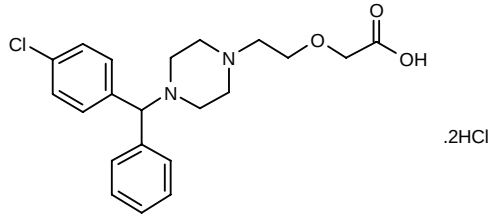

$C_{21}H_{25}ClN_2O_3.2HCl$

UCB; Pfizer; Daiichi Pharm.; Sumitomo

First results from the international, double-blind, randomized, placebo-controlled ETAC (Early Treatment of the Atopic Child) trial evaluating the effect of 18 months of cetirizine hydrochloride treatment on the development of asthma in infants with atopic dermatitis have been published. Infants (1-2 years, n = 817) suffering from atopic dermatitis and with a family history of atopic disease were randomized to receive either cetirizine (0.25 mg/kg b.i.d.) or placebo. Infants receiving placebo who had increased levels of total IgE or specific IgE for grass pollen, house dust mite or cat dander showed an elevated relative risk (RR = 1.4-1.7) for developing asthma. A significant reduction in the incidence of asthma in patients sensitized to grass pollen (RR = 0.5) or house dust mite (RR = 0.6) compared to placebo was observed in subjects given cetirizine. An intention-to-treat analysis including all infants with normal and elevated total or specific IgE, however, indicated no difference in the incidence of asthma between cetirizine- and placebo-treated infants. Side effects were similar in both groups. These results point to the predictive value of elevated total IgE and specific IgE levels to grass pollen, house dust mite or cat dander for the subsequent development of asthma. They also suggest that cetirizine should be considered for the primary prevention of the development of asthma in sensitized infants with atopic dermatitis (1).

UCB's cetirizine hydrochloride (Zyrtec®) is available in Japan, where it is distributed by Daiichi Pharmaceutical and Sumitomo. In Japan the product is indicated for the oral treatment of rhinitis, hives, eczema and dermatitis and is supplied as tablets, 5 and 10 mg (2).

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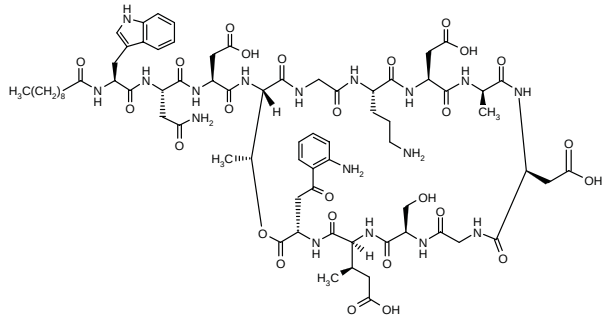

$C_{72}H_{101}N_{17}O_{26}$ **Lilly; Cubist**

In an *in vitro* study, daptomycin demonstrated excellent activity against resistant variants of Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MIC_{50} = 0.125-2 μg/ml), penicillin-resistant *Streptococcus pneumoniae* (MIC_{50} < 0.03-1 μg/ml) and vancomycin-resistant enterococci (MIC_{50} = 0.5-2 μg/ml). In general, the MICs for daptomycin were 2-4 times lower than those of vancomycin. Bactericidal activity was established in time-kill studies in MRSA and VRE (1).

In vitro resistance studies of daptomycin provided promising indications of low spontaneous resistance and a limited increase in MIC over the course of serial passages. These findings are considered to be promising for the clinical development of the compound (2).

The antimicrobial spectrum and pharmacodynamics of daptomycin were evaluated in a variety of Gram-positive bacteria. Daptomycin achieved a kill rate of more than 99% against all organisms tested. The MIC/MBC in methicillin-susceptible and -resistant *S. aureus* were 0.5/0.5 μg/ml, while against vancomycin-intermediate susceptible *S. aureus* they were 2.0/4.0 μg/ml (3).

Daptomycin has been reported to be active against emerging drug-resistant bacterial strains, known as vancomycin intermediately susceptible *S. aureus*, as shown in recent *in vitro* studies (4).

In fecal suspensions from healthy volunteers seeded with vancomycin-resistant enterococci (VRE), daptomycin induced concentration-dependent killing over the range 8-100 μg/ml; however, the compound's activity decreased as fecal concentrations increased. In order to reduce CFU/ml to undetectable levels in a 10, 20 or 30% fecal solution, respectively, 200, 400 and 400-800 μg/ml daptomycin was required. However, as the drug is orally active and high concentrations can be reached with oral dosing, this fact should not be an impediment to the therapeutic use of daptomycin for suppressing fecal carriage of VRE (5).

In an *in vivo* model, mice with systemic vancomycin-resistant *Enterococcus faecalis* infections were administered one dose of daptomycin (0.2, 1.0 or 5.0 mg/kg s.c.), vancomycin (50 mg/kg s.c.) or saline immediately after infection, followed 4 h later by a second dose. Based on 7-day survival, the PD_{50} for daptomycin was calculated to be 1.2 mg/kg s.c. All mice treated with vehicle or vancomycin died within 3 days of inoculation (6).

Two studies in dogs showed that once-daily dosing of daptomycin decreased muscle toxicity, suggesting an optimization of antimicrobial efficacy with this dosing schedule. Daptomycin at a dose of 25 mg/kg every 8 h resulted in a 4- to 5-fold greater increase in creatinine phosphate levels and increased myopathy as compared to 75 mg/kg/day. Although 5 mg/kg/day did not alter creatinine phosphate levels, the same dose given every 8 h increased these levels 3-fold. Thus, dosing interval of daptomycin had more influence on muscle toxicity than the actual dose (7).

Cubist Pharmaceuticals has initiated pivotal clinical trials for intravenous daptomycin. The FDA accepted Cubist's IND to enter two phase III investigator-blinded clinical trials to evaluate the safety and efficacy of daptomycin for the treatment of complicated skin and soft tissue infections. An IND was also accepted to enter an open-label phase II trial to evaluate three dose regimens of daptomycin in treating bloodstream infections not associated with endocarditis. One of the phase III trials for complicated skin and soft tissue infections will be conducted in the U.S. and the other in Europe, with each enrolling 400 patients. In the daptomycin treatment arm of each trial, 200 patients will receive 4 mg/kg intravenously once every 24 h for up to 14 days. The control arms will treat 200 patients with vancomycin or either nafcillin or oxacillin, the current standard of care for serious resistant bacterial infections. The primary endpoint for evaluating

efficacy will be clinical outcome as determined by disappearance of signs and symptoms. Secondary efficacy endpoints will be bacteriological eradication and time to reduce temperature to normal levels. In the open-label phase II trial, daptomycin dose levels of 4 mg/kg and 6 mg/kg administered intravenously once every 24 h will be compared to the 3 mg/kg 12-h regimen used in a previous phase II study. The trial will also compare daptomycin to conventional therapy with vancomycin or either nafcillin or oxacillin. The primary efficacy endpoint for evaluating patients will be clinical bacteriological eradication. The secondary efficacy endpoints will be clinical outcome, 28-day mortality, time to sterilization of blood and time to reduce temperature to normal levels (8-10).

Cubist Pharmaceuticals has filed regulatory submissions for the initiation of a pivotal phase III clinical trial of once-daily intravenous daptomycin in patients with complicated skin and soft tissue infections due to Gram-positive bacteria. Submissions were filed in six E.U. member countries and Israel. The pivotal phase III European efficacy and safety trial of daptomycin is expected to begin in August. The company's latest European regulatory filing was a Clinical Trial Exemption (CTX) application for daptomycin in the U.K. (11).

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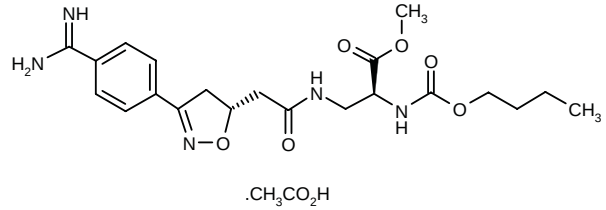

$C_{21}H_{29}N_5O_6.C_2H_4O_2$ **DuPont Pharm.**

The intranasal, intravenous and oral antiplatelet and antithrombotic efficacy of DMP-755 (roxifiban) have been compared. DMP-755 produced maximal inhibition of ADP-induced platelet aggregation (70-90%) in dogs following i.v. or intranasal administration of 0.025-0.1 mg/kg, whereas an oral dose of 0.1 mg/kg was much less active (maximum inhibition of about 40%). The drug's effects persisted for 24 h after i.v. or intranasal doses of 0.1 mg/kg. The nasal bioavailability of DMP-755 was estimated to be 85 ± 4% compared to 100% following i.v. administration. In dogs with electrolytic injury-induced arterial thrombosis, DMP-755 administered at 0.1 mg/kg intranasally or i.v. or 0.3 mg/kg p.o. completely prevented occlusion, significantly prolonged the time to occlusion and significantly reduced thrombus weight. In another model of femoral artery thrombosis these same doses of DMP-755 were associated with a significant reduction in the incidence of cyclic flow reductions. This study indicated that DMP-755 may have therapeutic potential as an intranasal antithrombotic agent for the treatment of various acute and chronic thromboembolic disorders (1).

Potent antiplatelet activity of oral DMP-754 (0.1, 0.3, 1.0 and 3 mg/kg p.o.) with extended duration was observed in *in vitro* and *in vivo* studies in baboons. *In vitro*, DMP-754 inhibited ADP-induced platelet aggregation (IC_{50} = 0.013 ± 0.003 mcM) and high affinity binding of XV-459, the active form of the agent, was shown using unactivated (K_d = 2.52 ± 0.98 nmol/l) and activated (0.80 ± 0.16 nmol/l) baboon platelets; dissociation $t_{1/2}$ from unactivated platelets was 8 ± 1 min. Dose- and time-dependent 24 h inhibition of platelet aggregation and modest effects on bleeding time prolongation were observed with oral and i.v. infusion (0.1 and 1 mg/kg for 30 min) of DMP-754 as compared to an 8-12 h duration in dogs. No significant effects of maximal antiplatelet doses were observed on platelet count, clinical chemistry or hemodynamic parameters in baboons (2).

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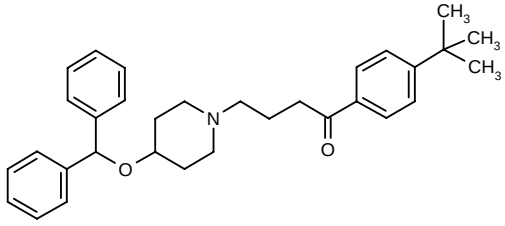

$C_{32}H_{39}NO_2$

Almirall Prodesfarma; Rhône-Poulenc Rorer

Possible direct antiinflammatory effects of ebastine have been recently demonstrated. Ebastine not only produced concentration-dependent inhibition of lipopolysaccharide-mediated TNF-α production in human monocytes (57% maximal inhibition at 10 μM), but also inhibited contractile responses to adenosine in guinea pig tracheal rings (~ 50% inhibition at 10 μM). Adenosine is thought to be involved in inflammation during allergic responses via an increase in LTC_4 production, resulting in histamine release from mast cells and bronchoconstriction. Thus, these results indicate that ebastine may also be useful in the treatment of allergic inflammatory disorders, including asthma (1).

The safety and efficacy of ebastine (10 or 20 mg), loratadine 10 mg and placebo administered once-daily for 4 weeks were compared in a double-blind study that enrolled 565 patients with seasonal allergic rhinitis. No significant differences were observed among treatment groups with respect to adverse event frequency. Ebastine and loratadine more effectively controlled the symptoms of seasonal allergic rhinitis and both drugs at 10 mg were equally effective. Ebastine at 20 mg afforded statistically and significantly greater improvement in total symptom scores as compared to loratadine 10 mg (2).

Rhône-Poulenc Rorer has received an action letter from the FDA indicating that its NDA for ebastine in the treatment of allergic rhinitis is not approvable on the basis of the information reviewed. The company has notified the FDA of its intention to file an amendment to the original NDA and will meet with the agency in the near future to discuss the next steps to be taken. Additional data from studies conducted following the filing of the NDA will be used to respond to the FDA letter (3).

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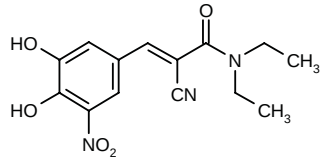
Entacapone
Comtan®
Comtess®

Antiparkinsonian
COMT Inhibitor

EN: 178077



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

In a double-blind, placebo-controlled, randomized, crossover trial, 15 patients with Parkinson's disease and "on-off" type motor fluctuations received either placebo or entacapone (200 mg) alone or in combination with a single levodopa/carbidopa tablet (200/50 mg) within 41-day treatment periods. Entacapone treatment increased the duration of clinical effect of levodopa assessed by the UPDRS motor score when combined with levodopa/carbidopa and also significantly increased the AUC of levodopa. Combination therapy was well tolerated (1).

A pharmacokinetic study with parkinsonian patients has demonstrated that entacapone enhanced levodopa action by reducing levodopa metabolism. Entacapone slowed the elimination of levodopa and increased AUC values, resulting in an increase in clinical "on" time. These results indicate the beneficial value of adjunct entacapone treatment to levodopa/carbidopa (2).

The clinical efficacy of entacapone (200 mg) as a levodopa enhancer was shown in a double-blind, 24-week, multicenter trial involving 171 parkinsonian patients. Entacapone significantly increased the "on" time of levodopa by 30-60 min and motor scores were improved. Patients receiving entacapone achieved significant reductions in levodopa daily doses. Although dyskinesias and other dopaminergic adverse effects (managed by lowering the levodopa dose) were experienced by some patients, entacapone was well tolerated (3).

In a placebo-controlled, double-blind, parallel-group, multicenter study, 205 parkinsonian patients were given entacapone (200 mg) or placebo in addition to carbidopa/levodopa and followed for 28 weeks. A significant increase in the percentage of "on" time was observed in entacapone-treated patients at weeks 8, 16 and 24 with improvements in UPDRS scores. A significant 12% reduction in daily levodopa doses was also observed in entacapone-treated subjects (4).

Entacapone as an adjunct to levodopa was found to be well tolerated in parkinsonian patients. Adverse effects included dopaminergic, gastrointestinal and dyskinesia observed within 24-48 h of entacapone administration. Dyskinesia was managed by decreasing the levodopa dose by 20-30% (5).

No plasma or erythrocyte accumulation of entacapone was observed in a study examining the pharmacokinetics of multiple dosing in 12 healthy male volunteers. Subjects received 200 mg of entacapone 8 times a day on days 1 and 6 (2 h intervals), 200 mg 10 times a day on days 3-5 and levodopa/carbidopa (100/25 mg) on days 1 and 6. No significant differences in entacapone t_{max}, half-life or AUC were observed between days 1-2 and 6-7. Erythrocyte COMT activity was reduced by 25% with stable values obtained during days of entacapone frequent dosing; COMT activity returned to baseline at the end of entacapone treatment. Pharmacokinetic parameters of levodopa and carbidopa were similar on days 1 and 6; the t_{max} of levodopa was slightly delayed (6).

The European Commission has issued a marketing authorization for entacapone for the treatment of patients with Parkinson's disease. Entacapone was discovered and developed by Orion, which will market it under the trade name Comtess® in the Nordic and Baltic countries as well as in Germany, the U.K. and Ireland. It is licensed to Novartis for marketing in all other European countries and elsewhere in the world under the name Comtan® (7, 8).

Orion has launched entacapone (Comtess®) in Sweden for the treatment of Parkinson's disease in combination with levodopa/dopa carboxylase inhibitor combinations. The compound is supplied as 200-mg tablets. Product introductions have also been made in Finland and Germany. Based on the recent safety concerns arising with another COMT inhibitor, the European Medicines Evaluation Agency has reevaluated the safety of entacapone and stated that no changes are required in the compound's Summary of Product Characteristics with regard to liver function or need for monitoring of liver enzymes (9).

Entacapone (Comtess®) has been introduced in the U.K. for use as an adjunct to levodopa and a dopa decarboxylase inhibitor in patients with Parkinson's disease and end-of-dose motor fluctuations. The product is available as film-coated tablets containing 200 mg of active ingredient (10).

According to the U.S. FDA Drug Approvals List, Orion's NDA for entacapone (Comtan®) has been deemed approvable (11).

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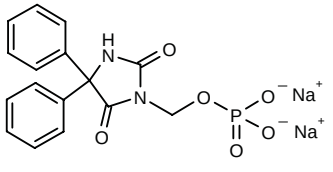
Fosphenytoin Sodium
Cerebyx®
Pro-Epanutin®

Anticonvulsant

EN: 126926



$C_{16}H_{13}N_2O_6P.2Na$ **Parke-Davis; DuPont Pharm.**

Healthcare workers' misinterpretations of Cerebyx® product labeling have led to massive overdoses that have provoked serious adverse events and even death. The misunderstanding was due to interpreting the amount of phenytoin equivalents (PE) per ml as the total amount of phenytoin equivalents in the vial (both 2-ml and 10-ml vials). Parke-Davis will revise the vial and carton labels for the drug, making it clear that the 2-ml vial contains 100 mg PE and the 10-ml vial contains 500 mg PE (1).

Fosphenytoin sodium has been launched in the U.K. by Parke-Davis (Warner-Lambert) under the trade name Pro-Epanutin®. It is supplied as 10-ml vials containing a solution for injection in strengths of 50 and 75 mg/ml and is indicated for the control of status epilepticus of the tonic-clonic type and for the prevention and treatment of seizures associated with neurosurgery and/or head trauma (2).

