Drugs of the Future 2001, 26(7): 695-722

CCC: 0377-8282/2001

Information Update

Volume 1-25, Number 7

Estimated developmental phase for this month's updated products:

Preclinical

NS-398 (COX-2 inhibitor; Taisho)
TC-440 (antiasthmatic, PDE4 inhibitor; Tanabe Seiyaku)

Phase I

AK-2123 (radiosensitizer; Adeka Fine Chem., Kyoto Univ.)
Imidacrine (oncolytic; Tech. Univ. Gdansk, BTG)

Phase II

Cilengitide (oncolytic, angiogenesis inhibitor; Merck KGaA)
F-1394 (hypolipidemic, ACAT inhibitor; UCB Japan)
Maribavir (anti-CMV; GlaxoSmithKline) (discontinued)
Oltipraz (chemopreventive; Aventis Pharma)
Triptolide (immunosuppressant; Kunming Inst. Botany, Pharmagenesis)

Phase III

CDP-571 (treatment of IBD, antiarthritic; Celltech Chiroscience)
Daptomycin (antibiotic; Cubist, Gilead, Emisphere)
Desmin-370 (anticoagulant; Alfa Wassermann, Opocrin)
Dexloxiglumide (treatment of IBS, CCK-A antagonist; Rotta, Forest)
Emivirine (anti-HIV, reverse transcriptase inhibitor; Mitsubishi Chem., Triangle Pharm., Abbott)
Ezetimibe (hypolipidemic, cholesterol absorption inhibitor; Schering-Plough)
INS-3653 (treatment of cystic fibrosis, treatment of COPD, lacrimal secretion stimulant; Inspire Pharm., Kissei, Santen, Allergan)
Prucalopride (treatment of IBS, treatment of constipation; Janssen)
Ramoplanin (glycopeptide antibiotic; Biosearch Italia, IntraBiotics)
Recombinant human thrombopoietin (Genentech, ZymoGenetics, Amgen, Kirin Brewery, Pharmacia)
Roxifiban acetate (platelet antiaggregatory, gpIIb/IIIa antagonist; DuPont Pharm.)

Preregistered

Azelnidipine (antihypertensive, calcium antagonist; Sankyo, Ube)
Tiotropium bromide (treatment of COPD, bronchodilator; Boehringer Ingelheim, Pfizer)

Registered/Year

Frovatripan (antimigraine, 5-$HT_{1B/1D}$ agonist; Vernalis, Elan, Draxis Health, Menarini)/2000

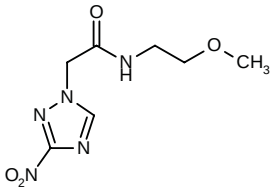
Launched/Year

Candesartan cilexetil (antihypertensive, angiotensin AT_1 antagonist; Takeda, AstraZeneca, Almirall Prodesfarma, Abbott)/1997
Celecoxib (antiarthritic, treatment of adematous polyposis, COX-2 inhibitor; Pharmacia, Pfizer, Yamanouchi)/1999
Entacapone (antiparkinsonian, COMT inhibitor; Orion Corp., Novartis, DuPont Pharm.)/1998
Gemtuzumab ozogamicin (treatment of AML; Celltech Chiroscience, Wyeth-Ayerst)/2000
Phentolamine Mesilate (treatment of erectile dysfunction, treatment of female sexual dysfunction; Novartis, Zonagen, Schering-Plough)/1998
Raloxifene hydrochloride (treatment of osteoporosis, prevention of osteoporosis, treatment of postmenopausal syndrome; Lilly, Gador, Esteve, Chugai)/1998
Rivastigmine tartrate (cognition enhancer; Novartis, Esteve)/1997
Tolterodine tartrate (treatment of urinary incontinence; Pharmacia, Almirall Prodesfarma)/2001
Valaciclovir (anti-HSV; GlaxoSmithKline, Theraplix, Aventis Pharma)/1995

AK-2123
Sanazole

Radiosensitizer

EN: 140350



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

A study examined the redox chemistry of sanazole using pulse radiolysis with e_{aq}^-, $CO_2^{-\bullet}$, 2-propanol and CH_2OH radicals. The agent reacted with e_{aq}^-, $CO_2^{-\bullet}$ and 2-propanol radicals at almost diffusion-controlled rates, yielding within a few seconds a nitro radical anion (λ_{max} = 290 nm). The radical anion reacted with oxygen at a rate constant of 3.4 x 10^6 dm^3/mol/s. In addition, an electron-transfer reaction occurred from the thymine radical anion to sanazole. The one-electron reduction potential of the agent in aqueous solution was –0.33 ± 0.02 V *versus* NHE (1).

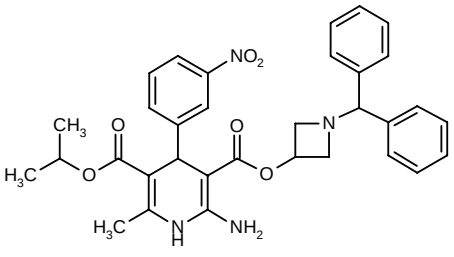
1. Kapoor, S., Mathew, R., Huilgol, N.G., Kagiya, T.V., Nair, C.K.K. *Redox reactions of sanazole (AK-2123) in aqueous solutions: A pulse radiolysis study.* J Radiat Res 2000, 41(4): 355.

Original monograph - Drugs Fut 1995, 20: 659.

Azelnidipine
Calblock®

Antihypertensive
Calcium Antagonist

EN: 141329



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

A study reported that CS-905 was extensively metabolized with 14 metabolites identified in the plasma and bile of rats and plasma and urine of dogs. Further studies *in vitro* using rat, dog and human liver microsomes showed that the agent was oxidized by CYP3A4 (1).

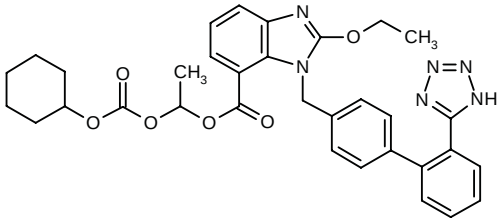
1. Uchiyama, M., Ishikawa, M., Ikeda, T., Kumamoto, K., Nakai, D., Kawabata, K., Inoue, T., Iwabuchi, H., Ikeda, T. *Metabolism of CS-905, a calcium antagonist.* Xenobiotic Metab Dispos 2000, 15(Suppl.): Abst 11PD-65.

Original monograph - Drugs Fut 1990, 15: 671.