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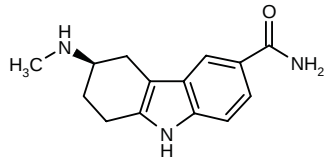
Frovatriptan
SB-209509
VML-251
Miguard®

Antimigraine
5-$HT_{1D/1B}$ Agonist

EN: 212285



$C_{14}H_{17}N_3O$ **Vanguard Medica; Elan; Draxis Health**

The efficacy of frovatriptan in functional coupling of human recombinant 5-HT_1 and 5-HT_7 receptor subtypes was evaluated in HEK293 cells expressing recombinant human receptors. The results showed that frovatriptan is a potent 5-$HT_{1B/1D}$ receptor agonist with moderate agonistic activity towards the 5-HT_7 receptor (1).

An *in vitro* study using basilar arteries obtained postmortem and coronary arteries from patients undergoing heart transplant showed that frovatriptan was a potent constrictor. A -log mean EC_{50} of 7.86 ± 0.07 was obtained

for basilar arteries which was 8-fold more potent than sumatriptan. In coronary arteries, 10-fold higher concentrations were needed to induce threshold contractile activity as compared to basilar arteries. The -log mean EC_{50}s of 7.38 ± 0.12 and 7.81 ± 0.2 were obtained for recipient and donor coronary arteries, respectively, and bell-shaped responses were observed with relaxations at concentrations > 6 μM in some tissues (2).

In vitro studies using isolated canine coronary artery have shown that while frovatriptan induced contraction at low concentrations (-log EC_{50} = 7.5 ± 0.08), higher concentrations (> 6 μM) reversed sumatriptan-induced contractions. Frovatriptan also relaxed U-46619 precontracted arteries resulting in a bell-shape concentration-response curve with a maximum response at 600 nM. *In vivo*, intracoronary or i.v. administration of frovatriptan (0.0001-1 mg/kg) to open-chest dogs had no significant effects on resting heart rate, blood pressure, aortic blood flow and other coronary hemodynamics, whereas sumatriptan (0.0003 mg/kg) slightly affected blood pressure and heart rate when administered i.v. and increased systemic peripheral resistance, increased coronary blood flow and reduced left ventricular diastolic pressure after intracoronary administration. Frovatriptan (0.1 mg/kg) had no effects on infarct size or coronary blood flow after reperfusion when administered in a model of myocardial infarction, in contrast to sumatriptan (1.0 mg/kg) which significantly reduced coronary blood flow after reperfusion (3, 4).

A global assessment of 5 randomized, double-blind, placebo-controlled clinical trials involving 3128 patients concluded that 24-h migraine recurrence with frovatriptan (2.5 mg p.o.) was low (7-25% *vs.* 20-31% for placebo and 32% for sumatriptan). The median time to migraine recurrence with frovatriptan was 11.0-21.4 h, compared to 6.2-13.4 h for placebo and 14.0 h for sumatriptan (5).

A major clinical study has evaluated the efficacy and tolerability of frovatriptan in the acute treatment of migraine attacks over a 12-month period in 496 patients. Subjects received frovatriptan (2.5 mg p.o.) at the onset of the first moderate to severe migraine, followed by open-label use of the drug as needed (maximum of 3 doses/24 h) to treat second and subsequent attacks for up to 1 year. A total of 13,878 attacks were treated with frovatriptan, producing significant relief of pain within 24 h of the first dose in 84% of the cases. Efficacy was consistent over subsequent uses, with meaningful relief in 80 and 75% of the second and last attacks treated, respectively. The drug was well tolerated and highly acceptable to patients; only 5% of the trial participants discontinued due to adverse events (6).

A review of safety data obtained during short-term and 12-month studies concluded that frovatriptan (2.5 mg p.o.) is well tolerated for up to 3 doses in a 24-h period, with an incidence of adverse events which is only slighter higher than that of placebo (47% *vs.* 34%). The drug was well tolerated by patients of both genders and of various ages, races and cardiovascular status, indicating that it is appropriate for use by a wide variety of patients. No serious treatment-related adverse events occurred in more than 2000 patients treated (7).

As certain other triptan compounds have been shown to act as substrates for monoamine oxidase, a study was conducted to determine this potential interaction in the case of frovatriptan. Twelve female subjects received 7 days of pretreatment with the MAO-A inhibitor moclobemide (150 mg b.i.d.), after which they were administered frovatriptan (2.5 mg p.o.) alone or in combination with moclobemide (150 mg p.o.) according to an open, randomized, 2-period, crossover design. Pharmacokinetic parameters indicated that moclobemide did not affect the systemic bioavailability of frovatriptan. No adverse effects on vital signs, ECGs or other safety measures were seen with frovatriptan alone or in combination with the MAO-A inhibitor (8).

A study in 12 healthy female volunteers has demonstrated minimal pharmacokinetic interactions between frovatriptan and ergotamine. Coadministration of the two antimigraine agents (5 mg p.o. frovatriptan + 2 mg sublingual ergotamine tartrate) reduced the bioavailability of frovatriptan slightly but did not affect its safety or tolerability (9).

In a double-blind study, 695 patients with migraine were randomized to placebo or a single oral dose of frovatriptan (0.5, 1, 2.5 or 5 mg). The 4-h response rates for 2.5 and 5 mg were 68 and 67% compared to 33% for placebo (p <0.005). Frovatriptan 2.5 mg was determined to be the lowest effective dose (10).

A total of 598 patients with migraine were administered a single oral dose of frovatriptan (0.5, 1, 2.5 or 5 mg) or placebo. Two-hour response rates for 2.5 and 5 mg were 38 and 37% compared to 25% for placebo. The 0.5 and 1 mg doses did not differ from placebo. Frovatriptan 5 mg exerted additional efficacy with a greater rate of adverse events. The optimal dose was determined to be 2.5 mg (11).

A total of 844 patients with migraine were administered either placebo or a single oral dose of frovatriptan (2.5, 5, 10, 20 or 40 mg). Two-hour response rates for all doses of frovatriptan (40-48%) were greater than placebo (22%). Frovatriptan was safe and effective in a broad dose range. While all doses were equally effective, a dose-dependent incidence of adverse events was observed (12).

An overview of three phase III studies evaluating frovatriptan (2.5 mg p.o.) in patients with migraine concluded that the study drug was consistently superior to placebo, giving 2-h and 4-h headache response rates of 39% and 56%, 46% and 65%, and 36% and 62% in the three studies (placebo responses ranged from 21-38%). The median times to first response to frovatriptan were 3.75, 2.67 and 3.75 h; the corresponding values for placebo in these studies were 5.57, 6.0 and 8.5 h. Migraine-associated symptoms consistently resolved more quickly with frovatriptan than with placebo, and the proportion of patients with little or no functional impairment was consistently higher with the study drug at all time points (13).

Propranolol was shown to have minimal effects on the pharmacokinetics and safety of frovatriptan in an open, randomized, crossover study in 12 male and female healthy volunteers pretreated for 7 days with propranolol (80 mg p.o. b.i.d.) and then given a single dose of frovatriptan (2.5 mg p.o.) alone or with propranolol. Increased bioavailability of frovatriptan was observed after combination treatment with blood $AUC_{(0-\infty)}$ increasing by 25% in both sexes and C_{max} increasing by 23% in males and 16% in females; t_{max} and $t_{1/2}$ were not affected although urinary excretion of unchanged frovatriptan was greater after combination treatment in both sexes. Treatments were well tolerated with no adverse effects observed (14, 15).

The pharmacokinetics of frovatriptan (2.5 mg p.o.) were investigated in 12 healthy young and elderly volunteers. Concentrations of frovatriptan were 2-fold higher in whole blood than in plasma. Mean blood C_{max} values were achieved at 2-4 h in 96% of the subjects and were 4.2. 7.0. 5.7 and 8.6 ng/ml in young males, young females, elderly males and elderly females, respectively; AUC blood values were 46, 94, 73 and 115 ng/h/ml, respectively, and a mean blood terminal half-life of 20-25 h was obtained. I.v. administration in young subjects suggested that age differences in blood concentrations may be due to higher bioavailability and lower clearance rates in females compared to males. It was concluded that no age-related dose adjustments were required (16, 17).

The pharmacokinetics of frovatriptan (2.5 and 40 mg p.o. or 0.8 mg 30 min i.v. infusion) were investigated in 12 healthy volunteers showing that all treatments were well tolerated. An elimination half-life of 25 h was found for both genders. Concentrations of frovatriptan were higher in whole blood than in plasma with mean peak blood concentrations with the 2.5 mg dose achieved by 2-4 h (4.2 and 7.0 ng/ml in males and females, respectively). AUC blood values were about 2-fold higher in females than males and gender differences were more apparent with the 40 mg dose. I.v. administration showed that gender differences may be due to bioavailability (30 in females *vs.* 24% in males) in addition to lower clearance rates (132 *vs.* 216 ml/min) and volume of distribution (3.0 *vs.* 4.2 l/kg) in females. It was concluded that no gender-related dose adjustments were required (18).

No effects on the cardiovascular system were observed in healthy male volunteers administered frovatriptan at single doses as high as 100 mg. Slight and transient increases in blood pressure were observed only at doses 32-40 times higher than the therapeutic dose level (19).

Several studies have demonstrated the antimigraine efficacy of frovatriptan. The lowest effective dose was found to be 2.5 mg p.o. in a randomized, placebo-controlled, double-blind study enrolling 695 patients. The drug was well tolerated at doses of up to 5 mg, although additional efficacy was not obtained at this higher dose (20).

Single-dose oral frovatriptan (0.5-40 mg) given during acute migraine attack was shown to be safe and effective in a placebo-controlled study in 1442 patients. Response rates were significantly higher than placebo and were similar for doses of 2.5-40 mg at 2 h posttreatment (38-40%); no significant differences were observed at 2 h between placebo (24%) and doses of 0.5 and 1 mg (30 and 26%, respectively). At 4 h postdosing, all doses produced response rates (51-72%) significantly superior to placebo (35%). Incidence of adverse effects were similar in placebo and groups receiving 0.5, 1 and 2.5 mg but increased in groups given 10 mg or more (21, 22).

Twelve migraineurs received a single oral dose of frovatriptan (2.5 mg) during a moderate or severe attack and 10 days later to assess the pharmacokinetics and tolerability during and outside an attack. An improvement from moderate/severe to mild/no headache was reported in 11 patients which occurred at a mean of 1.5 h postdose. C_{max} values differed among women and men during an attack (5.41 *vs.* 2.59 ng/ml, respectively) and outside an attack (4.95 *vs.* 2.37 ng/ml, respectively). Higher AUC values were also found in women than men during an attack (80.7 *vs.* 18.5 ng.h/ml) and outside an attack (51.7 *vs.* 17.1 ng.h/ml). Overall, the pharmacokinetics and tolerability of frovatriptan did not vary when taken during or outside a migraine attack (23).

In a randomized, placebo-controlled, multicenter study, one or two doses of frovatriptan (2.5 mg p.o.) were compared in 75 migraineurs at high risk of or with known coronary artery disease. Results showed a significantly higher incidence of significant 12-lead ECG changes at 4 h postdose in the placebo group. Frovatriptan was not associated with an increase in ST segments, heart rate or rhythm, blood pressure or troponin T (24).

The pharmacokinetics of a single dose of frovatriptan (2.5 mg) were evaluated in 11 patients with renal impairment. Peak plasma concentrations ranged from 0.88-6.61 ng/ml with no distinct differences between renally impaired and healthy controls. Likewise, no significant differences were found for t_{max} or AUC among subjects. Regression analysis revealed no relationship between plasma pharmacokinetics and renal impairment; as foreseen, renal clearance and urinary frovatriptan excretion decreased with increasing renal impairment (25).

Frovatriptan is the new proposed international nonproprietary name for SB-209509/VML-251 (26).

Vanguard Medica and Elan have received notification that the NDA submitted for frovatriptan (Miguard®) for the acute treatment of migraine has been accepted for review by the FDA. The full review process is expected to take approximately 12 months. The acceptance of the NDA triggers a second milestone payment from Elan to Vanguard. Further payments will be made over the next 3-4 years upon NDA approval and upon reaching agreed sales levels. Vanguard will continue to be responsible for the manufacture and supply of frovatriptan (27-30).

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20. Goldstein, J., Elkind, A., Keywood, C., Klapper, J., Ryan, R. *A low-dose range-finding study of frovatriptan: A potent selective 5-HT$_{1B/1D}$ agonist for the acute treatment of migraine.* 40th Annu Sci Meet Am Assoc Study Headache (June 26-28, San Francisco) 1998, 159.

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22. Rapoport, A.M., Keywood, C. *Frovatriptan - Dose response studies.* Headache 1999, 39(5): 375.

23. Buchan, P. et al. *Frovatriptan pharmacokinetics are unaffected during a migraine attack.* Cephalalgia 1999, 19(4): Abst II-G1-34.

24. Elkind, A. et al. *Cardiovascular safety of frovatriptan in patients at high risk of or with known coronary artery disease during a migraine attack.* Cephalalgia 1999, 19(4): Abst II-G1-35.

25. Cohen, A.F. et al. *Pharmacokinetics of frovatriptan in patients with renal impairment.* Cephalalgia 1999, 19(4): Abst II-G1-33.

26. *Proposed international nonproprietary names (Prop. INN): List 78.* WHO Drug Inf 1997, 11(4): 275.

27. *Elan obtains North American marketing rights for frovatriptan.* DailyDrugNews.com (Daily Essentials) Oct 9, 1998.

28. *Vanguard Medica: Six-month highlights.* DailyDrugNews.com (Daily Essentials) Oct 16, 1998.

29. *Vanguard Medica and Elan seek regulatory approval of Miguard in the U.S.* DailyDrugNews.com (Daily Essentials) Feb 2, 1999.

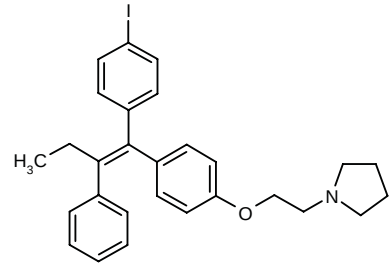
30. *NDA for frovatriptan accepted for FDA review.* DailyDrugNews.com (Daily Essentials) March 31, 1999.

Original monograph - Drugs Fut 1997, 22: 725.

Idoxifene

Treatment of Breast Cancer
Estrogen Receptor Modulator

EN: 143813



$C_{28}H_{30}INO$ **SmithKline Beecham; BTG**

The effects of idoxifene on the reproductive system have been studied using the endogenous estrogen response element (ERE). Idoxifene had no significant agonist effect through the ERE in human breast cancer MCF-7 cells and human endometrial cells, confirming that it acts like a SERM. Furthermore, it acted as an antagonist in reproductive tissues when given together with estrogen, and studies in female rats demonstrated a significant, dose-dependent (0.5-1.5 mg/kg/day x 8 weeks) reduction in uterine wet weight on idoxifene compared to placebo. Thus, its estrogen-antagonist effects in reproductive tissues together with its beneficial effects on bone and cholesterol suggest that idoxifene is a promising alternative to currently available hormone replacement therapies (1).

The effects of idoxifene and tamoxifen were compared in tumor-bearing ovariectomized athymic mice treated with estrogen and the drugs at 4 weeks of tumor growth. Both drugs significantly inhibited estrogen-dependent tumor growth and induced a 3-fold induction of apoptosis (2.5% *vs.* 0.8% in controls); estrogen withdrawal caused significant tumor regression. The effects of idoxifene were maintained for 3 months while tamoxifen effects returned to baseline. Proliferation at 4 weeks was reduced in tamoxifen (35.2%)- and idoxifene (32.5%)-treated animals as compared to controls (51.0%). Estrogen receptor induction with initial treatment, significant decreases in progesterone receptor with prolonged treatment and increases in p27 expression were seen with both agents; no effect on p21 expression was observed (2).

Idoxifene's effects on bone loss, serum cholesterol, uterine wet weight and histology were assessed in ovariectomized (Ovx) rats. Doses of 0.5 mg/kg/day prevented loss of lumbar and proximal tibial bone mineral density (BMD). Idoxifene (0.5 and 2.5 mg/kg/day) also prevented continued loss of lumbar and proximal tibial BMD in a 2-month treatment period started 1 month after surgery, when significant BMD had taken place in the Ovx control group. The agent decreased total serum cholesterol which reached maximum levels with 0.5 mg/kg/day, showed minimal uterotrophic activity in Ovx rats and inhibited the agonist activity of estrogen in intact rats (3).

In a randomized phase II pharmacokinetic study, 32 postmenopausal women with breast cancer were given either idoxifene (60 mg loading dose days 1-14 followed by 40 mg/day) or tamoxifen (40 mg/d). Idoxifene plasma levels were 280 ± 33 ng/ml at the end of the loading period followed by a gradual increase to 401 ± 59 ng/ml by week 12; idoxifene steady-state concentrations were 40% higher than tamoxifen. The major metabolites were the deaminated hydroxyl side-chain compound and the ring-oxidized pyrrolidinone with levels of the former continuing to increase and steady state achieved by the latter at 12 weeks. A minor metabolite of idoxifene, the aminoethyl side-chain compound, was also detected (4).

A randomized, double-blind, phase II study compared idoxifene (40 mg/day) with tamoxifen (40 mg/day) in 56 postmenopausal women with locally advanced/metastatic breast cancer resistant to 20 mg/day tamoxifen. No differences in time to progression or overall survival (18.6 and 21.3 months) were observed between groups. Of the 47 evaluable tamoxifen-resistant patients treated with idoxifene, 2 partial responses and 2 disease stabilizations for > 6 months were observed, while no objective responses and 2 stable diseases were observed in patients receiving tamoxifen. Both treatments were well tolerated and no differences in toxicities including hot flushes (13 and 15%) and mild nausea (33 and 27%) were observed between groups. Serum drug levels for idoxifene and tamoxifen at 12 weeks were 394 ± 41 and 265 ± 31 ng/ml, respectively. Significant decreases in FSH and LH and an increase in SHBG levels were observed after 4 weeks in idoxifene- and tamoxifen-treated patients failing prior tamoxifen therapy. No changes in serum estradiol or IGF-1 levels were detected and cholesterol levels were decreased by 11% for both groups (5).

The potential estrogenic effects of idoxifene have been evaluated in osteopenic postmenopausal women during a 3-month, double-blind, placebo-controlled trial. The compound was administered at doses of 2.5, 5.0 and 10.0 mg/day, and the corresponding decreases in markers of bone resorption and formation were similar to those that would conceivably be attained with estrogen. Urinary crosslaps decreased by 10.0, 15.8 and 25.1% from baseline in the respective dose groups, while serum osteocalcin decreased by 5.4, 7.8 and 16.1%, respectively. Serum LDL cholesterol and plasma fibrinogen levels also decreased significantly, indicating potential cardioprotective activity, and no estrogenic effects on endometrium were observed (6).

SmithKline Beecham has discontinued the development of idoxifene for the treatment of osteoporosis due to insufficient clinical benefit in phase III clinical trials. However, the company will continue to pursue the development of the compound for the treatment of advanced breast cancer, for which it is in phase II trials (7, 8).

1. Nuttall, M.A. et al. *Idoxifene antagonizes the effects of estrogen in the breast and endometrium: A therapeutically favorable profile over estrogen in reproductive tissues.* 2nd Jt Meet Am Soc Bone Miner Res Int Bone Miner Soc (Dec 1-6, San Francisco) 1998, Abst SA361.

2. Boeddinghaus, I.M. et al. *Idoxifene antagonizes estradiol-dependent MCF-7 breast cancer xenograft growth by sustained apoptosis.* Proc Amer Assoc Cancer Res 1999, 40: Abst 4201.

3. Nuttall, M.E. et al. *Idoxifene: A novel selective estrogen receptor modulator prevents bone loss and lowers cholesterol levels in ovariectomized rats and decreases uterine weight in intact rats.* Endocrinology 1998, 139(12): 5224.

4. Haynes, B.P., Grimshaw, R.M., Griggs, L.J. et al. *Pharmacokinetics of idoxifene and tamoxifen in a randomised phase II trial in breast cancer patients who have relapsed on tamoxifen.* 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 679.

5. Johnston, S.R.D. et al. *A phase II randomised double-blind study of idoxifene (40 mg/d) vs. tamoxifen (40 mg/d) in patients with locally advanced/metastatic breast cancer resistant to*

tamoxifen (20 mg/d). Proc Amer Soc Clin Oncol 1999, 18: Abst 413.

6. Weiss, S., Mulder, H., Chesnut, C., Greenwald, M., Delmas, P., Eastell, R., Kravitz, B., MacDonald, B. *Idoxifene reduces bone turnover in osteopenic postmenopausal women.* 80th Annu Meet Endocr Soc (June 24-27, New Orleans) 1998, Abst P3-72.

7. *BTG: six-month highlights.* DailyDrugNews.com (Daily Essentials) Dec 8, 1998.

8. *SmithKline Beecham: Annual report 1998/Q1 report 1999.* DailyDrugNews.com (Daily Essentials) April 27, 1999.

Original monograph - Drugs Fut 1995, 20: 666.

Additional References

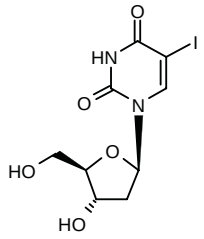
MacDonald, B.R. *Molecular and clinical studies on idoxifene: A novel selective estrogen receptor model.* 2nd Int Conf Osteoporos (Feb 18-19, Boston) 1999, Abst.

Nuttall, M.E. *Idoxifene: A selective estrogen receptor modulator with a unique tissue-specific profile and mechanism of action.* Int Symp Pharm Women (Jan 25-26, Scottsdale) 1999, Abst.

Idoxuridine

Antineoplastic

EN: 130013



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

Intravesical instillation of radioiodinated iododeoxyuridine (IUdR) was shown to be selectively localized to bladder tumors with minimal uptake by normal bladder tissue and minimal systemic absorption. Twenty intravesical instillation studies were performed in 24 patients with bladder cancer given the agent via a Foley catheter. The average tumor uptake was 0.185 ± 0.120% and preferential tumor uptake was observed in the 6 patients analyzed. Tumor/normal bladder ratio was 3.2-74000. Although instillation within 24 h of transurethral resection resulted in higher systemic uptake, levels were not considered dangerous. No increase in systemic absorption was observed 1-4 weeks after transurethral surgery and no redistribution of radioactivity was seen in other organs (1).

A phase I trial examined the efficacy and tolerability of sequential administration of Tomudex (1, 2 or 2.5 mg/m^2 15-min infusion) and IUdR (1050, 2100, 4200, 6300, 8300 or 10,400 mg/m^2 24-h infusion) in 27 patients with colorectal, small bowel and melanoma tumor types. Dose-limiting toxicities (grade 4 neutropenia) were observed in 2/3 patients treated with 2.5/10,400 Tomudex/IUdR. Of the 27 patients, 18 had grade 3 and 2 had grade 4 toxicities including neutropenia, anemia, chills, stomatitis and dermatotoxicity. Of 26 evaluable patients, 1 partial response, 15 stable disease and 10 progressive disease were observed. The recommended phase II dose was 2 mg/m^2 Tomudex and 10,400 mg/m^2 IUdR (2).

1. Chiou, R.K. et al. *Tumor localization and systemic absorption of intravesical radio-iodinated iododeoxyuridine (IUdR) in bladder cancer patients.* 94th Annu Meet Am Urol Assoc (May 1-6, Dallas) 1999, Abst 1217.

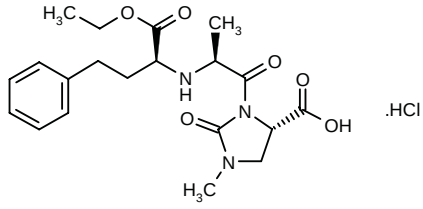
2. Galanis, E. et al. *Phase I trial of sequential administration of Tomudex and 5-iodo-2'-deoxyuridine (IdUrd).* Proc Amer Soc Clin Oncol 1999, 18: Abst 660.

Original monograph - Drugs Fut 1995, 20: 670.

Imidapril Hydrochloride
Novarok®
Tanatril®

Antihypertensive
ACE Inhibitor

EN: 184789



$C_{20}H_{27}N_3O_6.HCl$ **Nihon Schering; Tanabe; Trinity Pharm.**

Tanabe Seiyaku's antihypertensive imidapril hydrochloride (Tanatril®) has been launched in the U.K. by Trinity Pharmaceuticals for the treatment of hypertension, presented as tablets containing 5 mg and 10 mg. Imidapril is a long-acting ACE inhibitor for once-daily administration that exerts potent hypotensive effects via its metabolite imidaprilat (1).

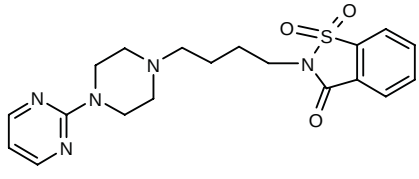
1. *First European launch for Tanatril.* DailyDrugNews.com (Daily Essentials) June 4, 1999.

Original monograph - Drugs Fut 1992, 17: 551.

Ipsapirone

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

EN: 127834



$C_{19}H_{23}N_5O_3S$ **Troponwerke**

In a randomized, double-blind, placebo-controlled study, 9 women with bulimia nervosa and 10 healthy controls were given either ipsapirone (20 mg p.o.) or placebo. Baseline oral temperature was the same for both groups; however, placebo-adjusted mean decrease in temperature was greater for bulimia patients. Results indicate a possible abnormally increased responsiveness of inhibitory presynaptic 5-HT_{1A} receptors in bulimic individuals (1).

A double-blind, placebo-controlled study examined the effects of ipsapirone (20 mg p.o.) in 25 personality disorder outpatients and 10 normal controls. The results from 10 normal controls and 9 personality disorder patients showed that the agent significantly reduced temperature and increased cortisol levels. The temperature effects were shown to be negatively correlated with prolactin response to fenfluramine and positively with the Barraft Impulsiveness scale (2).

Controlled-release ipsapirone (20 mg) and fluoxetine (80 mg) were assessed in 10 healthy volunteers for their ability to elicit 5-HT_{1A}-mediated corticotropin, cortisol and temperature responses after 3 weeks of treatment. Although long-term administration of both antidepressants did not alter plasma corticotropin and morning cortisol concentrations, it did reduce stimulation of corticotropin and cortisol release. This subsensitiviy was found to be reversible (3).

1. Wolfe, B.E. et al. *Serotonin-1A receptor function in bulimia nervosa: Temperature responses following ipsapirone pharmacological challenge.* 21st CINP Congress (July 12-16, Glasgow) 1998, Abst PW16067.

2. Reynolds, D.A. et al. *Ipsapirone as a serotonergic probe in personality disorder patients.* 152nd Annu Meet Am Psychiatr Assoc (May 15-20, Washington) 1999, Abst NR304.

3. Berlin, I. et al. *Blunted 5-HT_{1A}-receptor agonist-induced corticotropin and cortisol responses after long-term ipsapirone and fluoxetine administration to healthy subjects.* Clin Pharmacol Ther 1998, 63(4): 428.

Original monograph - Drugs Fut 1986, 11: 565.

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Huang, J., Azmitia, E.C. *5-HT_{1A} receptor agonist reverses the loss of the mature neuronal phenotypes induced by ADX in adult rat hippocampal dentate gyrus.* FASEB J 1998, 12(4, Part 1): Abst 2661.

Lopez Rubalcava, C. et al. *Blockade of the anxiolytic-like action of ipsapirone and buspirone, but not that of 8-OH-DPAT, by adrenalectomy in male rats.* Psychoneuroendocrinology 1999, 24(4): 409.

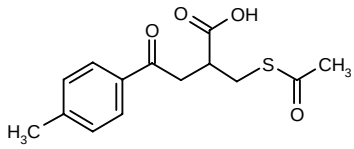
Schwartz, P.J. et al. *Serotonin hypothesis of winter depression: Behavioral and neuroendocrine effects of the 5-HT_{1A} receptor partial agonist ipsapirone in patients with seasonal affective disorder and healthy control subjects.* Psychiatry Res 1999, 86(1): 9.

Shiah, I.S. et al. *Enhanced cortisol response to ipsapirone in mania.* 21st CINP Congress (July 12-16, Glasgow) 1998, Abst PM03011.

To, C.T., Bagdy, G. *Anxiogenic effect of central CCK administration is attenuated by chronic fluoxetine or ipsapirone treatment.* Neuropharmacology 1999, 38(2): 279.

KE-298 *Antiarthritic*
Esonarimod

EN: 144187



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

The effects of KE-298 on synovium functions were examined *in vitro* using TNF-α stimulated synoviocytes from the knee joints of patients with rheumatoid arthritis and type B fibroblast-like synoviocytes. KE-298 significantly and concentration-dependently suppressed TNF-α-induced promatrix metalloproteinase-1 and IL-6 production; tissue inhibitor-1 production of metalloproteinases was unaffected by KE-298. Suppression of these products may be the mechanism by which KE-298 is effective in rheumatoid arthritis (1).

SCID mice reconstituted with peripheral blood mononuclear cells (PBMCs) from 3 rheumatoid arthritis patients or 3 healthy subjects were treated with KE-298 (2 mg/day for 5 days/week). Human immunoglobulin levels were stable at 8-10 weeks and no differences in IgG and IgM levels were observed between groups at 10 weeks. However, IgG-rheumatoid factor (RF) and IgM-RF from SCID mice with PBMCs from rheumatoid arthritis patients were significantly lower in the KE-298 animals as compared to controls (2).

Esonarimod is the proposed international nonproprietary name for KE-298 (3).

1. Takahashi, S., Inoue, T., Higaki, M., Mizushima, Y. *Suppressive effects of the new antirheumatic drug KE-298 on TNF-alpha-induced production of matrix metalloproteinases but not of tissue inhibitor-1 of metalloproteinases in human rheumatoid synoviocytes.* Drugs Exp Clin Res 1998, 24(2): 67.

2. Hamada, Y. et al. *An effect of KE-298 on antibody production by SCID mice reconstituted with peripheral blood mononuclear cells from rheumatoid arthritis patients.* Jpn Pharmacol Ther 1998, 26(10): 175.

3. *Proposed international nonproprietary names (Prop. INN): List 79.* WHO Drug Inf 1998, 12(2): 106.

Original monograph - Drugs Fut 1996, 21: 691.

Additional References

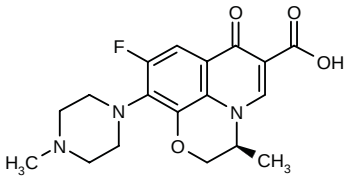
Nagahata, N. et al. *Development of a column switching HPLC method for quantifying KE-298 and its metabolite in human urine.* 118th Annu Meet Pharm Soc Jpn (March 31-April 2, Kyoto) 1998, Abst 02(YP)12-15.

Ohmi, N. et al. *Pharmacokinetics of KE-298, a novel anti-rheumatic agent (7): Identification of metabolic enzyme in rat and human hepatic microsome.* Xenobiotic Metab Dispos 1998, 13(Suppl.): Abst 12P064.

Levofloxacin
Levaquin®
Tavanic®

Fluoroquinolone Antibacterial

EN: 134320



$C_{18}H_{20}FN_3O_4$ **Daiichi Pharm.; Ortho-McNeil; Glaxo Wellcome; Hoechst Marion Roussel**

FDA approval was obtained for a new indication for levofloxacin (Levaquin®) Tablets/Injection. The new approval is for short-course therapy with levofloxacin once daily for 3 days in the treatment of mild to moderate uncomplicated urinary tract infection, such as acute cystitis, in women caused by *Escherichia coli*, *Klebsiella pneumoniae* or *Staphylococcus saprophyticus* (1).

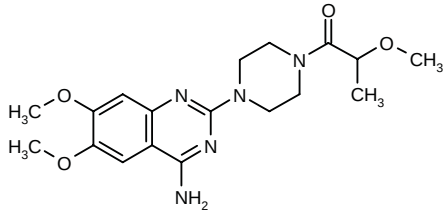
1. *Levofloxacin cleared for new indication by FDA.* DailyDrugNews.com (Daily Essentials) Jan 5, 1999.

Original monograph - Drugs Fut 1992, 17: 559.

Metazosin
VUFB-15111
Kenosin®

Treatment of BPH
Treatment of Heart Failure
α_1-Adrenoceptor Antagonist

EN: 101010



$C_{18}H_{25}N_5O_4$ **Res. Inst. Pharm. Biochem. (CZ)**

Clinical testing of metazosin has been conducted through phase III for the indications of benign prostatic hypertrophy and acute heart failure. The compound is available for licensing, wholly or in part, from VUFB (1).

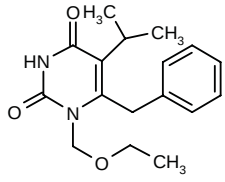
1. *Licensing opportunity from VUFB: α_2-Adrenoceptor antagonist for BPH and heart failure.* DailyDrugNews.com (Daily Essentials) Feb 16, 1999.

Original monograph - Drugs Fut 1990, 15: 680.

MKC-442
Emivirine
Coactinon®

Anti-HIV
Reverse Transcriptase Inhibitor

EN: 201056



$C_{17}H_{22}N_2O_3$ **Mitsubishi Chem.; Triangle; Abbott**

MKC-442 in combination with 3TC and AZT was more efficient than a two-drug combination in suppressing HIV replication *in vitro*. However, the triple-drug combination therapy was less efficient in inhibiting viral breakthrough from an AZT-resistant strain than from an AZT-sensitive strain (1).

The reproductive and developmental safety of MKC-442 have been evaluated in animal studies. The compound was administered orally to Sprague-Dawley rats and New Zealand white rabbits at doses of 10, 40 or 160 mg/kg/day in order to evaluate its effects on fertility, embryonic development, teratology and peri/postnatal development. At doses up to 8 times those in humans, MKC-442 had no effects on fertility, sperm count and motility or early embryonic development in rats. No increase in the incidence of fetal abnormalities was observed in either species, and both dams and offspring showed normal pregnancy rates, live birth indices and pup viability in peri/postnatal development studies in rats. These favorable safety findings, together with the compound's demonstrated anti-HIV efficacy in adult patients, make MKC-442 an attractive candidate for evaluation in pediatric AIDS (2).