Candesartan Cilexetil
Atacand®
Amias®
Blopress®

Antihypertensive
Angiotensin AT_1 Antagonist

EN: 179243



$C_{33}H_{34}N_6O_6$ **Takeda; AstraZeneca; Almirall Prodesfarma; Abbott**

A study conducted in 62 renal transplant recipients with proteinuria due to chronic rejection, glomerulonephritis, ciclosporin or tacrolimus nephrotoxicity or unknown cause showed the efficacy of candesartan cilexetil (4-12 mg/day) in controlling proteinuria and hypotension. Treatment significantly decreased urinary protein (from 0.63 ± 1 to 0.23 ± 0.6 g/day) and microalbumin excretion (from and 485 ± 909 to 296 ± 495 mg/day) at 2 months. Systolic (from 141 ± 15 to 118 ± 20 mmHg) and diastolic (from 89 ± 14 to 71 ± 10 mmHg) blood pressure were also significantly decreased. Serum creatinine levels were unaffected by treatment (1).

AstraZeneca and Takeda have initiated a 4-year, multicenter trial, the DIabetic REtinopathy Candesartan Trial (DIRECT), to evaluate the use of candesartan cilexetil for the prevention and slowing of the progression of diabetic retinopathy. The trial, which will involve 4500 patients from approximately 20 countries, will involve the once-daily administration of candesartan cilexetil or placebo. The DIRECT trial consists of three arms: the first arm will examine the effects of candesartan cilexetil in the prevention of diabetic retinopathy in insulin-dependent diabetic subjects; the second arm will observe the effects of the drug in slowing the progression of diabetic retinopathy in insulin-dependent diabetic subjects; and the third arm will evaluate the effects of the drug in slowing the progression of diabetic retinopathy in non-insulin-dependent diabetic patients. Candesartan cilexetil was launched in the U.S. for the treatment of hypertension alone or in combination with other antihypertensive agents in October 1998 as Atacand® and is currently available in 33 countries (2).

AstraZeneca has completed patient enrollment in the CHARM (Candesartan Heart Failure Assessment of Reduction in Mortality and Morbidity) clinical program, the

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largest angiotensin II receptor blocker (ARB) program in heart failure patients. The program has randomized more than 7500 patients from 26 countries, including approximately 1800 in the U.S. The objective of CHARM is to evaluate the effects of candesartan cilexetil on survival, cardiovascular mortality and hospitalizations in patients with symptomatic heart failure. CHARM consists of three trials investigating a broad range of patient types and treatment scenarios. The first trial includes patients with impaired left ventricular systolic function who are intolerant to ACE inhibitors. This trial allows a comparison of candesartan cilexetil and placebo without concomitant treatment with ACE inhibitors. The second trial will evaluate the use of candesartan cilexetil in combination with conventional ACE inhibitor therapy, and the third trial will involve patients with congestive heart failure and preserved left ventricular systolic function (LVEF 40%), a population not previously studied. In addition, most patients in the third trial are not receiving ACE inhibitor therapy. In the CHARM program, patients are permitted as clinically indicated to use background therapies such as diuretics, digoxin, beta-blockers and spironolactone (3).

AstraZeneca has commenced a clinical trial to evaluate candesartan cilexetil as add-on therapy with the ACE inhibitor lisinopril for lowering blood pressure. The AMAZE trial consists of 2 parallel, 8-week, multicenter, double-blind, randomized, parallel-group, forced-titration studies involving approximately 1000 hypertensive patients from 150 sites in the U.S. The trial will evaluate the efficacy of adding candesartan cilexetil to lisinopril compared to increasing the dose of lisinopril alone for lowering blood pressure. Following an initial open-label treatment period with once-daily lisinopril, patients whose blood pressure remains uncontrolled will be randomized to one of two treatment groups. The first group will be treated with lisinopril plus candesartan cilexetil once daily as add-on therapy. The second group will be administered double the initial dose of lisinopril monotherapy once daily. Results from another trial, ACTION, an open-label, large-scale study, showed that candesartan cilexetil (16-32 mg/day) as add-on therapy further reduced systolic and diastolic blood pressure in patients on an ACE inhibitor (4).

1. Tanabe, K., Tokumoto, T., Shimizu, T. et al. *Effect of candesartan cilexetil in renal transplant recipients with hypertension and/or proteinura.* 18th Int Congr Transplant Soc (Aug 27-Sept 1, Rome) 2000, 158.

2. *DIRECT trial begins for prevention and progression of retinopathy in diabetic patients.* DailyDrugNews.com (Daily Essentials) Nov 7, 2000.

3. *Patient enrollment complete in AstraZeneca's CHARM program for heart failure.* DailyDrugNews.com (Daily Essentials) March 14, 2001.

4. *Atacand/Zestril combination trial begins.* DailyDrugNews.com (Daily Essentials) June 15, 2001.

Original monograph - Drugs Fut 1993, 18: 609.

CDP-571
Bay-10-3356
Humicade®

Treatment of IBD
Antiarthritic

EN: 197386

Celltech Chiroscience

A randomized, double-blind, placebo-controlled trial examined the efficacy of CDP-571 in 169 Crohn's disease patients. After dose response assessment with single doses of either 10 or 20 mg/kg of CDP-571 or placebo, patients received 10 mg/kg CDP-571 or placebo every 8 or 12 weeks. At week 2 of the 24-week trial, 45% of patients treated with CDP-571 had a clinical response, defined as a decrease in Crohn's Disease Activity Index score of at least 70 points. A clinical response was found in 27% of the placebo group (p = 0.023). Retreatment with the study drug appeared to be beneficial over the course of 24 weeks, though this conclusion requires further study. Severe or serious adverse events frequency was similar in all groups (1).

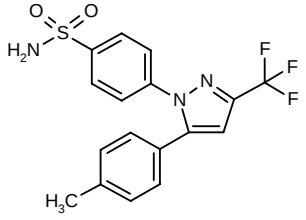
1. Sandborn, W.J., Feagan, B.G., Hanauer, S.B. et al. *An engineered human antibody to TNF (CDP571) for active Crohn's disease: A randomized double-blind placebo-controlled trial.* Gastroenterology 2001, 120(6): 1330.

Original monograph - Drugs Fut 2000, 25: 669.

Celecoxib
Celebra®
Celebrex®
Solexa®

Antiarthritic
Treatment of Adenomatous Polyposis
COX-2 Inhibitor

EN: 228583



$C_{17}H_{14}F_3N_3O_2S$

Pharmacia; Pfizer; Yamanouchi

The results of the double-blind, multicenter Celecoxib Long-term Arthritis Safety Study (CLASS) indicate that celecoxib causes fewer adverse effects than conventional NSAIDs. Celecoxib 400 mg twice daily, ibuprofen 800 mg 3 times daily or diclofenac 75 mg twice daily were randomly administered to 7968 patients with either osteoarthritis or rheumatoid arthritis. After the 6-month treatment period, annualized incidence rates for upper gastrointestinal (GI) ulcer complications were 0.76% and 1.45% for the celecoxib and NSAID groups, respectively.

Upper GI toxicity was reduced to a greater extent in patients not taking aspirin concomitantly. The incidence of chronic GI blood loss, GI intolerance, hepatotoxicity and renal toxicity was lower for patients treated with celecoxib. Cardiovascular event incidence was the same in the NSAID and celecoxib groups. In addition, the study demonstrated the superior side effect profile of celecoxib despite using doses of the drug 2-4 times higher than those indicated clinically (1).