Triangle Pharmaceuticals is currently conducting pivotal clinical trials in the U.S., Europe and Africa with emivirine (Coactinon®, formerly MKC-442) as part of coactive or combination regimens in HIV-infected patients. These studies are designed to demonstrate the safety and efficacy, as measured by viral load, of emivirine. In phase I studies in HIV-positive volunteers, the compound was well tolerated and produced minor side effects only at the highest dose levels; these higher doses, however, were much higher than the concentrations required to suppress 90% of the HIV virus *in vitro*. Preliminary data from a phase I/II double-blind, placebo-controlled study evaluating the safety and efficacy of multiple oral doses of emivirine (100-1000 mg b.i.d. for up to

2 months) in 49 patients indicate that viral load was reduced by an average of 96% after just 1 week of drug therapy in all patients treated at a dose level of 750 mg b.i.d. This reduction was sustained for 2 weeks, followed by a gradual increase in viral load from the nadir to baseline levels. Emivirine was generally well tolerated in the latter study, with transient headache, rash, diarrhea, nausea and vomiting being the most frequently reported adverse events (3).

1. Yuasa, S., Nakade, K., Piras, J., Baba, M. *Drug combination studies on MKC-442 with RT inhibitors in long-term culture of HIV-1-infected cells.* 12th World AIDS Conf (June 28-July 3, Geneva) 1998, Abst 12362.

2. Grizzle, T.B., Rousseau, F.S., Moxham, C.P., Szczech, G.M. *Favorable reproductive and developmental safety profile of MKC-442, a new non-nucleoside reverse transcriptase inhibitor (NNRTI).* 38th Interci Conf Antimicrob Agents Chemother (Sept 24-27, San Diego) 1998, Abst I-12.

3. *Pivotal studies of anti-HIV drug candidate under way on three continents.* DailyDrugNews.com (Daily Essentials) April 16, 1999.

Original monograph - Drugs Fut 1998, 23: 718.

Additional References

Blum, M.R. et al. *A pharmacokinetic interaction evaluation of MKC-442 and nelfinavir (NFV) in healthy male and female volunteers.* 12th World AIDS Conf (June 28-July 3, Geneva) 1998, Abst 12380.

De Clercq, E. *The role of non-nucleoside reverse transcriptase inhibitors (NNRTIs) in the therapy of HIV-1 infection.* Antivir Res 1998, 38(3): 153.

Harris, J. et al. *Development of genotypic and phenotypic resistance to MKC-442, a potent and selective inhibitor of HIV-1 replication.* Antivir Res 1998, 37(3): Abst 73.

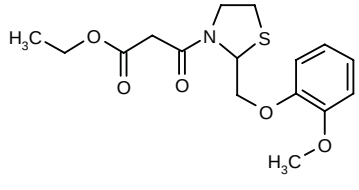
McCreedy, B. et al. *Genotypic and phenotypic analysis of HIV-1 from patients receiving combination therapy containing two nucleoside reverse transcriptase inhibitors (NRTIs) and the non-NRTI, emivirine (MKC-442).* Antivir Ther 1999, 4(Suppl. 1): Abst 13.

Moxham, C. et al. *Evaluation of potential interactions between MKC-442 and zidovudine (ZDV)-lamivudine (3TC), and stavudine (d4T)-didanosine (ddI) in healthy volunteers.* 12th World AIDS Conf (June 28-July 3, Geneva) 1998, Abst 12374.

Moguisteine

Antitussive

EN: 147986



$C_{16}H_{21}NO_5S$ **Roche**

The antitussive properties of moguisteine were shown to be mediated by peripheral mechanisms as evaluated in conscious and anesthetized guinea pigs. Moguisteine (2.5-10 mg/kg i.v.) dose dependently decreased the cough reflex provoked by 7.5% citric acid aerosol (ED_{50} = 0.55 mg/kg) in conscious guinea pigs. In anesthetized animals, the compound administered i.v. (4 and 20 mg/kg) and i.c.v. (20 μg) had no effect on electrically stimulated cough reflex (1, 2).

1. Ishii, R. et al. *Effects of moguisteine on the cough reflex induced by afferent electrical stimulation of the superior laryngeal nerve in guinea pigs.* Eur J Pharmacol 1998, 362(2-3): 207.

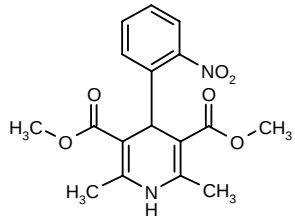
2. Ishii, R., Furuta, M., Hashimoto, M., Naruse, T., Gallico, L., Ceserani, R. *Antitussive effect of moguisteine on the cough reflex induced by electrical stimulation of the superior laryngeal nerve in guinea pigs.* Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 39.13.

Original monograph - Drugs Fut 1991, 16: 618.

Nifedipine Slofedipine XL®

Antianginal
Antihypertensive
Calcium Antagonist

EN: 133799



$C_{17}H_{18}N_2O_6$ **Sanofi-Synthélabo; Pfizer; Bayer**

The U.K. Medicines Control Agency approved for launch a controlled-release version of nifedipine (Slofedipine XL®) which utilizes Penwest's patented TIMERx® controlled-release delivery system. The product is indicated for the treatment of hypertension and prophylaxis of chronic stable angina pectoris and will be supplied as tablets containing 30 and 60 mg. Sanofi expects to introduce the product immediately in the U.K. and plans to launch it in other countries throughout Europe. Penwest is in the process of obtaining approval in other markets (1).

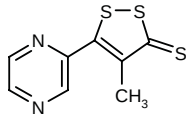
1. *U.K. approval for new controlled-release nifedipine based on TIMERx technology.* DailyDrugNews.com (Daily Essentials) Dec 2, 1998.

Original monograph - Drugs Fut 1981, 6: 427.

Oltipraz

Chemopreventive

EN: 090895



$C_8H_6N_2S_3$ **Rhône-Poulenc Rorer**

Oltipraz was shown to exert protective effects in phase 1 and 2 metabolism of aflatoxin in a study involving 234 healthy subjects randomized to receive oltipraz (125 mg/day or 500 mg/week p.o.) or placebo. A 51% decrease in urinary excretion levels of the phase 1 metabolite aflatoxin M1 was observed after 1 month administration of 500 mg; no effects on the phase 2 metabolite aflatoxin-mercapturic acid were observed. Daily oltipraz treatment resulted in a significant 2.6-fold increase in aflatoxin-mercapturic acid excretion but had no effects on aflatoxin M1. Induction of phase 2 enzymes may serve as a chemopreventive strategy (1).

1. Wang, J.-S. et al. *Protective alterations in phase 1 and 2 metabolism of aflatoxin B_1 by oltipraz in residents of Qidong People's Republic of China.* J Natl Cancer Inst 1999, 91(4): 347.

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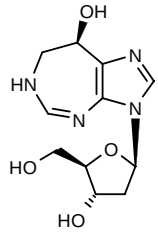
Pentostatin
Nipent®

Antineoplastic

EN: 090779



$C_{11}H_{16}N_4O_4$ **Warner-Lambert; SuperGen**

SuperGen filed a supplemental NDA with the FDA seeking approval for new indications for its already marketed drug pentostatin (Nipent®). The indications requested are for the treatment of various mature T-cell lymphomas, particularly cutaneous T-cell lymphoma and peripheral T-cell lymphoma (1).

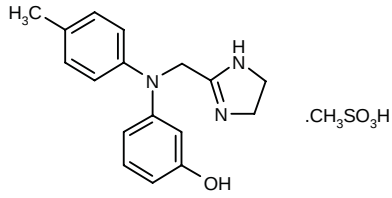
1. *SuperGen files sNDA for Nipent in mature T-cell malignancies.* DailyDrugNews.com (Daily Essentials) March 2, 1999.

Original monograph - Drugs Fut 1981, 6: 419.

Phentolamine Mesilate
Regitin®
Vasomax®
Vasofem®

α-Adrenoceptor Antagonist
Treatment of Erectile Dysfunction

EN: 091428



$C_{17}H_{19}N_3O.CH_4O_3S$ **Zonagen; Schering-Plough**

Dosing of subjects has begun in a U.S. phase I trial of Vasofem® for the treatment of female sexual dysfunction. The study is being conducted by the Chicago Center for Clinical Research and is designed to evaluate the safety and pharmacokinetics of the product in 60 healthy subjects (1).

Zonagen and Schering-Plough have decided to forego a June FDA advisory panel review of the NDA for phentolamine mesilate (Vasomax®) until the results of additional clinical studies can be submitted to the FDA. The two companies believe that inclusion of new data from the ongoing studies should enhance the regulatory filing and the commercial product profile for Vasomax®.

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Zonagen expects to submit the data to the FDA as an amendment to the NDA. Vasomax® was launched in Mexico in June 1998 and in Brazil in April 1999 and a regulatory application was filed in the U.K. in August 1998 as the first step in a mutual recognition procedure for the E.U. (2-4).

1. *Phase I clinical trials of female sexual dysfunction Rx commence.* DailyDrugNews.com (Daily Essentials) Dec 11, 1998.

2. *U.K. filing announced for MED treatment option.* DailyDrugNews.com (Daily Essentials) Sept 11, 1998.

3. *Schering-Plough initiates manufacture of Vasomax.* DailyDrugNews.com (Daily Essentials) March 1, 1999.

4. *Zonagen and Schering-Plough to forego FDA advisory panel review of Vasomax NDA.* DailyDrugNews.com (Daily Essentials) May 11, 1999.

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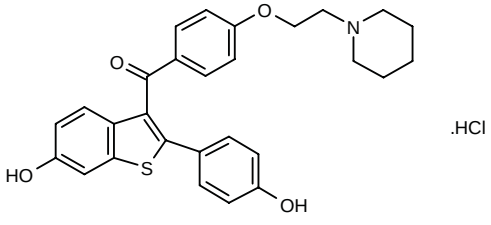
Raloxifene Hydrochloride

Evista® *Treatment of Postmenopausal Syndrome*
Loxifen® *Estrogen Receptor Modulator*

EN: 090328



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

Raloxifene was shown to inhibit growth of human colon cancer cells *in vitro*. Proliferation was significantly inhibited and viable cell number was dose-dependently decreased in cells incubated with the agent (0.05, 0.5, 1.0, 5.0 and 50 μM) for 72 h. These results suggest the presence of an estrogen-independent pathway and possible involvement of estradiol metabolites in the growth of these cell types (1).

The effects of raloxifene were evaluated on isolated rabbit and human coronary arteries, both with and without endothelium. Raloxifene produced significant relaxation of rabbit preparations precontracted with $PGF_{2\alpha}$ and human coronary artery rings precontracted with U-46619, with significantly greater effects in rings with intact endothelium compared to endothelium-denuded preparations. The relaxant effect of raloxifene in rabbit coronary artery rings with endothelium was significantly inhibited by L-NAME, BaCl and ICI-182780. These findings provide support for endothelium-dependent coronary artery relaxant effects for raloxifene, which appear to involve nitric oxide and estrogen receptors. Further studies also suggested that an effect on calcium conductance may be involved in its actions at higher doses (2).

The neurotrophic and neuroprotective properties of raloxifene were compared to those of estrogen replacement therapy in cultured neurons from rat cerebral cortex, hippocampus and basal forebrain. Conjugated equine estrogens produced significant neurotrophic effects in all three brain regions, whereas raloxifene induced a neurotrophic effect only in hippocampal neurons, demonstrating the different response profiles of the two treatments (3).

The effects of raloxifene on neuronal outgrowth and survival were evaluated in cultured neurons from rat cerebral cortex, hippocampus and basal forebrain. In general, exposure to raloxifene midrange in the dose response (5-50 ng/ml) produced a 20-40% neuroprotective effect, which diminished at a concentration of 1 μg/ml, and produced increased toxicity at 5 μg/ml. The results indicated that raloxifene exerts mixed effects ranging from negative to positive on neuronal outgrowth and survival *in vitro* (4).

The response profile of raloxifene on choline acetyltransferase was evaluated in the hippocampus of ovariectomized rats. Administration of raloxifene (3 mg/kg/day) for 3 or 10 days increased the compromised hippocampal choline acetyltransferase activity to a similar extent as 17β-estradiol (0.03 or 0.3 mg/day). Raloxifene thus acts as an estrogen receptor agonist in terms of choline acetyltransferase activity in rat hippocampus (5).

The ability of raloxifene to prevent atherosclerosis was evaluated in a long- and short-term study in ovariectomized, cholesterol-fed rabbits receiving raloxifene at doses of 10, 30 or 60 mg/kg/day for 2 weeks or 20 or 60 mg/kg/day for 42 weeks. The treatments demonstrated significant antiatherogenic properties with a favorable tolerability similar to that of estrogen treatment (6).

A role for estrogen receptor (ER)β in inhibition of coronary artery atherosclerosis has been demonstrated in a

study examining the effects of tamoxifen and raloxifene in a postmenopausal nonhuman primate model. Surgical menopause via ovariectomy was performed and animals were fed a moderately atherogenic diet. Treatment with conjugated equine estrogens was the most effective in improving plasma lipid/lipoprotein levels and a 70-80% inhibition of coronary artery atherosclerosis was observed. Both drugs were less effective in improving plasma lipid profiles and although raloxifene had no effect on atherosclerotic development, tamoxifen treatment resulted in a 50% reduction in incidence of the disease (7).

Results from a 3-year, double-blind, randomized, placebo-controlled study have shown that raloxifene (60 mg/day) prevented spinal bone loss and increased hip bone mineral density in early postmenopausal women with differences between placebo and treated groups of 1.9 and 2.7% for total body and spine and hip, respectively. Preliminary data were also presented from another 3-year, ongoing, double-blind, randomized study in which 2 doses of raloxifene (60 and 120 mg/day) were compared in over 2000 women (8).

In a multicenter, parallel, double-blind study, 143 postmenopausal women with osteoporosis were randomized to raloxifene (60 or 120 mg/day p.o.) or placebo for 12 months to assess the compound's effects on cognitive function and mood. Raloxifene was superior to placebo on memory and performance assessment scores and was associated with a better outcome on the Geriatric Depression Scale. Findings indicate that raloxifene does not impair cognition or affect mood (9).

The impact of raloxifene and hormone replacement therapy in postmenopausal women was reported in a study which used a Markov model composed of 78 health states. Life expectancy of healthy 50 year old women was increased with hormone replacement therapy and raloxifene as compared to women receiving no intervention. Hormone replacement therapy was found to be optimal for populations with low to average breast cancer risk and increased coronary heart disease risk, while raloxifene was preferred for all other risk profiles (10).

A 1-year prospective, double-blind, randomized trial in 143 women with established postmenopausal osteoporosis was performed to evaluate the safety and potential beneficial effects on bone and lipid profiles of raloxifene hydrochloride. Patients had at least 1 vertebral fracture and low bone mineral density (BMD) and were divided into groups to receive raloxifene 60 or 120 mg/day or calcium (750 mg/day) and vitamin D (400 IU/day) supplements (controls). At 1 year, significant changes were noted in raloxifene-treated patents compared to controls on the following bone turnover markers: serum bone alkaline phosphatase (–14.9% and –8.87%, respectively, on 60 and 120 mg/day), serum osteocalcin (–20.7% and –17.0%, respectively) and urinary C-telopeptide fragment of type I collagen/creatinine (–24.9% and –30.8%, respectively). Furthermore, BMD significantly increased in total hip (1.66% on 60 mg/day) and ultradistal radius (2.92% and 2.50%, respectively, on 60 and 120 mg/day), and nonsignificant increases were observed in lumbar spine, total body and total hip (120 mg/dat). No differences among groups regarding the incidence of uterine bleeding, thrombophlebitis, breast abnormalities or increased endometrial thickness were observed, but reductions in serum total cholesterol (7.0% on 60 mg/day), LDL cholesterol (11.4% on 60 mg/day) and LDL/HDL cholesterol ratio (13.2% and 8.3% respectively, on 60 and 120 mg/day) were found in the raloxifene-treated patients. A dose-dependent reduction in the incidence of severe vertebral fractures was also seen on raloxifene (11).

The effects of raloxifene (60 or 150 mg/day) and conjugated equine estrogen (CEE; 0.625 mg/day) on fibrinolysis were compared in 56 hysterectomized healthy postmenopausal women in a double-blind, randomized, placebo-controlled 2-year study. CEE was found to significantly reduce tissue-type plasminogen activator antigen and plasminogen activator inhibitor-1 antigen, indicating fibrinolytic activity although no increases in plasmin-antiplasmin complexes or D-dimer, other markers of activity, were observed. Raloxifene treatment had no effect on fibrinolysis (12).

Data from the Multiple Outcomes of Raloxifene Evaluation (MORE) study indicated that raloxifene hydrochloride significantly reduced the risk of new spinal fractures among postmenopausal women after 2 years of treatment. The study was designed primarily to evaluate the effect of daily raloxifene therapy on bone mineral density (BMD) and spinal fractures in 7705 postmenopausal women (average 66.5 years) with osteoporosis. Women taking the drug were 52% less likely to have a first spinal fracture and women with a previous spinal fracture were 38% less likely to have new spinal fractures as compared to women taking a placebo supplemented with calcium and vitamin D (13).

Additional results of the MORE study indicate that the risk of invasive breast cancer in raloxifene-treated women was 76% lower than in women randomized to receive placebo. Women with osteoporosis included in the study were randomly assigned to treatment with raloxifene (60 or 120 mg/day p.o.) or placebo for three years; all women also received daily supplements containing calcium (500 mg) and cholecalciferol (400-600 IU). Over a mean follow-up period of 40 months, breast cancer was detected in 56 of the 7705 women originally enrolled in the study; 54 cases are included in the analysis. Twelve cases were classified as ductal carcinoma *in situ* (5, 3 and 4 cases in the placebo, 60 mg raloxifene and 120 mg raloxifene groups, respectively), and 40 cases of breast cancer were classified as invasive (27/2576 in the placebo group and 13/5129 in the combined raloxifene groups). The risk of estrogen receptor-positive invasive breast cancer was decreased by 90% with raloxifene treatment, although the risk of estrogen receptor-negative breast cancer and endometrial cancer was not reduced. The risk of venous thromboembolic disease was 3.1 times higher among raloxifene-treated women than in the placebo group, and more women in the raloxifene group reported new or worsening diabetes (1.2% *vs.* 0.5%). The

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Box 1: The effects of raloxifene on the risk of breast cancer (14) [Prous Science CSline database].

Design	Multicenter, randomized, double-blind, placebo-controlled clinical study
Population	Patients with menopause and osteoporosis (n = 7705)
Treatments	Raloxifene (R), 120 mg/d p.o. + calcium 500 mg/d and cholecalciferol 400-600 IU/d x 40 months (n = 2572) R, 60 mg/d p.o. + calcium 500 mg/d and cholecalciferol 400-600 IU/d x 40 months (n = 2557) Placebo (P) (n = 2576)
Withdrawals	R: 1152 (22.5%) P: 652 (25.3%)
Adverse events	(%) R120, R60, P: influenza syndrome (13.4, 13.5, 11.4), vasodilation (11.5, 9.7, 6.4), hypertension (7.5, 6.9, 9.0), leg cramps (6.9, 7.0, 3.7), endometrial cavity fluid (8.7, 8.1, 5.7), peripheral edema (6.6, 5.2, 4.4), hypercholesterolemia (1.9, 2.2, 4.7), vaginal bleeding (2.8, 2.6, 2.4), hematuria (1.3, 1.4, 2.1), bradycardia (0.7, 0.5, 1.2), diabetes (1.1, 1.2, 0.5), deep vein thrombosis (0.8, 0.7, 0.2), pulmonary embolism (0.3, 0.4, 0.1)
Results (at 40 months)	Breast cancer rate (per 1000 women-years of follow-up): P (4.3) > R (1.5) Breast cancer (% of patients): P (1.2) > R (0.4) [p <0.001] RR (95% CI) of breast cancer: R 0.24 (0.13-0.44) [p <0.001] Invasive breast cancer rate (per 1000 women-years of follow-up): P (3.6) > R (0.9) Invasive breast cancer (% of patients): P (1.0) > R (0.3) [p <0.001] RR (95% CI) of estrogen receptor-positive invasive breast cancer: R 0.1 (0.04-0.24) Endometrial cancer (% of patients): R (0.25) = P (0.2) [p >0.05] RR (95% CI) of endometrial cancer: R 0.8 (0.2-2.7) RR (95% CI) of venous thromboembolic disease: R 3.1 (1.5-6.2)
Conclusions	After 3 years of treatment, raloxifene decreased the risk of invasive breast cancer by 76% in postmenopausal women with osteoporosis

overall mortality rate was similar in the placebo group and the combined raloxifene groups (1.0% and 0.8%, respectively). The results of this ongoing trial appear to support the efficacy of raloxifene in decreasing the risk of estrogen receptor-positive breast cancer in postmenopausal women with osteoporosis and no prior history of breast cancer (14). Box 1.

Following receipt of European-wide marketing approval, Lilly introduced raloxifene hydrochloride (Evista®) in the U.K. It is indicated for the prevention of nontraumatic vertebral fractures in postmenopausal women at increased risk of osteoporosis and is supplied as 60-mg tablets (15).

The Health Protection Branch of Health Canada has approved raloxifene hydrochloride (Evista®) for the prevention of postmenopausal osteoporosis (16).

The FDA has granted a priority review for the supplemental NDA that Lilly filed earlier this year for an osteoporosis treatment indication for raloxifene hydrochloride (Evista®). Evista® has been on the market since January 1998 and is the only selective estrogen receptor modulator available for the prevention of osteoporosis in postmenopausal women. The sNDA is based on interim results from the MORE study (17).

Raloxifene hydrochloride has been launched in Argentina, where it is marketed by Gador as Loxifen®, for the treatment of menopausal disorders. It is supplied as 60-mg tablets (18).

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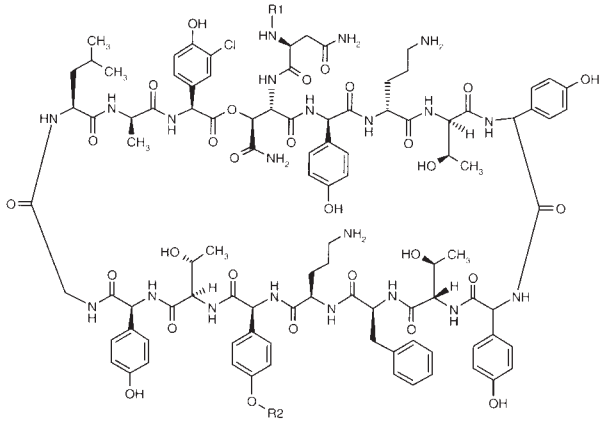
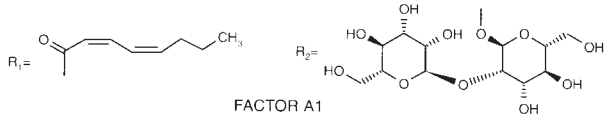
Ramoplanin

Glycopeptide Antibiotic

EN: 091144





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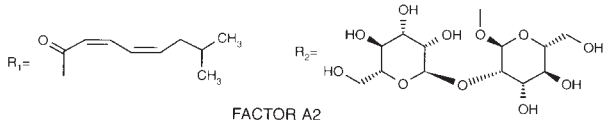

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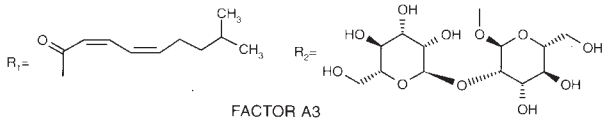
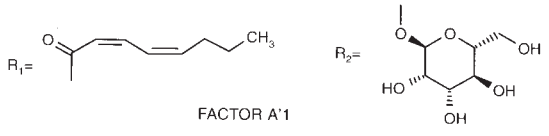
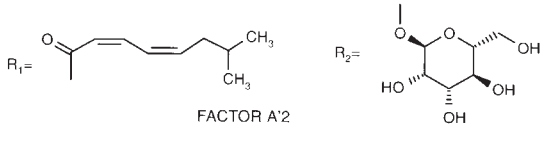


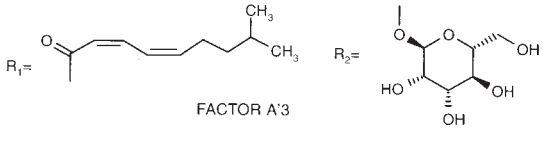
FACTOR A3



FACTOR A'1



FACTOR A'2



FACTOR A'3

Biosearch Italia; Hoechst Marion Roussel; IntraBiotics

IntraBiotics has begun a double-blind, randomized, placebo-controlled phase II clinical trial to determine whether ramoplanin ointment can effectively eradicate nasal carriage of *Staphylococcus aureus* in healthy human volunteers. Nine sites across the U.S. will enroll a total of 250 volunteers who carry *S. aureus* in their nose. All volunteers will receive 4 days of treatment with ramoplanin or placebo and will then be monitored for 90 days to evaluate nasal carriage of this bacterium (1).

IntraBiotics has successfully completed a phase II trial of oral ramoplanin for the suppression of vancomycin-resistant enterococci (VRE) carried in the intestinal tracts of infected individuals. The drug was shown to suppress VRE below detectable levels in nearly all of the patients who carried VRE prior to the study. Due to the efficacy observed, an independent data safety monitoring board recommended early termination of phase II in order to prepare for phase III testing (2, 3).

1. *IntraBiotics begins phase II clinical trial of ramoplanin ointment.* DailyDrugNews.com (Daily Essentials) Jan 14, 1999.

2. *Ramoplanin enters phase II trials in U.S. for eliminating VREF from intestine.* DailyDrugNews.com (Daily Essentials) Oct 22, 1998.

3. *Ramoplanin successfully completes phase II as VRE therapy.* DailyDrugNews.com (Daily Essentials) July 16, 1999.

Original monograph - Drugs Fut 1990, 15: 689.

Repaglinide
Actulin®
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Antidiabetic

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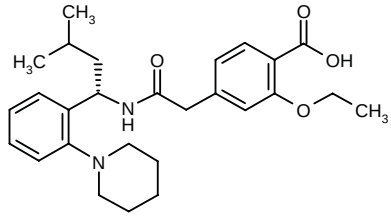
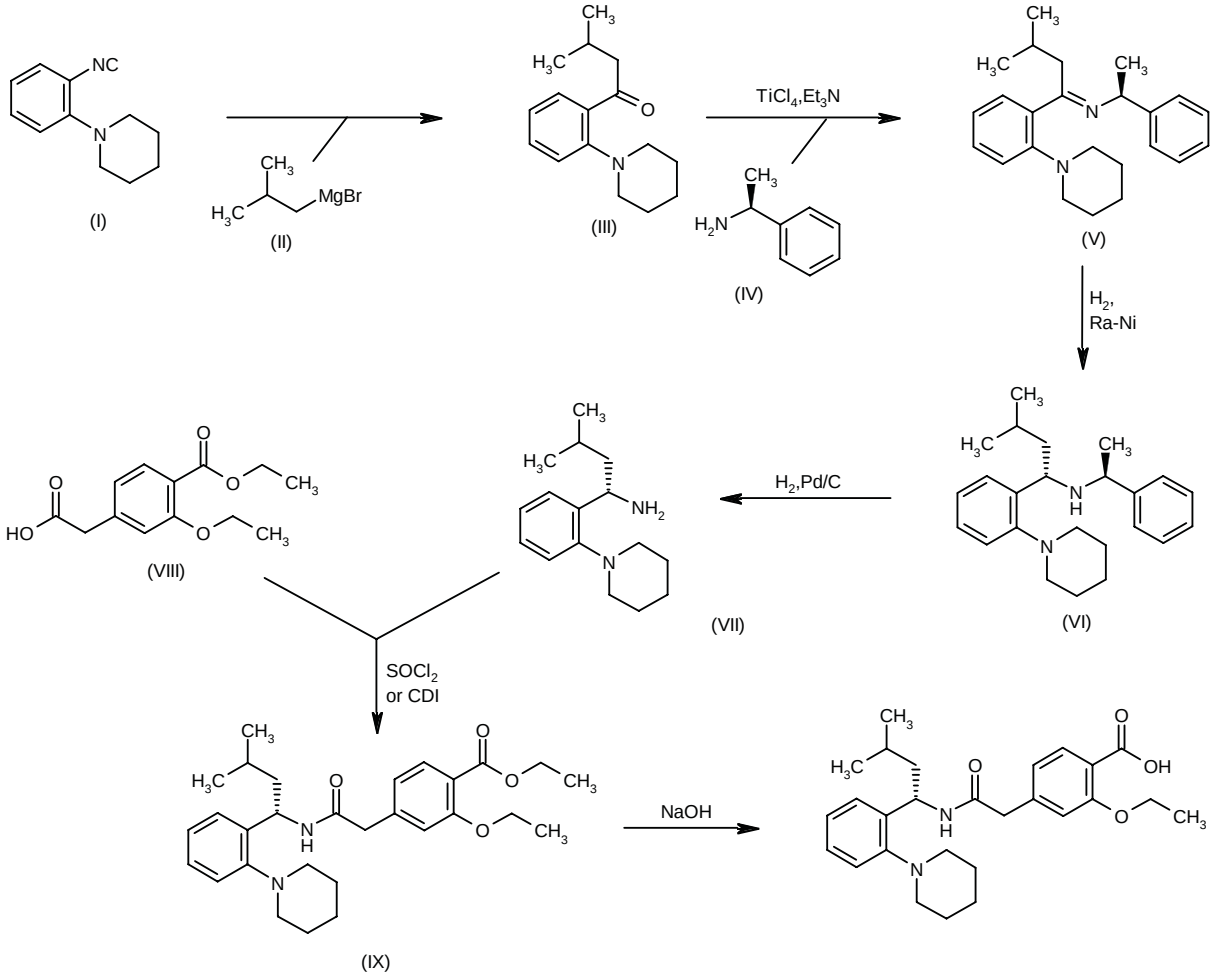


$C_{27}H_{36}N_2O_4$

Boehringer Ingelheim; Novo Nordisk

A new synthesis of repaglinide has been described: The reaction of 2-(1-piperidinyl)benzonitrile (I) with isobutylmagnesium bromide (II) in THF followed by hydrolysis with aqueous NH_4Cl/NH_3 gives 3-methyl-1-[2-(1-piperidinyl)phenyl]butanone (III), which is condensed with 1(*S*)-phenylethylamine (IV) by means of $TiCl_4$/triethylamine in toluene yielding the imine (V). The hydrogenation of (V) with H_2 over Raney nickel in ethanol affords the chiral secondary amine (VI), which is further hydrogenated with H_2 over Pd/C in ethanol/aqueous HCl, giving 3-methyl-2(*S*)-[2-(1-piperidinyl)phenyl]butylamine (VII). The condensation of (VII) with 4-(carboxymethyl)-2-ethoxybenzoic acid ethyl ester (VIII) by means of $SOCl_2$ or carbonyldiimidazole (CDI) or triphenylphosphine/CCl_4/triethylamine gives the ethyl ester of repaglinide (IX),

Scheme 1: Synthesis of Repaglinide



which is finally hydrolyzed with NaOH as usual (1). Scheme 1.

The long-term efficacy and safety of repaglinide were found to be similar to glyburide in a 1-year, prospective, randomized, double-blind, parallel-group, multicenter trial in which 576 patients with type II diabetes were given repaglinide preprandially (0.5-4 mg with 3 meals) or glyburide (2.5-15 mg). Glycemic control was similar in both groups and maintained for 12 months in patients previously treated with oral hypoglycemic agents (OHA). OHA-naive patients exhibited a decrease (9.4% to 7.6%) in HbA1c within the first 3 months which was maintained for the rest of the study. Morning fasting levels were similar in each group although C-peptide levels were significantly increased in glyburide-treated patients as compared to repaglinide. Adverse effects reported for both groups were headache, dizziness, tremor and increased appetite. After 14 months, body weight decreased (–0.3 kg) in previously treated patients and increased (2.4 kg) in naive patients (2).

The results of a multicenter, double-bind, randomized, placebo-controlled phase II trial aimed at assessing the efficacy and safety of repaglinide in the treatment of type II diabetes have been reported. Ninety-nine patients were randomized, following a 2-week washout period, to receive repaglinide at increasing daily doses of 0.25, 0.5, 1.0, 2.0, 4.0 and 8.0 mg or placebo for 6 weeks during a dose-adjustment period, followed by a 12-week maintenance period. At the last visit, patients treated with repaglinide showed a significant decrease in mean glycosylated hemoglobin (HbA1c; from 8.5% at baseline to 7.8%) compared to those treated with placebo, who showed an increase from 8.1% at baseline to 9.3% at the last visit. Similarly, a significant difference was observed between treatment groups at the last visit as regards mean fasting plasma glucose and postprandial glucose levels, those on repaglinide showing a decrease and those on placebo an increase in these parameters. Finally, levels of fasting and postprandial insulin and C-peptide were lower at the last visit compared to baseline

  CCC: 0377-8282/99

in patients treated with placebo, whereas they were higher in those treated with repaglinide, the difference being statistically significant. Repaglinide was well tolerated, the major event in both treatment groups being episodes of mild to moderate hypoglycemia. The findings from this study demonstrate that repaglinide treatment is associated with both an overall improvement in glycemic control as well as potent postprandial glucose-lowering effects (3).

In a single center, open-label, crossover study involving 14 healthy subjects, the pharmacokinetics of theophylline (300 mg b.i.d. p.o. days 1-4 and once on day 5) were not affected by repaglinide (2 mg t.i.d. days 1-2 and once on day 5). Coadministration was well tolerated and repaglinide did not alter the safety profile or pharmacokinetics of theophylline (4).

In a phase II randomized, double-blind, placebo-controlled study, no accumulation of repaglinide was observed in 143 patients with type II diabetes receiving the drug (0.25, 0.5, 1.0, 2.0 or 4.0 mg t.i.d.) for 4 weeks. AUC values were dose proportional with women exhibiting higher values than men. When AUC values were normalized for dose and weight, no gender differences were observed (5).

The pharmacokinetics of single and multiple doses of repaglinide were assessed in healthy volunteers and patients with mild to severe renal impairment showing that dose adjustments are not required in renally impaired subjects although initial doses should be increased gradually. Nonhemodialysis and healthy subjects received a single 2-mg dose on days 1 and 2, preprandial (3 meals/day) multiple dosing for 5 days and a final 2-mg dose on day 7. Hemodialysis patients received a 2-mg dose on 2 days separated by a washout period of 7-14 days. AUC values were significantly different between renally impaired and healthy subjects with more pronounced increases observed from day 1-7 in impaired individuals; no difference in AUC was observed between patients with different degrees of impairment. C_{max} was unchanged after multiple dosing in healthy patients but was increased in renally impaired and hemodialysis patients; t_{max} and half-lives were similar between all groups. Side effects were similar in both groups and included hypoglycemia, dizziness, tremor and sweating (6).