Data from a head-to-head safety comparison of rofecoxib and celecoxib in elderly hypertensive patients with osteoarthritis have been presented. Results from this 6-week, multicenter, randomized, double-blind, parallel trial in 810 patients found a statistically significant increase (about 3 mmHg) in mean systolic blood pressure in those receiving rofecoxib as compared to those receiving celecoxib. In addition, 17% of patients taking rofecoxib did not maintain blood pressure control (defined as increases in systolic blood pressure of > 20 mmHg, with an absolute value of > 140 mmHg) compared to 11% of those taking celecoxib. Moreover, 9.5% of rofecoxib-treated patients experienced a clinically significant increase in edema, as compared to 4.9% of celecoxib-treated patients. Among the patients who developed edema, the changes in mean systolic blood pressure were significantly greater at 6 weeks in those receiving rofecoxib. The most commonly reported adverse events were headache, dyspepsia, diarrhea and abdominal pain in the rofecoxib group and upper respiratory tract infection and dyspepsia in the celecoxib group (2).

Celecoxib has been introduced on the German market as Celebrex® for the treatment of the symptoms of osteoarthritis and rheumatoid arthritis. The product is available as capsules of 200 mg (3).

The Arthritis Advisory Committee of the FDA has recommended changes to the prescribing information for Celebrex® (celecoxib) to reflect, among other things, data showing gastrointestinal safety advantages compared to conventional NSAIDs. In addition, the committee agreed that the prescribing information for Celebrex® should reflect the fact that it does not confer cardioprotective benefits and is not a substitute for low-dose aspirin (4).

Pharmacia and Pfizer have received an approvable letter from the FDA for revised labeling for celecoxib for the treatment of both osteoarthritis and adult rheumatoid arthritis (5).

1. Silverstein, F.E., Faich, G., Goldstein, J.L. et al. *Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis.* JAMA - J Am Med Assoc 2000, 284(10): 1247.

2. White, W.B., Whelton, A., Bello, A.E., Fort, J.G. *Loss of blood pressure control and rates of edema in older treated hypertensive patients following administration of the COX-2 specific inhibitors celecoxib vs. rofecoxib.* J Am Coll Cardiol 2001, 37(2, Suppl. A): 261A.

3. *Celebrex introduced in major European market.* DailyDrugNews.com (Daily Essentials) Oct 23, 2000.

4. *FDA advisory committee recommends changes in Vioxx and Celebrex labeling.* DailyDrugNews.com (Daily Essentials) Feb 22, 2001.

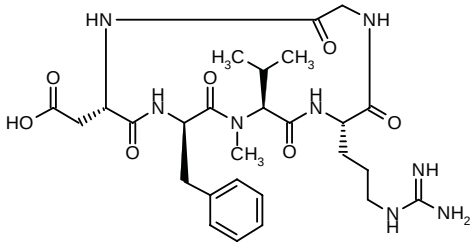
5. *FDA issues approvable letter for Celebrex revised labeling.* DailyDrugNews.com (Daily Essentials) April 18, 2001.

Original monograph - Drugs Fut 1997, 22: 711.

Cilengitide
EMD-85189
EMD-121974

Oncolytic
Angiogenesis Inhibitor

EN: 253338



$C_{27}H_{40}N_8O_7$

Merck KGaA

An ongoing phase I trial conducted in 37 patients with miscellaneous solid tumors examined the efficacy of cilengitide (30, 60, 120, 180, 240, 400, 600, 850, 1200 and 1600 mg/m^2 i.v. infusion). Patients were treated for a median of 42 days. The dose-limiting toxicity has not been reached. No hematological toxicities were observed. Mild nonhematological toxicities seen included nausea, anorexia, diarrhea, fatigue and malaise. Pharmacokinetics with doses up to 1200 mg/m^2 were approximately linear. Values for t_{max}, $t_{1/2}$, total clearance and steady-state volume were 1 h, 3-5 h, 30-70 ml/min/m^2 and 9-12 l/m^2, respectively; renal clearance of the unchanged compound was responsible for the majority of the total clearance. Peak plasma concentrations which inhibit tumor growth preclinically were achieved with a dose of 120 mg/m^2. Stable disease lasting 164 and 168 days was seen in 2 patients with renal cell carcinoma, respectively, and 1 patient with colorectal carcinoma had stable disease lasting 168 days (1).

1. Eskens, F., Dumez, H., Verweij, J., Brindley, C., Perschi, A., Kovar, A., Wynendaele, W., van Oosterom, A. *Cilengitide (EMD 121974) inhibits angiogenesis by blocking alpha$_v$beta$_3$ and alpha$_v$beta$_5$ integrins: Mature results of a phase I and pharmacological study.* Clin Cancer Res 2000, 6(Suppl.): Abst 296.

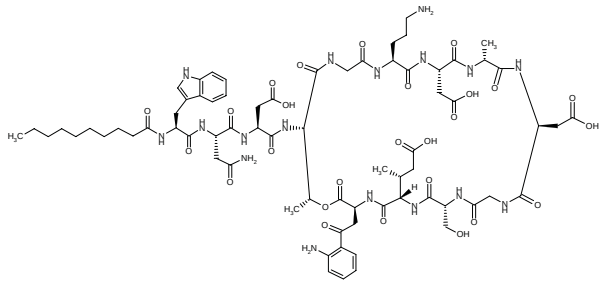
Original monograph - Drugs Fut 2000, 25: 674.

  CCC: 0377-8282/2001

Daptomycin
Cidecin®
Dapcin®

Antibiotic

EN: 111916



$C_{72}H_{101}N_{17}O_{26}$

Cubist; Gilead; Emisphere

An *in vitro* study examining spontaneous resistance incidence, serial passage with increasing drug concentrations and chemical mutagenesis investigated the emergence of resistant mutations to daptomycin. The organisms used were *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Enterococcus faecium* and *Streptococcus pneumoniae*. No spontaneous resistant mutations were observed. The daptomycin MICs for stable *S. aureus* mutants were 8- to 32-fold higher as compared to the parental strain and many mutants exhibited significant growth defects and showed phenotypes different from typical *S. aureus* small colony variants. Some of the resistant mutants obtained were found to have decreased virulence when tested *in vivo*. However, *in vitro* resistance was greater than *in vivo* susceptibility, indicating that infection with daptomycin-resistant strains can still be treatable with daptomycin (1).

The *in vitro* activity of daptomycin was examined against 2789 recent clinical isolates of Gram-positive bacteria in test broth containing normal and higher concentrations of calcium (20-25 *vs.* 50 mg/l). When broth contained additional calcium to mimic human serum, the MICs obtained were 2- to 4-fold lower. However, the percentages of strains except enterococci inhibited by 2 μg/ml daptomycin were comparable in broths containing normal and supplemented calcium. In contrast, 2 μg/ml daptomycin inhibited 92% *versus* 35% of the enterococci strains tested in broths containing supplemented and normal calcium, respectively (2).

The *in vitro* activities of daptomycin, arbekacin, vancomycin and gentamicin alone or in combination were examined against 2 glycopeptide intermediate-resistant *S. aureus* isolates (Mu-150; HIP5836) and a methicillin-resistant *S. aureus* isolate (MRSA-67). The MIC and minimal bactericidal concentrations (MBC) (MIC/MBC) for daptomycin against Mu-50, HIP5836 and MRSA-67 were 0.5/1, 0.5/1 and 0.125/0.5 μg/ml, respectively, with significant kill observed against Mu-50 and HIP5836. MIC/MBC values for arbekacin were 2/8, 0.125/0.5 and 0.125/0.25 μg/ml, respectively; these values for vancomycin and gentamicin were 8/8, 8/8 and 0.5/1 μg/ml, respectively. Synergistic activity was observed with a combination of daptomycin and arbekacin against Mu-50. The AUC/MIC and C_{max}/MIC ratios for daptomycin against both Mu-50 and HIP5836 were 80-116 and 6-12, respectively, and 320-461 and 24-48, respectively, against MRSA-67 (3).

The bactericidal activity of daptomycin (6 or 10 mg/kg/day) was examined using an *in vitro* model with simulated endocardial vegetations due to glycoprotein-intermediate susceptible *S. aureus* (GISA-992), vancomycin-resistant *E. faecium* (VREF-590) or methicillin-resistant *S. aureus* (MRSA-494). The MIC/MBC values (μg/ml) for the 2 doses against GISA, VREF and MRSA were 0.5/1 and 16/16, 2/2 and 32/32, and 0.25/0.25 and 1/4, respectively. At 8 h the 2 doses reduced inoculum (log_{10} CFU/g) of the respective strains by 5 and 6, 3.4 and 5, and 6.4 and 6.5, respectively. Dose-dependent killing effects were observed (4).

The activity of daptomycin against Gram-positive bacteria was demonstrated in a study using a murine neutropenic thigh model of *S. aureus* infection. The MICs for the 3 *S. aureus* isolates were 0.1-0.2 μg/ml in Mueller-Hinton broth and 1 μg/ml in mouse serum. A linear dose-dependent relationship was observed between serum C_{max} and AUC values following i.p. dosing in infected mice; a serum $t_{1/2}$ value of about 1.8 h was obtained. The ED_{50} value following single dosing was 3.7 mg/kg i.p. and the stasis dose was 7.1 mg/kg. The AUC/MIC ratio was determined to be a dynamically linked variable (5).

A study comparing 2 regimens of repeated i.v. administration of daptomycin (25 or 75 mg/kg every 8 or 24 h for 20 days) in dogs showed that the skeletal muscle effects associated with treatment were related to dosing interval rather than C_{max} or AUC values. Greater increases in serum creatine phosphokinase activity and incidence of myopathy were seen with 25 mg/kg every 8 h as compared to 75 mg/kg every 24 h. Thus, once-daily dosing with the agent minimized the potential daptomycin-associated skeletal muscle effects (6).

The pharmacological profile and recent clinical results for daptomycin have been reported. Analysis of data from 2 ongoing phase II open-label clinical trials in patients with bacteremia and other serious Gram-positive infections demonstrated a clinical success rate of 86% for daptomycin at a dose of 4 mg/kg every 24 h, compared to a 69% success rate for vancomycin 1 g every 12 h. Adverse event profiles were similar on both antibiotics (7).

Cubist Pharmaceuticals and Emisphere Technologies have established a research and development collaboration to utilize Emisphere's oral drug delivery technology for Cubist's late-stage investigational drug daptomycin for injection and other lipopeptides. This agreement follows successful completion of proof-of-principle feasibility studies using Emisphere carrier molecules and daptomycin. Under the terms of the agreement, Emisphere could receive fees, research funding and milestone payments in the event of a successfully marketed product.

Emisphere would also receive a royalty on sales of any product resulting from the collaboration, while Cubist would be responsible for drug development and would receive exclusive worldwide commercialization rights to any oral products (8).

Preliminary results were recently reported from the first completed pivotal phase III clinical trial of daptomycin for injection for the treatment of complicated skin and soft tissue infections caused by Gram-positive bacteria. Study 9901 is part of a larger clinical trial program for daptomycin referred to as EDGE (Evaluation of Daptomycin against Gram-positive Entities). The primary endpoint, demonstrating equivalency to comparator agents, was achieved. The trial compared the efficacy and safety of daptomycin to either vancomycin or approved semisynthetic penicillins (9).

Cubist has achieved the first milestone in its collaboration with Gilead following the successful completion of Study 9901, its pivotal phase III trial examining the safety and efficacy of daptomycin for injection in the treatment of complicated skin and soft tissue infections caused by Gram-positive bacteria. Upon review of the data from Study 9901, Gilead has agreed to pay Cubist USD 1.25 million for meeting the primary endpoint of the clinical trial. In January 2001, Cubist and Gilead jointly announced the signing of a licensing agreement for the exclusive rights to commercialize daptomycin for injection (Cidecin™) and oral daptomycin in 16 European countries following regulatory approval. Cubist will continue to be responsible for the worldwide clinical development of daptomycin for injection and oral daptomycin, while Gilead will be responsible for regulatory filings in the covered territories (10).

Cubist Pharmaceuticals has completed enrollment in Study 9801, the second of its pivotal phase III trials examining the efficacy and safety of daptomycin for injection for the treatment of complicated skin and soft tissue infections. Study 9801 was conducted at multiple centers, predominantly in the U.S. The primary endpoint is clinical efficacy (signs and symptoms) and secondary endpoints are bacteriological efficacy, duration of intravenous therapy and time to defervescence. Daptomycin is being compared to vancomycin or a semisynthetic penicillin, and is required to show equivalence or noninferiority to the comparator agents. Cubist also announced that it had completed enrollment in its phase II/III feasibility study evaluating the safety and efficacy of daptomycin for injection in the treatment of complicated urinary tract infections caused by Gram-positive pathogens. In addition to the studies to be included in the initial regulatory filings, Cubist expects to commence a phase II/III clinical research study examining the safety and efficacy of daptomycin for injection in the treatment of endocarditis in the second half of 2001 (11).

1. Silverman, J.A., Oliver, N., Andrew, T., Li, T. *Resistance studies with daptomycin.* Antimicrob Agents Chemother 2001, 45(6): 1799.

2. Barry, A.L., Fuchs, P.C., Brown, S.D. *In vitro activities of daptomycin against 2,789 clinical isolates from 11 North American medical centers.* Antimicrob Agents Chemother 2001, 45(6): 1919.