In a single-center, multiple-dose, open-label study, 6 healthy male volunteers were given repaglinide (2 mg q.i.d. for 13 days) and the distribution of ^{14}C-repaglinide in whole blood, plasma, urine and feces was examined. Rapid absorption was indicated (0.5 h) with 2-fold differences in AUC (298 ng.h/ml) and C_{max} (27.74 ng/ml). Radioactivity in red blood cells was negligible and the ratio of 14C in plasma *vs.* whole blood was 1.62. Repaglinide was recovered from plasma (61%) and cleared 3-5 h postdosing with no plasma radioactivity detected 36 h later. Three days after dosing, 90 and 8% of ^{14}C was recovered in feces and urine, respectively, with maximum fecal and renal excretion observed at 0-4 and 24-72 h, respectively. Almost no parent compound was excreted in urine and only 2% was in feces. The aromatic amine and dicarboxylic acid metabolites were recovered in urine while the latter was the major metabolite in feces (7).

In a single-center, single dose, open-label study, the pharmacokinetics of repaglinide (4 mg following a 10-h fast) were examined in 12 healthy volunteers and 12 subjects with chronic liver disease (CLD). CLD subjects had significantly higher and more prolonged serum levels of total and unbound repaglinide and AUC and C_{max} were significantly different from healthy subjects. AUC values for CLD subjects correlated with caffeine clearance and $t_{1/2}$ ranged from 0.6-14.7 h. Protein binding was the same for both groups (97%). Adverse effects were not serious and were similar in both groups with 36 and 29 events reported by 12 CLD and 11 healthy subjects, respectively; a total of 24 hypoglycemic events were reported in 10 individuals from both groups (8).

Twenty-four healthy male volunteers were administered repaglinide 2 mg as a tablet or oral solution twice each on 4 separate occasions, 7 days apart. In another study, 12 healthy male volunteers received repaglinide 2 mg as a tablet or a 15-min i.v. infusion once each on 2 different occasions with a washout period of 7-10 days. The tablet formulation did not result in greater variation in serum profiles. The drug was rapidly absorbed and eliminated when given orally or intravenously under fasting conditions. The tablet and oral solution showed similar total availability (9).

Results from a single-center, double-blind, randomized study in 43 patients with type II diabetes receiving 2 meals on day 1 and 3 meals on days 2 and 3 or *vice versa* showed that preprandially administered repaglinide was superior to glyburide (once or twice daily before breakfast and dinner) in terms of hypoglycemic events. No differences were observed between groups in average blood glucose excursions from fasting glucose. Significant differences in minimum blood glucose levels were observed between groups when meals were omitted; these levels after 2 meals were unchanged in the repaglinide group (78 mg/dl) as compared to a decrease from 77 to 61 mg/dl in the glyburide group. No hypoglycemic events were observed in the repaglinide groups as compared to 6 in the glyburide group, which were all associated with omitting lunch (10).

The long-term efficacy of repaglinide as compared to glibenclamide was evaluated in a 1-year, randomized, double-blind multicenter trial. Following a 6-8 week titration period, 424 patients with type II diabetes were given repaglinide (0.4-4 mg t.i.d.) or glibenclamide (1.75-10.5 mg/day). Discontinuation of subjects in both groups was due to hyperglycemia and 320 patients completed the study. HbA1c levels decreased in both groups and then increased during the second half year in both groups. A sustained improvement in metabolic control was observed in OHA-naive patients in both groups; however, this affect was significantly better in the glibenclamide-treated group (HbA1c change –2.4% *vs.* –1.0%). Similar results were observed with fasting plasma glucose levels.

No difference in adverse effects was noted between groups (11).

A randomized, double-blind, placebo-controlled, parallel-group study reported a dose-response relationship between repaglinide (0.25, 0.5, 1, 2 or 4 mg preprandially with 3 meals for 4 weeks) and 24-h mean serum glucose in 143 patients with type II diabetes. While serum glucose levels remained constant in the placebo group, levels dropped in all repaglinide-treated groups with significantly lower values during week 1; parallel changes in fasting serum glucose levels were observed. Glucose levels were stabilized and maintained by week 2 or 3 in all treated groups. Adverse effects were mostly mild with only 11% related to repaglinide treatment and 9% of patients reported mild hypoglycemic events (12).

The safety and efficacy of repaglinide was evaluated in a phase II randomized, placebo-controlled, multicenter trial in which 99 type II diabetes patients received the placebo or the drug (0.25-8 mg preprandially with 3 meals) for 12 weeks after a 6-week period of dose adjustment to achieve 90-160 mg/dl fasting plasma glucose levels. Mean HbA1c decreased from 8.3% to 7.8% in repaglinide-treated groups and increased from 8.1% to 9.3% in the placebo group. Parallel changes in fasting plasma glucose and 2-h postprandial glucose levels were observed. Fasting and 2-h postprandial insulin and C-peptide levels were also significantly higher in the repaglinide group at the last visit. Repaglinide treatment was well tolerated with improved glycemic control and potent efficacy observed during the postprandial period (13).

Repaglinide (1 mg preprandially) was shown to maintain glycemic control in type II diabetes patients irrespective of the number of meals consumed. In a 28-day study, 25 patients were randomized to receive fixed 3 meals/day or repeating patterns of 2, 3 or 4 meals/day (mixed meal) over a 20-day period. Mean fructosamine concentrations significantly decreased in both meal regimens (3.10 to 2.68 mmol/l *vs.* 3.37 to 2.85 mmol/l in mixed meal) although no differences were observed between groups. Fasting blood glucose levels and serum glucose were not altered after stabilization to the number of meals consumed. AUC_{24h} values were not different between groups. Repaglinide was well tolerated with no hypoglycemic episodes observed (14).

The efficacy of repaglinide was compared to glipizide in a randomized, double-blind, parallel-group, multicenter trial in which 250 patients with type II diabetes were given repaglinide (0.5-4 mg at each meal) or glipizide (5-15 mg/day) for 12 months. Repaglinide was significantly superior to glipizide in the mean change of HbA1c (0.6%) and fasting blood glucose (0.9 mM). Glipizide-treated patients had a higher tendency for hypoglycemic episodes as compared to the repaglinide group (15).

A randomized, double-blind, placebo-controlled, multicenter trial with 365 type II diabetes patients showed the efficacy and safety of repaglinide (1 or 4 mg preprandially with 3 meals). Repaglinide treatment was well tolerated and adverse effects were reported in 24% and 21% in patients receiving the placebo and repaglinide, respectively. The most common adverse effect was dizziness occurring in 4% of placebo-treated and 1% and 5% of patients given 1 and 4 mg repaglinide, respectively; fatigue and headache were also reported. Mild hypoglycemic episodes dose-dependently increased in the repaglinide-treated group. At 24 weeks, mean decreases in the proportion of total HbA1c from baseline were observed in OHA-naive patients receiving 1 (0.093 to 0.076) and 4 mg (0.092 to 0.074) repaglinide, while levels increased in the placebo group (0.085 to 0.092). HbA1c levels also decreased in previously treated patients (16).

Combination repaglinide and metformin therapy resulted in superior glycemic control in a randomized, double-blind, parallel-group, multicenter study in which 83 patients with type II diabetes previously receiving metformin (1-3 g/day) for more than 6 months without adequate glycemic control were given either metformin + placebo, metformin + repaglinide (0.5 mg t.i.d. titrated to 1.0, 2.0 and 4.0 mg) or repaglinide alone. HbA1c and fasting plasma glucose levels in patients given combination therapy were significantly decreased from 8.3% to 6.9% and by 2.2 mmol/l, respectively; no significant reductions in these levels were observed in patients receiving repaglinide or metformin alone. At the end of the trial, significantly increased fasting insulin levels were observed in patients receiving combination therapy (4.23 ± 1.50 mU/ml) and repaglinide alone (4.04 ± 1.56 mU/l). Significant increases in body weight occurred in repaglinide and combination therapy groups (2.4 ± 0.5 and 3.0 ± 0.5 kg, respectively) and gastrointestinal adverse events were reported in the metformin group (17).

Novo Nordisk has introduced repaglinide (NovoNorm®) in the U.K. for the treatment of type II diabetes. The compound is a nonsulfonylurea insulin secretagogue with a rapid onset and short duration of effect and is designed to be taken preprandially before each main meal. NovoNorm® is supplied as tablets in strengths of 0.5, 1 and 2 mg (18, 19).

An open-label, comparative pharmacokinetic study in 24 healthy adults, half of whom were aged 65 or older, has shown that repaglinide is as well tolerated in the elderly as in young adults, with similar pharmacokinetics in both age groups. The drug's short half-life and mode of excretion from the body may help to lower the risk of hypoglycemia in elderly patients with type II diabetes, many of whom have declining kidney function (20).

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Risedronate Sodium
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Bisphosphonate
Treatment of Osteoporosis
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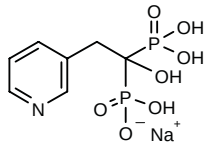

$C_7H_{10}NO_7P_2.Na$

Procter & Gamble; Takeda; Ajinomoto; Hoechst Marion Roussel

Linear pharmacokinetics were demonstrated in a study of multiple dosing of risedronate (2.5 or 5 mg/day p.o.) for 169 days in 62 postmenopausal women. Steady-state levels of risedronate were reached on day 57 and a terminal half-life of 460 h was obtained. C_{max}, C_{avg}, C_{min} and AUC values showed dose proportionality. There was a 2-fold increase in C_{avg} and a 15% increase in C_{max} at steady state. An 8- to 10-fold increase in C_{min} was also observed, indicating equilibrium between binding and release of the agent on bone (1).

Results from two multicenter, randomized, placebo-controlled trials in 518 patients on chronic corticosteroid therapy for up to 3 or 6 months or more given calcium (500 or 1000 mg/day) with or without vitamin D (400 IU/day) showed the efficacy and tolerability of risedronate (2.5 or 5 mg p.o. for 12 months) in the prevention of corticosteroid-induced osteoporosis with a reduction in incidence of vertebral fractures. Significant mean changes in bone mineral density were observed in the group receiving 5 mg risedronate as compared to the placebo group and incidence of vertebral fracture was about 70% lower in the treated group. Adverse events, discontinuations and laboratory analyses were similar in all groups (2, 3).

In a randomized, double-blind, placebo-controlled, 12-month multicenter study, risedronate (2.5 or 5.0 mg/day p.o.) was found to be well tolerated with no indication of oversuppression of bone turnover in 290 patients on chronic corticosteroid therapy (15 mg/day); patients were also given elemental calcium (1 g/day) and vitamin D (400 IU/day). Patients treated with risedronate had increases in bone mass density and a lower incidence of vertebral fractures as compared to the placebo group (5.3% for 2.5 mg and 5.2% for 5 mg *vs.* 15.3%). Adverse events and discontinuations were similar in all groups (4, 5).

An open-label multicenter study showed the efficacy and safety of oral risedronate (30 mg/day) in 162 patients with moderate to severe Paget's disease of bone treated for 84 days followed by 112 days of no treatment. Treatment was well tolerated with only 5 patients withdrawing due to nondrug-related adverse events. After the first and second cycle, significant decreases in serum alkaline phosphatase (65.7 and 69.1%, respectively) and urinary hydroxyproline/creatinine (50.4 and 66.9%, respectively) were observed; serum alkaline phosphatase was normalized in 53 patients in the first cycle and 33 in the second cycle and significant reports of decreases in bone pain were observed on days 84 and 196 (6).

An open-label, single-dose, single-center study showed the efficacy and safety of oral risedronate (30 mg/day) in 13 patients with severe Paget's disease of bone treated for 8 weeks followed by 16 weeks of no treatment. Treatment was well tolerated with only 1 patient withdrawing due to diarrhea related to treatment. After the first and second course, mean decreases in serum alkaline phosphatase of 77 and 87%, respectively, were observed; all patients exhibited reductions in these levels of at least 77% by the end of the trial. Urinary hydroxyproline/creatinine decreased by 64% during the first course and by 79% in the second course. Transient asymptomatic reductions in serum calcium and phosphorus levels and urinary calcium/creatinine ratios also decreased while urinary PTH and 1,25-dihydroxyvitamin D levels transiently increased (7).

In a randomized, double-blind, placebo-controlled, 12-month multicenter study, risedronate (2.5 or 5.0 mg/day p.o.) was found to be well tolerated, preventing spine and hip bone loss and reducing the incidence of vertebral fractures in 228 patients beginning (up to 3 months) corticosteroid therapy (at least 7.5 mg/day); patients were also given elemental calcium (500 mg/day). While bone mass density was maintained in risedronate-treated patients, significant bone loss was observed in the placebo group. The incidence of vertebral fractures was decreased by 71% and the rate of fractures was reduced by 97% in the group receiving 5 mg risedronate as compared to the placebo group. Adverse events were similar in all groups (8, 9).

Hoechst Marion Roussel and Procter & Gamble Pharmaceuticals have filed simultaneous approval applications in the U.S. and Europe seeking regulatory approval to market risedronate sodium (Actonel®) for the prevention and treatment of postmenopausal osteoporosis and corticosteroid-induced osteoporosis. In Europe, the companies are also seeking approval to market risedronate for the treatment of Paget's disease (10).

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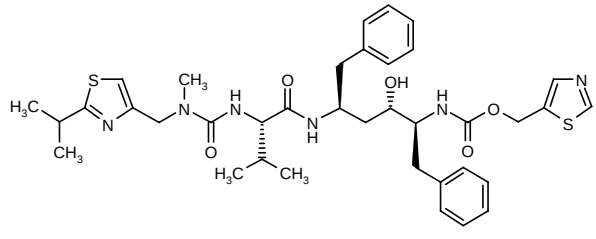

$C_{37}H_{48}N_6O_5S_2$ **Abbott; Dainippon; Triangle**

An *in vitro* test system using porcine primary brain capillary endothelial cell (BCEC) monolayers was used to compare the effects of ritonavir and SDZ-PSC-833 on the uptake kinetics of saquinavir. This system functionally expressed class I P-glycoprotein isoform P-gp1A, but not the P-gp1B or P-gp1D isoforms, as confirmed by polymerase chain reaction and Western blot analysis. SDZ-PSC-833 was able to nearly double the net uptake of saquinavir into cultured BCECs in a concentration-dependent manner (IC_{50} = 1.13 μM). Ritonavir inhibited P-glycoprotein at a significantly low concentration (IC_{50} = 0.20 μM), being approximately 6-fold more potent than SDZ-PSC-833. These results indicate that the cerebral bioavailability of saquinavir may be greatly improved by coadministration of a P-glycoprotein inhibitor such as ritonavir (1).

Abbott has received FDA approval for a new, soft-gelatin capsule formulation of ritonavir (Norvir®) for the treatment of HIV infection. The new formulation requires refrigerated storage at 36-46 °F until dispensed to patients. Refrigeration by patients is recommended but not required if used within 30 days and stored below 77 °F. Norvir® is approved for twice-daily use and should be taken with food if possible. Norvir® has also been approved by the FDA for use in children aged 2-16 years. The soft-gelatin capsules have also been approved for marketing in Switzerland (2).

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Rivastigmine
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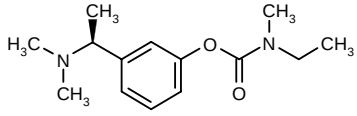

$C_{14}H_{22}N_2O_2$ **Novartis**

Rivastigmine (4 or 6 mg/day) demonstrated a good tolerability profile in elderly patients with probable Alzheimer's disease (AD). Of the 402 subjects in this multicenter, placebo-controlled, double-blind study, those treated with the drug had better scores on the Clinical Global Impression of Change Scale than those on placebo (42.72% *vs.* 29.91%, respectively). In addition, patients treated with rivastigmine showed better outcomes than those taking placebo on the Digit Symbol Substitution and the Fuld Object-Memory Evaluation tests (1).

In an open-label, multiple-dose trial involving 18 patients with AD, rivastigmine (1-6 mg b.i.d.) was shown to cause a rapid, dose-dependent and sustained inhibition of acetylcholinesterase in cerebral spinal fluid, which significantly correlated with plasma rivastigmine and

Box 2: The efficacy and safety of rivastigmine in patients with Alzheimer's disease (6) [Prous Science CSline database].

Design	Multicenter, randomized, double-blind, placebo-controlled clinical study
Population	Patients with mild to moderately severe AD (n = 725)
Treatments	Rivastigmine (R), 1 mg/d p.o. → 4 mg/d x 12 wk according to response, then fixed dose/day x 14 wk (n = 243) R, 6 mg/d p.o. → 12 mg/d x 12 wk according to response, then fixed dose/day x 14 wk (n = 243) Placebo (P) (n = 239)
Withdrawals	R1: 34 (14%) [AEs 18 (7%), treatment failure 1 (0.4%)] R6: 79 (32.5%) [AEs 55 (23%), treatment failure 2 (0.8%)] P: 31 (13%) [AEs 16 (7%), treatment failure 2 (0.8%)]
Adverse events	R1: 172 (71%) [nausea (17%), vomiting (8%), dizziness (10%), diarrhea (10%)] R6: 220 (91%) [nausea (50%), vomiting (34%), dizziness (20%), headache (19%)] P: 172 (72%) [nausea (10%), vomiting (6%), dizziness (7%), headache (8%)]
Results	Improvement in Alzheimer's disease assessment scale score: R6* (+1.17) > R1 (–1.24) > P (–1.41) [*p <0.05 *vs.* P] Clinican interview impression of change: R6* (3.93) < R1 (4.2) < P (4.34) [*p <0.05 *vs.* P] Progressive deterioration scale, mean change: R6* (1.3) > P (–1.9) > R1 (–2.9) [*p <0.05 *vs.* P]
Conclusions	Rivastigmine was well tolerated and improved cognition, participation in daily living activities and global evaluation ratings

metabolite concentrations; a maximum inhibition of 62% occurred at 5.6 h with the 6-mg dose (2).