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4. Akins, R.L., Rybak, M.J. *Bactericidal activities of two daptomycin regimens against clinical strains of glycopeptide intermediate-resistant Staphylococcus aureus, vancomycin-resistant Enterococcus faecium, and methicillin-resistant Staphylococcus aureus isolates in an in vitro pharmacodynamic model with simulated endocardial vegetations.* Antimicrob Agents Chemother 2001, 45(2): 454.

5. Louie, A., Kaw, P., Liu, W., Jumbe, N., Miller, M.H., Drusano, G.L. *Pharmacodynamics of daptomycin in a murine thigh model of Staphylococcus aureus infection.* Antimicrob Agents Chemother 2001, 45(3): 845.

6. Oleson, F.B. Jr., Berman, C.L., Kirkpatrick, J.B., Regan, K.S., Lai, J.-J., Tally, F.P. *Once-daily dosing in dogs optimizes daptomycin safety.* Antimicrob Agents Chemother 2000, 44(11): 2948.

7. Snydman, D.R. *Daptomycin.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst 1125.

8. *Cubist and Emisphere collaborate on oral delivery of daptomycin.* DailyDrugNews.com (Daily Essentials) Nov 13, 2000.

9. *Initial results from pivotal trial of Cubist's Cidecin announced.* DailyDrugNews.com (Daily Essentials) March 16, 2001.

10. *Cubist achieves milestone for Cidecin, triggering payment from Gilead.* DailyDrugNews.com (Daily Essentials) April 12, 2001.

11. *Enrollment complete in second pivotal phase III trial of Cidecin.* DailyDrugNews.com (Daily Essentials) July 18, 2001.

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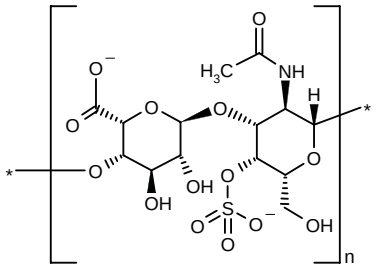
  CCC: 0377-8282/2001

Desmin-370

Anticoagulant

EN: 210239



$C_{14}H_{21}NO_{14}S$ **Alfa Wassermann; Opocrin**

A study conducted in 18 patients with moderate to severe chronic renal insufficiency grouped according to creatinine clearance (moderate, > 50 ml/min; severe, 10-15 ml/min; hemodialysis, < 10 ml/min) and given a single s.c. dose of low-molecular-weight dermatan sulphate showed that clearance of the agent was significantly correlated with creatinine clearance, indicating that elimination is dependent of renal function. The half-lives were 2.79 ± 2.60, 6.15 ± 4.02 and 11.51 ± 6.54 h for the moderate, severe and hemodialysis groups, respectively. Clearance results from the chromogenic specific heparin cofactor II-dependent anti-IIa assay were 13.98 ± 6.25, 4.12 ± 2.64 and 2.94 ± 1.53 l/h, respectively (1).

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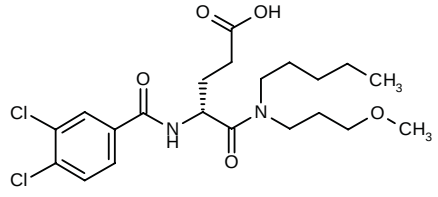
Original monograph - Drugs Fut 1994, 19: 638.

Dexloxiglumide
CR-2017

Treatment of IBS
CCK-A Antagonist

EN: 180635



$C_{21}H_{30}Cl_2N_2O_5$ **Rotta; Forest**

Evidence indicating a role for cholecystokinin (CCK) in dyspepsia in response to the ingestion of fat led researchers to investigate the effects of a CCK-A receptor antagonist, dexloxiglumide, in patients with functional dyspepsia undergoing duodenal lipid infusion and gastric distension. In initial studies, duodenal infusion of 10% or 20% lipid produced an increase in gastric volume compared to saline in both healthy controls and patients with functional dyspepsia, particularly the former, and an increase in plasma CCK levels was seen in both patients and healthy subjects, which reached statistical significance on 20% lipid. During gastric distension and infusion of 20% lipid, dyspeptic patients had higher symptom scores than healthy subjects, whereas healthy subjects had a greater increase in gastric compliance than the patients. In a second study, 12 patients with functional dyspepsia were given dexloxiglumide (5 mg/kg/h) during duodenal infusion of 20% lipid with or without gastric distension. Treatment with dexloxiglumide completely prevented the increase in gastric volume and dyspeptic symptoms during lipid infusion. Dexloxiglumide also decreased gastric compliance and symptom scores during gastric distension and appeared to reduce the patients' sensitivity to distension. The response to CCK-A blockade in this study indicates that functional dyspepsia involves CCK-A-dependent mechanisms. These results provide a rationale for the use of CCK-A antagonists in the treatment of such patients. Dexloxiglumide is being developed primarily for the treatment of irritable bowel syndrome (IBS) (1).

Forest has entered into an agreement with Rotta concerning the U.S. development and marketing of Rotta's dexloxiglumide for the treatment of constipation-prone IBS. Results from a phase II study in Europe supported the promising activity of dexloxiglumide in patients with IBS whose primary symptom was constipation. Phase III trials of the compound are expected to begin in the U.S. in the first half of next year (2).

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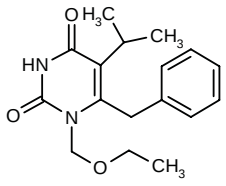
Original monograph - Drugs Fut 1999, 24: 725.

Emivirine
MKC-442
Coactinon®

Anti-HIV
Reverse Transcriptase Inhibitor

EN: 201056



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

An article has described novel DABOs and reported their structure-activity relationships. The 2-alkylthio-3,4-

dihydropyrimidin-4(3*H*)-one derivatives of F2-S-DABO series which bore small alkyl groups at the C-5 position were found to be the most potent inhibitors of HIV-1 replication *in vitro* using HIV-1-infected MT-4 cells. The selectivity indices (CC_{50}/EC_{50} ratio) for these compounds were 250 to > 2500. Values for CC_{50}, EC_{50} and selectivity index for MKC-442 were 200, 0.03 and 6666, respectively (1).

An *in vitro* study using MT-4 cells infected with HIV-1 (IIIB strain) compared the effects 3-drug combination treatment including emivirine (EMV) + d4T + 3TC and therapy with EMV + d4T + ddI. Both 3-drug combinations synergistically inhibited HIV-1 replication in cells although higher synergism was observed with EMV + d4T + ddI. The 3-drug combinations also exhibited higher synergism than 2-drug therapies (*e.g.*, EMV + d4T, EMV + 3TC, EMV + ddI, d4T + 3TC, d4T + ddI). Examination of breakthrough viruses following long-term culture of HIV-infected MT-4 cells showed that while both 3-drug combinations at a dose 10 times the EC_{50} inhibited HIV-1 replication for at least 40 days, breakthrough viruses were detected in cultures treated with EMV alone, 3TC alone, ddI alone, d4T + ddI and in cells treated with the 3-drug combinations at a dose 5 times the EC_{50}. Only those viruses obtained in the presence of EMV alone and 3TC alone were significantly less susceptible to EMV (215-fold) and 3TC (77-fold), respectively (2).

After reviewing results of the phase III Study MKC-401, Triangle Pharmaceuticals has decided to move forward with clinical development of emivirine for the treatment of HIV infection. This action follows notification from the FDA in December 1999 that additional phase III studies would be required for product approval. An additional 280 patients will be enrolled in Study MKC-401, although the dose of emivirine will be administered at 500 mg twice daily rather than at the 750 mg twice-daily dose used thus far. The decision to use the 500 mg twice-daily dose was based on analysis of results from Study MKC-202, which showed the lower dose to have comparable efficacy but superior tolerability. In the trial, emivirine is being evaluated in combination with stavudine and emtricitabine *versus* a combination of abacavir, stavudine and emtricitabine (3).

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2. Nitanda, T., Wang, X., Somekawa, K., Yuasa, S., Baba, M. *Three-drug combinations of emivirine (EMV), d4T and 3TC versus EMV, d4T and ddI in vitro: Long-term culture of HIV-1-infected cells and breakthrough viruses.* Antivir Res 2001, 50(1): Abst 54.

3. *Triangle Pharmaceuticals to proceed with Coactinon development.* DailyDrugNews.com (Daily Essentials) Aug 17, 2000.

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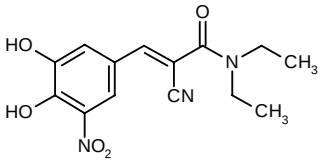
Entacapone
Comtan®
Comtess®

Antiparkinsonian
COMT Inhibitor

EN: 178077



$C_{14}H_{15}N_3O_5$ **Orion Corp.; Novartis; DuPont Pharm.**

Novartis and Orion have signed an agreement to develop tablet formulations combining three active drug substances for the treatment of Parkinson's disease. The product under development will contain Orion's entacapone (Comtan®), a COMT inhibitor, in combination with levodopa and carbidopa, well-known treatments for Parkinson's disease. The combination will facilitate more convenient dosing of these drugs, as entacapone is always taken concomitantly with levodopa and carbidopa several times daily. Under the terms of the agreement, Novartis will have exclusive marketing rights to the new product in the U.S. and Orion retains the option to copromote the product in the U.S. Marketing applications seeking approval for the triple combination are expected to be submitted to the FDA in 2003, with launches and worldwide commercialization expected for 2004 (1).

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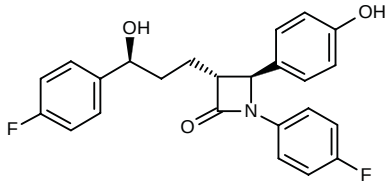
Original monograph - Drugs Fut 1994, 19: 641.

Ezetimibe
SCH-58235

Hypolipidemic
Cholesterol Absorption Inhibitor

EN: 224366



$C_{24}H_{21}F_2NO_3$ **Schering-Plough**

  CCC: 0377-8282/2001

Ezetimibe has been shown to reduce plasma cholesterol levels in animals and humans, but its effects on the combined dyslipidemia (hypercholesterolemia and hypertriglyceridemia) typical of type 2 diabetes and obese insulin-resistant subjects have not been established. A preclinical study was therefore performed in which hamsters were made obese, hyperinsulinemic, hypercholesterolemic, hypertriglyceridemic and hyperleptinemic by feeding with a cholesterol (0.12%)- and triglyceride (15%)-containing diet. The animals treated with ezetimibe (1 mg/kg in the diet for up to 84 days) showed no change in body weight, insulin or leptin but had normalized VLDL + LDL cholesterol and triglyceride levels and a significant decrease in LDL cholesterol to below levels in animals fed normal chow. The treatment also significantly increased the HDL:LDL cholesterol ratio. The hepatic accumulation of cholesteryl ester and free cholesterol was completely reversed by ezetimibe. According to these findings, ezetimibe may represent an effective pharmacological intervention in patients with combined dyslipidemia, thereby reducing the risk of cardiovascular disease in this patient population (1).

A study using intact hamsters and rats showed that ezetimibe (1 and 3 mg/kg) potently inhibited intestinal free cholesterol absorption (> 95%) independent of pancreatic exocrine function. The agent did not alter triglyceride absorption in contrast to orlistat and, unlike cholestyramine, had no effect on vitamin A, vitamin D or taurocholate absorption (2).

Researchers determined the ability of ezetimibe (0.3 mg/kg/day, 1 mg/kg/day, 3 mg/kg/day and 10 mg/kg/day) to reduce cholesterol absorption in apoE +/+ and –/– knockout mice. At 3 mg/kg/day, ezetimibe inhibited cholesterol absorption by 90% in the apoE –/– mice. At 10 mg/kg/day, the drug caused a greater than 90% reduction in cholesterol absorption in both apoE +/+ and –/– mice. In addition, 6 months of ezetimibe (5 mg/kg/day) administration caused a reduction in plasma cholesterol levels from 516 mg/dl to 178 mg/dl in apoE –/–- mice. In the LDL fraction, however, cholesterol levels increased from 27 mg/dl to 45 mg/dl. Atherosclerotic lesion cross-sectional area decreased by 91% in the carotid artery and 81% in the aorta with ezetimibe treatment. These results suggest that ezetimibe may inhibit atherogenesis in individuals on cholesterol-restricted diets (3).

An *in vivo* study conducted in monkeys fed a high cholesterol (375 mg/day) diet showed the efficacy of ezetimibe (0.1 mg/kg) in decreasing hypercholesterolemia. In rhesus monkeys, 0.1 mg/kg of the agent prevented the doubling of plasma cholesterol levels (ED_{50} = 0.0005 mg/kg) seen in untreated controls. Treatment dose-dependently reduced LDL-C without affecting plasma triglycerides or HDL-C levels. A significant 41% reduction in chylomicron apoB-100 content was also observed with no affects on apoB-48. Experiments conducted in cynomolgus monkeys fed a single cholesterol-containing meal showed that single-dose ezetimibe significantly reduced cholesterol in chylomicrons during the postprandial phase by 69%; chylomicron triglyceride content was unaffected. Thus, it was concluded that ezetimibe-induced reductions in chylomicron cholesterol content indirectly lead to decreases in LDL-C (4).

A study determined the tissue localization and effects of ezetimibe on intestinal cholesterol metabolism. The compound was shown to localize to the brush border of the small intestinal enterocytes, where the drug inhibited cholesterol uptake and absorption right before the point at which cholesterol reaches ACAT for esterification. In addition, ezetimibe maintains cholesterol in the lumen of the intestine for excretion (5).