The long-term (78 weeks) efficacy of rivastigmine was evaluated in a randomized, open-label, placebo-controlled study in 699 patients with mild to moderate AD receiving the agent titrated to the best tolerated dose. Effects of rivastigmine were maintained for more than 26 weeks. After 38 weeks, results from ADAS-Cog indicated that patients receiving the highest doses of rivastigmine (6-12 mg) had a slight decline in performance as compared to 26 weeks, although performance was still higher than at baseline. MMSE scores of at least 20 were above baseline for 44 weeks in patients receiving high doses. Scores decreased in all patients between weeks 44 and 104 (3).

The efficacy of antiemetic therapies with glycopyrrolate, ondansetron, trimethobenzamide or trihexyphenidyl were evaluated in a prospective, randomized, open-label pilot study in which AD patients on rivastigmine (3 mg/day titrated weekly up to 12 g/day) were treated with one of the 4 therapies. Results from the Emetic Process Rating Scale every 4 h and the Clinical Global Impression scale at 72 h for severity of nausea and vomiting showed that only the centrally acting agents, trimethobenzamide and trihexyphenidyl, were effective in preventing symptoms (89 and 90% success rates, respectively), suggesting that nausea and vomiting in patients treated with rivastigmine is centrally mediated (4).

Results from several double-blind, parallel-group, placebo-controlled studies involving 1845 patients with AD with vascular high risk factors showed that rivastigmine treatment (1-4 or 6-12 mg/day for 26 weeks) significantly improved cognition in patients with high Hachinski scores as compared to patients with scores of 0 and the placebo group (5).

In a multicenter, double-blind, parallel-group trial, 725 patients with mild to moderate AD were randomized to rivastigmine (1-4 or 6-12 mg/day) or placebo. Those patients administered the 6-12 mg dose showed significantly greater improvement on the AD assessment scale and in global functioning as compared to placebo. In addition, the 6-12 mg dose of rivastigmine was associated with significantly less progressive deterioration (6). Box 2.

Novartis has received an approvable letter from the U.S. FDA for rivastigmine tartrate capsules (Exelon®), a new drug for the treatment of mild to moderate AD. To date, the drug has been cleared for marketing in almost 50 countries worldwide, including all 15 member states of the E.U., New Zealand, Argentina, Brazil and Mexico. The NDA submitted for Exelon® contains data from the largest and most extensive clinical program of an AD medication, involving more than 3700 patients worldwide. The 6-month clinical trials demonstrated improvement in cognition and global evaluation compared to placebo. The most common side effects include nausea, vomiting, anorexia, dyspepsia and asthenia, which are generally mild to moderate, transient and occur most frequently when the dose is increased (7-9).

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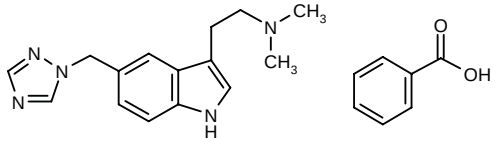

$C_{15}H_{19}N_5.C_7H_6O_2$ **Merck & Co.**

Rizatriptan as compared to sumatriptan had greater craniovascular selectivity over coronary artery selectivity with its vasconstricting effects mediated by 5-HT$_{1B}$ receptors. In an *in vitro* study using human isolated middle meningeal and coronary arteries, EC_{50} values of 0.032, 0.090 and 0.071 μM were obtained for 5-HT, rizatriptan and sumatriptan, respectively, with all agents being 10-fold more effective in producing contraction in meningeal versus coronary arteries. While rizatriptan produced significantly greater contractions in meningeal arteries, sumatriptan was more effective in coronary arteries. Meningeal arteries were found to have significantly higher 5-HT$_{1B}$ receptor expression as compared to coronary arteries (1, 2).

A long-term (up to 1 year), multicenter, randomized study involving 1831 migraine patients compared the efficacy of rizatriptan (5 or 10 mg) with sumatriptan. Both rizatriptan doses were effective, with 10 mg being significantly better than sumatriptan, resulting in 90% relief of attacks and 50% pain relief at 2 h postdosing. Tachyphylaxis was not observed and nausea, somnolence and asthenia/fatigue were the common side effects (3).

An open, single-dose, 4-period, randomized crossover study examined the pharmacokinetics and tolerability of rizatriptan (0.5, 1, 2.5 and 5 mg i.v.) in 8 healthy female subjects. Treatment was well tolerated and linear kinetics were obtained with doses up to and including 2.5 mg. Dose (0.5 mg)-adjusted AUC ratios were 1.04, 1.09 and 1.18 for 1, 2.5 and 5 mg, respectively, and plasma clearance ranged from 859-941 ml/min with 0.5-2.5 mg but was below 800 ml/min for 5 mg. Plasma $t_{1/2}$ was 1.5-2.2 h for all doses and urinary excretion ranged from 14.5-34.6% of the dose (4).

A pharmacokinetic study of rizatriptan (10 mg) showed a tendency for higher plasma concentrations of the agent in 12 adolescent migraineurs as compared to 54 healthy adults. The mean AUC was 82.68 ng/h/ml in adolescents and 73.8 ng/h/ml in adults with greater differences observed between females. C_{max} values were 27.2 and 22.8 ng/ml for adolescents and healthy adults, respectively, and a similar half-life was observed for both groups (1.7 h and 1.8 h) (5).

Results from a double-blind, placebo-controlled trial in 547 migraine patients showed that rizatriptan (5 and 10 mg) was significantly superior to placebo in relieving migraine-associated nausea in patients with nausea at baseline and did not cause more nausea in patients without baseline nausea (6).

Results from a randomized, double-blind, double-masked, double-dummy, placebo-controlled, multicenter trial in 522 patients treating a single migraine attack showed that rizatriptan (10 mg) was more effective than naratriptan (2.5 mg) resulting in earlier headache relief and pain-free response. The hazard ratio for intent-to-treat for time to pain-free response within 2 h for rizatriptan *versus* naratriptan was 1.62. More patients on rizatriptan were pain-free at 1, 1.5 and 2 h as compared to naratriptan (44.8% *vs.* 20.7% at 2 h). Rizatriptan provided earlier relief of migraine symptoms within 2 h and more patients returned to normal function within 2 h (39.3% *vs.* 22.6%). Both treatments were well tolerated with the most common side effects for rizatriptan including asthenia/fatigue, nausea, somnolence and dizziness; the most common side effects for naratriptan were dizziness and asthenia/fatigue (7).

The efficacy of oral treatment with rizatriptan was shown to be superior to that of sumatriptan in a 1538-patient study. The study drug was administered at doses of 5 and 10 mg and its efficacy was compared to that of placebo and sumatriptan (25 and 50 mg) in patients with moderate to severe migraine. Migraine relief was obtained in as little as 30 min with rizatriptan, and 75% of patients treated at the higher dose obtained pain relief within 2 h of administration (8).

Rizatriptan (5 and 10 mg) was more effective than sumatriptan (100 mg) in relieving migraine-associated symptoms, such as photophobia, phonophobia and nausea in patients with these symptoms at baseline. Furthermore, sumatriptan was associated with significantly greater induction of nausea in patients without nausea at baseline than rizatriptan (9).

In a placebo-controlled crossover study, 473 patients with moderate to severe migraine were randomized to treat 4 migraine attacks with rizatriptan (10 mg for 4 attacks or 3/4 attacks + placebo for 1 attack) or placebo. A significantly higher response rate was observed for the rizatriptan group after the first attack as compared to the placebo group (77% *vs.* 37%) and similar 75-80% response rates were observed for the rizatriptan group with subsequent attacks. No tolerance was observed. Adverse events included mild and transient dizziness and somnolence which decreased after the first attack (10).

Results from a double-blind, double-dummy stratified trial in 766 patients treating a single migraine attack showed that rizatriptan (10 mg) resulted in earlier pain-free response as compared to zolmitriptan (2.5 mg). The hazard ratio for intent-to-treat for time to pain-free response within 2 h for rizatriptan *versus* zolmitriptan was 1.26. More patients on rizatriptan (43.2%) were pain-free at 2 h as compared to zolmitriptan (35.6%). Rizatriptan provided more relief from photophobia (35.6% *vs.* 46.5%) and nausea (25.2% *vs.* 32.5%) and more patients returned to normal function within 2 h (45.5% *vs.* 37%). Both treatments were well tolerated with the most common adverse events for rizatriptan being asthenia/fatigue, somnolence and dizziness; the most common adverse event for zolmitriptan was dizziness (11).

A total of 555 migraineurs were administered rizatriptan wafer (5 or 10 mg) or placebo in a double-blind study. More rizatriptan-treated patients were pain-free at 30 min postdose than placebo patients. At 2 h, significantly more patients experienced pain relief on rizatriptan 10 mg (74%) or 5 mg (59%) compared to placebo (28%); 42, 35 and 10% of patients reported being pain-free at 2 h in the rizatriptan 10-mg, 5-mg and placebo groups, respectively. Rizatriptan was well tolerated and highly effective in the treatment of acute migraine (12).

A study examining the productivity cost benefit of Maxalt® (10 mg) as compared to other migraine therapies in the U.S. used results from a triple-blind, placebo-controlled, randomized, open-label trial involving 164 patients. Maxalt®-treated patients reported significantly fewer hours absent from work (1.3 h *vs.* 2.4 h), greater efficacy at work (62.1% *vs.* 48.6%) and overall less difficulty performing work tasks as compared to other treatments. An economic value of $45.45 was estimated per migraine episode (13).

Rizatriptan benzoate has been launched in Germany for the acute treatment of migraine attacks with or without aura and is available in both tablet (Maxalt®) and orally disintegrating tablet (Maxalt® Lingua) formulations. Tablet and wafer formulations of rizatriptan benzoate are currently under regulatory review in Canada (14, 15).

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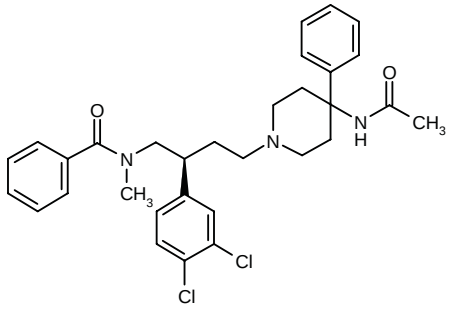

$C_{31}H_{35}Cl_2N_3O_2$ **Sanofi-Synthélabo**

The effects of saredutant (200 mg p.o.) on neurokinin A-induced bronchoconstriction were evaluated in 12 asthmatic patients in a double-blind, placebo-controlled, crossover trial. Saredutant administration before provocation with increasing concentrations of neurokinin A significantly prevented NKA-induced bronchoconstriction, as measured by FEV_1 and specific airways conductance. These results provide the first evidence that a selective tachykinin antagonist is capable of inhibiting bronchoconstriction induced by a sensory neuropeptide in humans (1).

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EN: 213238

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

Whole blood from healthy subjects incubated with MGDF (10 and 100 ng/ml) and stimulated with thrombin (0.1 U/ml) had a significantly higher platelet microparticle generation and formation of platelet aggregates than blood incubated with thrombin alone. These differential effects were not observed in MGDF-treated blood from patients with thrombocytopenia or other hematologic diseases such as acute myeloid leukemia, multiple myeloma and Glanzman's thrombasthenia. Results indicate that MGDF should be safe and effective without risk of causing thromboocclusive disease in patients with hematologic conditions (1).

A pilot study has shown that administration of rhTPO (2.5 μg/kg i.v.) to 28 older patients with newly diagnosed acute myeloid leukemia following induction therapy with idarubicin and ara-C continuous infusion was well tolerated but did not affect the duration of thrombocytopenia when compared to a historical cohort. G-CSF (250 μg/kg) was administered if marrow aplasia was observed on day

10 and rhTPO was given every other day starting on day 3 and continued until platelet count was at least 50,000/μl or for 21 doses. Remission was achieved in 18 patients; 5 died and 5 had refractory acute myeloid leukemia. Adverse events included allergic reactions in 2 patients, severe bone pain resulting in discontinuation in 1 patient and aortic thrombosis associated with sepsis and DIC in 1 patient (2).

In a randomized, double-blind, placebo-controlled trial, rhTPO with G-CSF mobilization therapy did not increase the risk of tumor cell contamination of leukapheresis product in 71 breast cancer patients undergoing autologous peripheral blood progenitor cell transplant. Patients were treated with rhTPO (1.5 μg/kg i.v.) or placebo and G-CSF (10 μg/kg/day) on day 5 or G-CSF alone. Only 8% of patients treated with rhTPO + G-CSF had tumor cell contamination as compared to 19% receiving G-CSF alone. The decrease in tumor cell contamination was due to a decrease in the number of phereses performed due to the addition of rhTPO (3).

Results of a randomized, double-blind, placebo-controlled trial in 35 newly diagnosed acute myeloid leukemia patients showed that MGDF administered as adjunct to induction and consolidation therapy was well tolerated with no effects on the duration of thrombocytopenia or number of required transfusions (4).

In a randomized, double-blind, placebo-controlled phase II trial in 134 patients with breast cancer undergoing peripheral blood progenitor cell transplant, rhTPO with G-CSF mobilization therapy was safe and well tolerated. Patients were treated with rhTPO (1.5 μg/kg i.v.) on mobilization days 1 or 5, rhTPO (0.5 μg/kg i.v.) on days 3 and 5 or placebo; all groups received G-CSF (10 μg/kg/day) on day 5 and leukapheresis on day 9 until at least 5 x 10^6 $CD34^+$ cell/kg were collected or after 6 phereses. rhTPO had no effect on posttransplant platelet recovery and a high incidence of rash (grade 1-2) was noted in groups receiving the agent (52% *vs.* 24% in placebo). No significant differences were observed in incidence of side effects including clotting and bleeding events (5).

Results from a clinical trial have shown that rhTPO predosing in a 4-day or more schedule with chemotherapy (adriamycin and ifosfamide) was more effective resulting in earlier platelet nadir. Patients with sarcoma were given adriamycin and ifosfamide chemotherapy alone for 1 cycle followed by a rhTPO (i.v.) bolus prior to and after chemotherapy (days 0-3) in one of 3 schedules (A: days -1, 4, 6, 8; B: days -1, -3, 4, 6; C: days -5, -3, -1, 4) in cycle 2. The differences in platelet nadir (x 10^3/mcl) from cycle 2 to 1 were -15 ± 8, -7 ± 5 and 31 ± 24 for regimens A, B and C, respectively. Out of 6 patients given schedule C, only 1 had cycle 2 platelet nadir levels lower than cycle 1 as compared to 5/6 patients in A and B groups each. Bone marrow progenitor cell assays showed the presence of colonies after chemotherapy and the last dose of rhTPO in 0/2, 1/2 and 3/4 patients receiving regimens A, B and C, respectively (6).

Kirin Brewery plans to restart clinical trials with TPO, which were stopped at phase II due to reports of the production of neutralizing antibodies in healthy volunteers in studies conducted by Amgen in the U.S. No evidence of neutralizing antibodies in either healthy volunteers or patients was found by a panel of experts and they recommended that Kirin continue with clinical trials for the treatment of thrombocytopenia in patients undergoing chemotherapy or radiotherapy (7).

1. Matzdorff, A., Pralle, H. *Megakaryocyte growth and development factor (MGDF) increases reactivity of platelets from healthy individuals but not platelets from patients with hematologic diseases.* Blood 1998, 92(10, Suppl. 1, Part 2): Abst 3753.

2. Cripe, L. et al. *A pilot study of recombinant human thrombopoietin (rh-TPO) and GM-CSF following induction therapy in patients older than 55 years with acute myeloid leukemia (AML).* Blood 1998, 92(10, Suppl. 1, Part 1): Abst 2539.

3. Moss, T.J. et al. *Recombinant human thrombopoietin (rhTPO) does not enhance tumor cell (TC) mobilization in patients (pts) undergoing peripheral blood progenitor cell (PBPC) mobilization.* Blood 1998, 92(10, Suppl. 1, Part 1): Abst 2967.

4. Schiffer, C.A. et al. *A double blind, placebo controlled trial evaluating pegylated recombinant human megakaryocyte growth and development factor (MGDF) as an adjunt to induction and consolidation therapy in patients with acute myeloid leukemia (AML).* Blood 1998, 92(10, Suppl. 1, Part 1): Abst 1283.

5. Linker, C. et al. *A randomized, placebo-controlled, phase II trial of recombinant human thrombopoietin (rhTPO) in subjects undergoing high dose chemotherapy (HDC) and PBPC transplant.* Blood 1998, 92(10, Suppl. 1, Part 1): Abst 2809.

6. Vadhan-Raj, S. et al. *Schedule-dependent reduction in thrombocytopenia by recombinant human thrombopoietin (rhTPO) in patients with sarcoma receiving high dose chemotherapy (CT) with adriamycin (A) and ifosfamide.* Proc Amer Soc Clin Oncol 1999, 18: Abst 193.

7. *Kirin to restart clinical trials of TPO.* DailyDrugNews.com (Daily Essentials) Feb 3, 1999.