A pharmacokinetic study conducted in 24 young (18-45 years) and elderly (> 65 years) subjects showed that once-daily oral ezetimibe for 10 days was safe and well tolerated. Ezetimibe was found to be rapidly absorbed and extensively conjugated (about 90%) to its glucuronide. Although there were no differences in the pharmacokinetics of unconjugated ezetimibe between young and old subjects, plasma conjugated ezetimibe concentrations were significantly greater (2-fold) in older subjects as compared to younger subjects. This difference may be due to a possible reduced elimination rate of glucuronide in the elderly. It was concluded that the differences observed were probably not clinically significant (6).

The pharmacokinetics of once-daily oral ezetimibe (for 14 days) were described in rats (2000 mg/kg gavage), dogs (100 mg/kg gavage) and humans (10 or 20 mg tablet). Treatment was well tolerated with a favorable safety profile obtained. All species showed gender-independent pharmacokinetics with rapid absorption (C_{max} occurred at about 1 h postdosing), possible enterohepatic recycling and extensive conjugation to its glucuronide. Plasma AUC values for rats, dogs and humans were approximately 99, 95 and 90%, respectively, and accumulation indices for total ezetimibe were 0.9, 1.2 and 1.9, respectively. The $t_{1/2}$ value in dogs was about 8 h as compared to 22 h in humans (7).

Results of 2 double-blind, placebo-controlled studies conducted in a total of 411 hypercholesteremia patients administered ezetimibe (0.25, 1.5, 5 or 10 mg for 12 weeks) revealed a relationship between ezetimibe plasma concentrations and the LDL-cholesterol (LDL-C) lowering response. Ezetimibe plasma concentrations were classified into 3 groups: I = 0.2 ng/ml, II = 2-15 ng/ml and III = > 15 ng/ml. A significant correlation was observed between plasma concentrations of the agent and LDL-C reductions (10, 15 and 20% for the respective groups) as compared to placebo. For patients to achieve LDL-C reductions of > 15%, trough concentrations of the agent had to be sustained at levels of > 15 ng/ml and it was shown that those patients receiving the 10 mg dose were most likely to maintain these trough levels (8).

Results from a randomized, double-blind, placebo-controlled study conduced in 113 subjects showed that treatment with ezetimibe (10 mg once daily for 12 weeks) did not alter serum concentrations of vitamin A, vitamin D (25-hydroxy vitamin D and 1,25-dihydroxy vitamin D), vitamin E (α- and γ-tocopherol) and α- and β-carotenoids.

Prothrombin time was also not altered by treatment, suggesting no changes in vitamin K (9).

Results from a randomized, double-blind, placebo-controlled, parallel-group study conducted in 827 subjects with primary hypercholesterolemia, on the NCEP Step I or stricter diet, showed the safety and efficacy of ezetimibe (10 mg p.o. once daily in the AM for 12 weeks). The study included a washout period of 2-12 weeks and a 4-week single-blind, placebo lead-in period. Treatment was well tolerated with similar safety profiles obtained for ezetimibe and placebo. Treatment significantly decreased LDL-C with peak effects seen by week 2 which were maintained throughout the dosing period (–17.7 ± 0.6 *vs.* 0.8 ± 0.9% in placebo). Treatment also significantly improved total cholesterol (–12.4 ± 0.4 *vs.* 0.6 ± 0.6%), apoB, HDL-C (1 ± 0.5 *vs.* –1.3 ± 0.8%) and lipoprotein a levels as compared to placebo. A trend toward a decrease in triglycerides was also seen (–1.7 ± 1.4 *vs.* 2.4 ± 2.2%). Furthermore, treatment did not affect responses to cosyntropin (0.25 mg i.v.) stimulation (10, 11).

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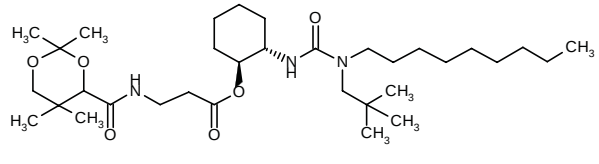
F-1394

Hypolipidemic
ACAT Inhibitor

EN: 177583



$C_{33}H_{61}N_3O_6$

UCB Japan

A study using rabbits fed a high cholesterol or regular diet for 4 weeks and subjected to denuding of the left common carotid arteries to induce arterial hyperplasia examined the effects of F-1394 on atherosclerotic procession. Hypercholesterolemia induced macrophage-derived foam cell accumulation in lesions, an effect enhanced by the presence of macrophages. The agent (p.o.) significantly decreased neointimal thickening and the number of macrophages in lesions as compared to controls; treatment had no effect on serum cholesterol. Results suggest that F-1394 may be effective in the treatment of restenosis following PTCA in hyperlipidemic patients (1).

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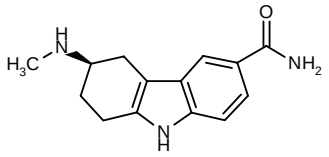
Frovatriptan
Migard®

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

EN: 212285



$C_{14}H_{17}N_3O$

Vernalis; Elan; Draxis Health; Menarini

The therapeutic index (TI) of frovatriptan was evaluated in a review of adverse events from 21 studies involving 369 subjects. Adverse events that occurred within 48 h of the final dose from each treatment period were analyzed in relation to frovatriptan exposure as indicated by C_{max} values. Though the incidence of adverse events was higher in the frovatriptan periods than in the placebo periods, the drug was found to have a broad TI. Only when frovatriptan C_{max} values were > 50 ng/ml, corresponding to mean blood levels achieved at 6-10 times the clinical dose of 2.5 mg, did adverse events increase (1).

Open-label studies of 6 and 12 months of frovatriptan 2.5 mg have shown that the drug might be useful in the treatment of mild migraine headache. In each study, patients recorded the time to meaningful relief, defined as resolution of headache pain and other migraine symptoms. In both studies, the median time to meaningful relief was related to the initial severity of the headache, with headaches of greater initial severity taking longer to resolve. The incidence of recurrence was low and was not related to headache severity (2).

The effect of CYP1A2 inhibitors on the metabolic clearance of frovatriptan was evaluated in a crossover study including 24 subjects: 8 men and 8 women using the combined oral contraceptive (COC) pill, which inhibits CYP1A2, and 8 female non-COC users. Oral frovatriptan 2.5 mg was administered alone or on day 8 of an 11-day treatment with fluvoxamine 100 mg daily. Administration of 100 mg caffeine and measurement of the urinary caffeine metabolite ratio confirmed that fluvoxamine strongly inhibited CYP1A2. The systemic exposure to coadministered frovatriptan was increased, with the frovatriptan $AUC_{0\text{-}24h}$ increased by 39, 41 and 28% in male COC users, female COC users and female non-COC users, respectively. C_{max} was increased by 28, 49 and 27% in these groups, respectively. The mean $t_{1/2}$ of frovatriptan was similar in all groups and was shorter when coadministered with fluvoxamine than when taken alone (17 *vs.* 24 h). Female COC users had the highest frovatriptan exposure due to the inhibition of CYP1A2 by both fluvoxamine and COC. Men had the lowest frovatriptan exposure. The difference in $AUC_{0\text{-}24h}$ between genders was 10-30%. C_{max} values were highest for female COC users but were similar in men and women not using COC. C_{max} values of frovatriptan were well below those found in other studies where frovatriptan 40 mg was well tolerated. It was concluded that coadministration with fluvoxamine or any other potent CYP1A2 inhibitor is safe and does not warrant dose adjustment (3).