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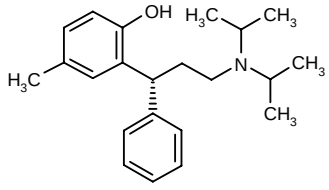

$C_{22}H_{31}NO$ **Pharmacia & Upjohn**

An asymmetric total synthesis of tolterodine has been described: The regioselective addition of 2-benzyloxy-5-methylphenyl bromide (II) to 4(*R*)-phenyl-3-[3-phenyl-2(*E*)-propenoyl]oxazolidin-2-one (I) by means of Mg/CuBr/dimethylsulfide in THF gives 3-[3(*R*)-(5-benzyloxy-2-methylphenyl)-3-phenylpropionyl]-4(*R*)-phenyloxazolidin-2-one (III), which is hydrolyzed with $LiOH/H_2O_2$ in THF/water to the corresponding free acid (IV). The reaction of (IV) with $SOCl_2$/pyridine in benzene yields the acid chloride (V), which is treated with diisopropylamine to afford the corresponding amide (VI). The reduction of (VI) with $LiAlH_4$ in ethyl ether gives the tertiary amine (VII), which is finally debenzylated by hydrogenation with H_2 over Pd/C in methanol (1). Scheme 2.

The effects of tolterodine and its major active metabolite PNU-200577 on carbachol-, KCl-, $CaCl_2$- and electrical field-stimulated contractions were examined in isolated urinary bladder detrusor smooth muscle preparations obtained from total malignant bladder cystectomies from 20 patients. Results showed that the effects of tolterodine and the metabolite were via antimuscarinic actions without Ca^{2+} channel antagonism, suggesting potential use of the agent for symptoms of overactive bladder (2).

Tolterodine tartrate has been launched in the U.K. and Germany as Detrusitol® for the treatment of unstable bladder with symptoms of frequency, urgency or urge incontinence. The compound was also approved in Canada as Detrol® for the treatment of urinary incontinence (3, 4).

1. Andersson, P.G. et al. *Asymmetric total synthesis of (+)-tolterodine, a new muscarinic receptor antagonist, via copper-assisted asymmetric conjugate addition of aryl Grignard reagents to 3-phenyl-prop-2-enoyl-oxazolidinones.* J Org Chem 1998, 63(22): 8067.

2. Yono, M., Yoshida, M., Wada, Y., Kikukawa, H., Takahashi, W., Inadome, A., Seshita, H., Ueda, S. *Pharmacological effects of tolterodine on human isolated urinary bladder.* Eur J Pharmacol 1999, 368(2-3): 223.

3. *Detrusitol launched in U.K. and Germany.* DailyDrugNews.com (Daily Essentials) March 11, 1998.

4. *Health Canada approves first new incontinence medication in over a decade.* DailyDrugNews.com (Daily Essentials) Dec 3, 1998.

Original monograph - Drugs Fut 1997, 22: 733.

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Brynne, N. et al. *Tolterodine does not affect the human in vivo metabolism of the probe drugs caffeine, debrisoquine and omeprazole.* Br J Clin Pharmacol 1999, 47(2): 145.

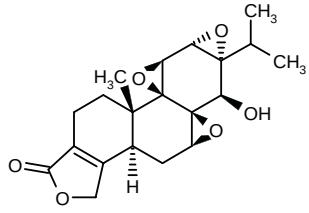
Diokno, A.C. et al. *Tolterodine (Detrol(R)) improves incontinence and nocturia in urologist based study.* 94th Annu Meet Am Urol Assoc (May 1-6, Dallas) 1999, Abst 987.

Wein, A.J. et al. *Tolterodine is effective and well tolerated during long-term use in patients with overactive bladder.* 94th Annu Meet Am Urol Assoc (May 1-6, Dallas) 1999, Abst 125.

Triptolide

Immunosuppressant

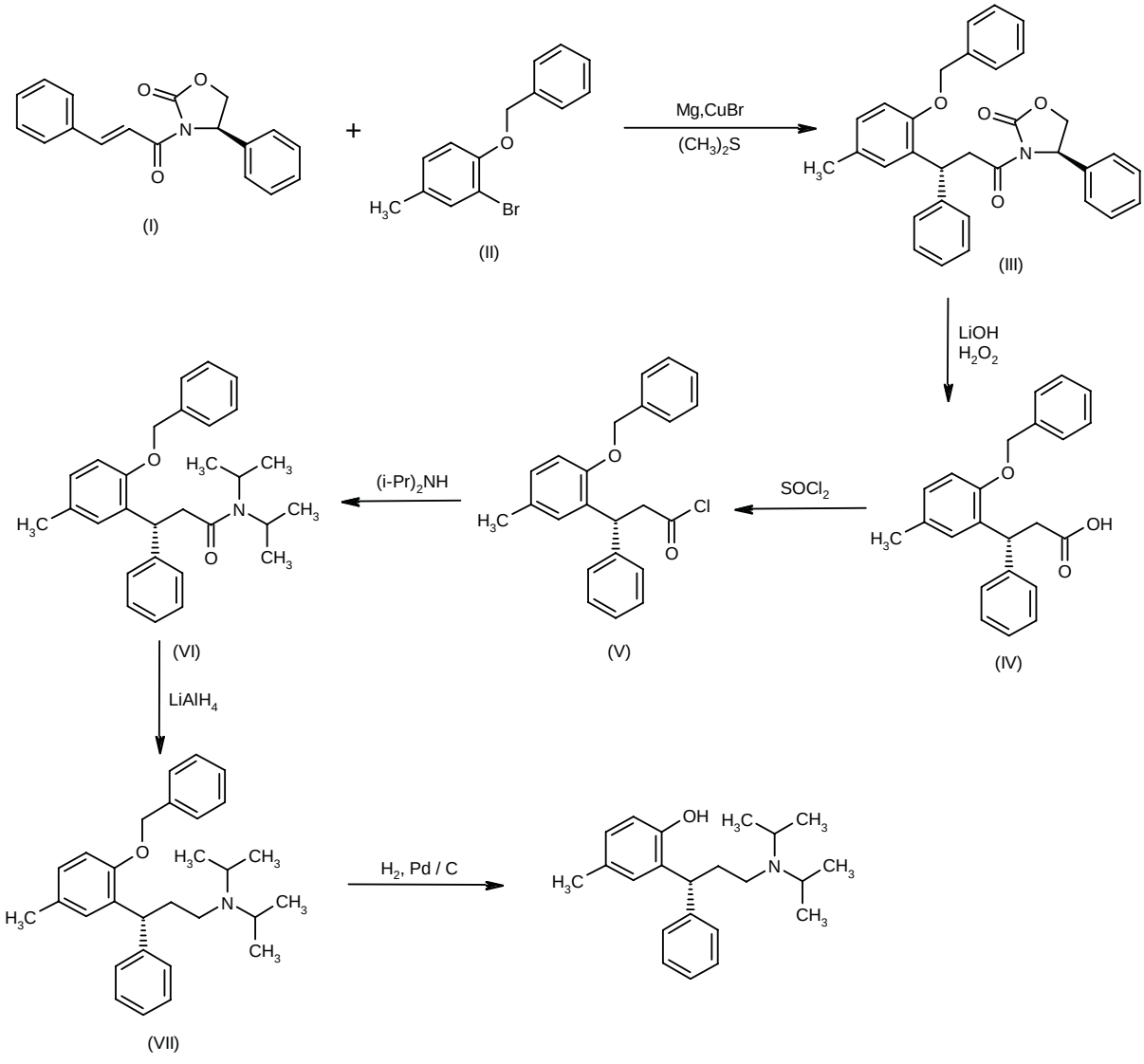
EN: 090968



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

The mechanism of T- and B-cell immunosuppression by triptolide has been investigated. PBMCs were obtained from patients with rheumatoid arthritis and from healthy control subjects, and T-cells were purified, removed and incubated for 3 days in various concentrations of triptolide (0-15 nM). Subsequent stimulation with PHA caused an immediate influx of intracellular calcium; this increase was unaffected in cells from healthy controls as well as in cells from patients treated with triptolide at concentrations above 7.5 nM. At concentrations of 7.5 nM or higher, triptolide significantly inhibited PBMC protein biosynthesis in cells from both controls and RA patients. Thus, it appears that inhibition by triptolide of lymphocyte activation is not related to calcium mobilization or the early signal transduction process; however, one of the mechanisms of action of triptolide may be the inhibition of PBMC protein biosynthesis (1).

Scheme 2: Synthesis of Tolterodine



The effects of triptolide on the activity and viability of T-cells, B-cells and synoviocytes from patients with RA were investigated. PBMCs were obtained from healthy controls and RA patients and incubated with triptolide at various concentrations (0-15 nM). Proliferation of PBMCs in response to PHA, IL-2 or PMA/ionomycin was suppressed by triptolide in a dose-dependent fashion, with IC_{50}s in healthy control PBMCs of 2.7, 3.7 and 6.7 nM, respectively; the IC_{50}s for RA patient-derived PBMCs were 3.2, 3.5 and 6.1 nM, respectively. Triptolide had similar effects on synovial cell proliferation. Production of IgG and IgM in healthy donor and RA cells following stimulation by SAC was inhibited significantly by triptolide at a concentration of ~ 3 nM. Inhibitory activity was observed during the first 3 days of a 10-day culture period, indicating that the compound blocks the initial stages of B-cell activation. Cell killing by triptolide was seen at doses of 15 nM or higher in the trypan blue exclusion test (2).

1. Tong, K.K. et al. *Effects of triptolide, an alcohol extract of a Chinese herb, Thunder God Vine, on peripheral blood mononuclear cell protein synthesis and signal transduction in rheumatoid arthritis (RA).* 14th Eur Leag Against Rheum Congr (June 6-11, Glasgow) 1999, Abst 204.

2. Tong, K.K. et al. *Effects of triptolide, an alcohol extract of a Chinese herb, Thunder God Vine, on peripheral blood T cell proliferation and B cell immunoglobulin production in rheumatoid arthritis (RA).* 14th Eur Leag Against Rheum Congr (June 6-11, Glasgow) 1999, Abst 205.

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Lee, K.Y. et al. *PG490 (triptolide) cooperates with tumor necrosis factor-α to induce apoptosis in tumor cells.* J Biol Chem 1999, 274(19): 13451.

Box 3: Valaciclovir in the prevention of cytomegalovirus after renal transplantation (1) [Prous Science CSline database].

Design	Multicenter, randomized, placebo-controlled, double-blind clinical study
Population	CMV-negative (n = 208) and CMV-positive (n = 408) kidney recipients
Treatments	CMV-negative: Valaciclovir (V), 2 g q.i.d. p.o. x 90 d (n = 102); Placebo (P) (n = 106) CMV-positive: V 2 g p.o. q.i.d. x 90 d (n = 204); P (n = 204)
Withdrawals	CMV-negative: V: 16% [AEs (7%)]; P: 29% [AEs (8%)] CMV-positive: V: 19% [AEs (5%)]; P: 17% [AEs (3%)]
Results	Incidence of CMV disease at 90 d after transplantation: [CMV-negative] P (45%) > V (3%); [CMV-positive] P (6%) > V (0%) Risk of CMV disease (% reduction) at 6 months: [CMV-negative] V (78) [p <0.001 *vs.* P]; [CMV-positive] V (82) [p = 0.03 *vs.* P] Incidence of CMV disease at 6 months after transplantation: [CMV-negative] P (45%) > V (16%); [CMV-positive] P (6%) > V (1%) Rate of biopsy-confirmed acute graft rejection: [CMV-negative] P (52%) > V (26%) [p = 0.001]; [CMV-positive] P (36%) > V (30%) [p = 0.4]
Conclusions	Prophylactic treatment with valaciclovir prevented CMV disease after renal transplantation; adverse events were not severe or treatment limiting

Mao, Y.P. et al. *Pharmacokinetics of triptolide. Development and application of a high performance liquid chromatographic method for quantitation of triptolide in plasma.* J Liq Chromatogr Relat Technol 1999, 22(9): 1355.

Qiu, D.M. et al. *Immunosuppressant PG490 (triptolide) inhibits T-cell interleukin-2 expression at the level of purine-box/nuclear factor of activated T-cells and NF-κB transcriptional activation.* J Biol Chem 1999, 274(19): 13443.

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Yang, D. et al. *A concise and stereoselective total synthesis of triptolide.* 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst ORGN 096.

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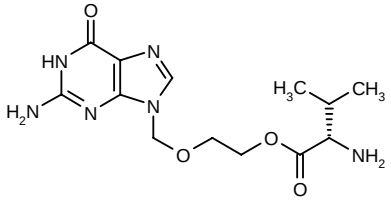

$C_{13}H_{20}N_6O_4$

Glaxo Wellcome; Theraplix; Hoechst Marion Roussel

Prophylaxis with valaciclovir hydrochloride was shown to reduce the risk of developing cytomegalovirus (CMV) infection in kidney transplant recipients. A multicenter U.S. and European study included 616 kidney transplant recipients randomized to high-dose valaciclovir (2 g q.i.d., adjusted for kidney function) or placebo. Treatment regimens began a maximum of 3 days after transplantation and continued for 90 days. During the first 3 months, the incidence of CMV disease among the 208 CMV-seronegative patients was 45% in the placebo group *versus* only 3% in the valaciclovir group. Among the 408 CMV-seropositive patients, the incidence was 6% and 0% in the placebo and valaciclovir groups, respectively. At the end of the 6-month follow-up, the incidence of CMV disease among CMV-seronegative patients was 45% for the placebo group and 16% for the valaciclovir group. Based on the data from the study, the risk of developing CMV disease during the first 6 months after transplantation was reduced by 78% in seronegative patients who received prophylaxis with valaciclovir. Similarly, the rates were 82% lower in the seropositive recipients of valaciclovir. Additionally, among the CMV-seronegative group, the incidence of kidney rejection in the patients who received valaciclovir was 26%, a figure that was significantly lower than that for the placebo group (52%). Valaciclovir prophylaxis also led to a decrease in the incidence of other infections, such as herpes simplex virus and some associated bacterial and fungal infections. In both groups, prophylaxis with valaciclovir reduced the number of hospital admissions. Side effects were similar between the placebo and valaciclovir groups, with the exception of hallucinations and confusion, which were more common among those receiving valaciclovir. These side effects were generally mild, not treatment-limiting and amenable to reversal with an adjustment in dose (1). Box 3.

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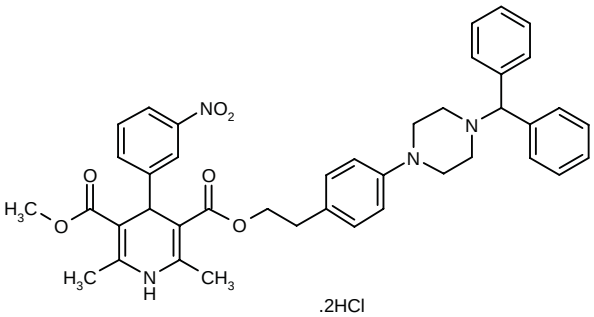

$C_{41}H_{42}N_4O_6.2HCl$ **Yoshitomi**

AE-0047 was suggested to inhibit renal nerve stimulation-induced antidiuretic effects via norepinephrine (NE) overflow from the renal nerve in a study using anesthetized dogs. Low-frequency renal stimulation (0.5-2.0 Hz) reduced urinary flow and urinary and fractional excretion of sodium and increased NE secretion with no effects on renal hemodynamics. High-frequency stimulation (2.5-5.0 Hz) decreased renal hemodynamics and resulted in more potent decreases in urine formation and increases in NE secretion. AE-007 (50 ng/kg/min intrarenal arterial infusion) did not affect renal hemodynamics, but attenuated low- and high-frequency-stimulated antidiuretic effects including increases in NE secretion; basal urine formation was also increased with treatment and AE-0047 significantly suppressed high-frequency-induced renal vasoconstriction (1).

1. Yamasaki, T. et al. *Inhibitory effects of AE0047, a new dihydropyridine Ca^{2+} channel blocker, on renal nerve stimulation-induced renal actions in anesthetized dogs.* Jpn J Pharmacol 1999, 79(Suppl. I): Abst O-2.

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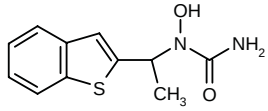

$C_{11}H_{12}N_2O_2S$ **Abbott**

Ten aspirin-sensitive asthmatic volunteers were pretreated with zileuton (600 mg q.i.d.) 6 days before aspirin challenge (up to 650 mg) in a double-blind, placebo-controlled study. During the challenge, subjects continued to take zileuton. Results showed that zileuton did not consistently inhibit aspirin-induced respiratory reactions (1).

The results obtained in a small pilot study indicate that zileuton may be effective in the treatment of atopic dermatitis, leading the investigators to recommend larger, placebo-controlled efficacy trials. In this study, 7 patients meeting diagnostic criteria for atopic dermatitis were treated for 6 weeks with oral zileuton (600 mg q.i.d.). Efficacy was evaluated in terms of patient reporting and on skin exams. Mean skin erythema score decreased from a baseline value of 24 (out of a possible 60) to 14 after the 6-week treatment period. Pruritus scores also showed a tendency to improve over the treatment period, from a baseline mean of 7.3 (out of a possible 10) to 4.3 at the end of the study. Disease dissatisfaction scores also decreased after 6 weeks on zileuton, from a baseline of 8.0 (out of a possible 10) to 4.4. Based on these early findings in a limited group of patients with atopic dermatitis, larger studies evaluating this potential new indication for zileuton appear to be warranted (2).

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Nsouli, T.M. et al. *Cough-variant asthma responsive to zileuton: A new clinical application.* Annu Meet Am Coll Allergy Asthma Immunol (Nov 6-11, Philadelphia) 1998, Abst P98.