Frovatriptan (Migard®), which is being developed by Vernalis under an agreement with SmithKline Beecham, has been granted French regulatory approval, opening the way for approval in other European Union markets under the mutual recognition procedure. The company expects that marketing of the drug in Europe will begin in the first half of next year. Marketing rights for frovatriptan have been licensed to Elan in the U.S. and to Menarini for Europe. Applications seeking approval for marketing were made in the U.S. and France in 1999 (4).

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Gemtuzumab Ozogamicin *Treatment of AML*
WAY-CMA-676
CDP-771
CMA-676
Mylotarg®

EN: 198455

Celltech Chiroscience; Wyeth-Ayerst

Treatment of a 48-year female patient with Philadelphia/bcr-abl-positive acute myeloid leukemia (AML) with 2 doses (9 and 9 mg/m^2 19 days later) of gemtuzumab ozogamicin resulted in complete morphological and cytogenetic remission. A 3-log reduction in bone marrow tumor mass was observed. Mild muscle cramping for 3 days, oropharyngeal HSV infection and pancytopenia lasting for about 15 days occurred after the first dose. Pancytopenia lasting for about 20 days occurred after the second dose (1).

Results from 3 phase II studies involving 142 patients with AML in first relapse classified the type of remission observed following treatment with gemtuzumab ozogamicin (9 mg/m^2 i.v. every 2 weeks for 2 doses). Forty-two patients achieved remission of whom 23 had complete remission (CR; 100,000 platelets/μl) and 19 had complete remission with incomplete platelet recovery (CRp; < 100,000 platelets/μl). No difference in progression-free survival (9.7 and ≥ 7.7 months) and landmark survival (12.6 and ≥ 11.1 months) were observed between CR and CRp patients. Rates of hematopoietic stem cell transplantation (HSCT) and 100-day survival after HSCT were also similar between CR and CRp patients. CR patients required fewer platelet transfusions but the incidence of severe bleeding was similar in CR and CRp patients. Pretreatment platelet counts appeared to be the only variable predicting a CRp, possibly due to the effect of gemtuzumab on CD33-expressing platelet precursor cells (2).

Results from 3 phase II studies involving 142 patients with AML in first relapse showed the efficacy and safety of gemtuzumab ozogamicin (9 mg/m^2 i.v. every 2 weeks for 2 doses) with no differences observed between younger (< 60 years) and older (> 60 years) patients. Forty-two patients achieved remission (< 5% blasts in marrow, 1500 neutrophils/ml and platelet transfusion independent) of whom 34% were young and 26% were older; the median survival for all patients was 5.9 months. Of the 42 patients achieving remission, 19 were administered postremission therapy (hematopoietic stem cell transplantation [HSCT] or combination therapy) of whom 14 were younger and 5 were older. Of the 23 remaining patients in remission, 6 continue to be leukemia-free. No differences in adverse events were observed between younger and older patients. The adverse events seen included infusion-related symptom complex (self-limited fever and chills and occasionally hypotension and shortness of breath), grade 4 neutropenia and thrombocytopenia and transient increases in bilirubin and/or hepatic transaminase levels (3).

The European Commission has designated gemtuzumab ozogamicin (Mylotarg®) an orphan medicinal product. Gemtuzumab ozogamicin, the first in a new class of anticancer therapy known as antibody-targeted chemotherapy, is indicated for the treatment of patients aged 60 and over with CD33-positive relapsed AML. This decision follows a positive opinion adopted on September 13, 2000 by the Committee on Orphan Medicinal Products of the European Agency for the Evaluation of Medicinal Products. The drug is being codeveloped by Wyeth-Ayerst, the pharmaceutical division of American Home Products, and Celltech Group (4).

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2. Sievers, E.L., Larson, R.A., Estey, E., Stadtmauer, E.A., Appelbaum, F.R. *Remission classification for patients with acute myeloid leukemia in first relapse treated with gemtuzumab ozogamicin (CMA-676).* Clin Cancer Res 2000, 6(Suppl.): Abst 460.

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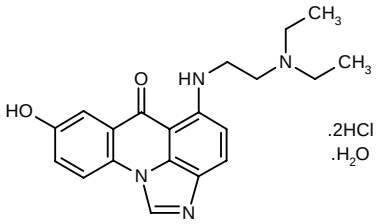
Imidacrine
C-1311

Oncolytic

EN: 227463



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

A study using a horse radish peroxidase (HRP)/H_2O_2 system examined the relationship between enzymatic activation of C-1311 and its noncovalent binding to DNA. Results showed that following intercalation of the agent into DNA, the agent was activated by a HRP-mediated mechanism. The result was an intercalated species that irreversibly bound to DNA (1).

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Additional Reference

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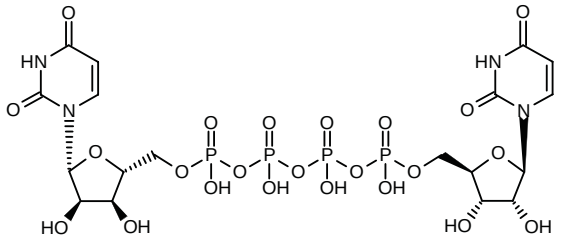
INS-3653
KPY-998

Treatment of Cystic Fibrosis
Treatment of COPD
Lacrimal Secretion Stimulant

EN: 263630



$C_{18}H_{26}N_4O_{23}P_4$ **Inspire Pharm.; Kissei; Santen; Allergan**

INS-365 can be obtained by several different ways:

1) Dimerization of uridine-5'-monophosphate tributylammonium salt (I) with bis(triethylammonium) pyrophosphate (II) by means of CDI, followed by purification by semipreparative ion–exchange chromatography.

2) Reaction of uridine-5'-diphosphate (III) with CDI in DMF gives the corresponding adduct (IV), which is then condensed with more uridine-5'-diphosphate (III), affording INS-365 which is purified by chromatography as before.

3) Reaction of uridine-5'-triphosphate tributylammonium salt (V) with CDI in DMF gives the cyclic triphosphate (VI), which is then condensed with uridine-5'-monophosphate (I) in hot DMF to provide INS-365 which is purified by chromatography as before (1). Scheme 1.

INS-365 can also been obtained by the following ways:

1) Dimerization of uridine-5'-monophosphate tributylammonium salt (I) with bis(tributylammonium) pyrophosphate (II) by means of CDI, followed by purification by semipreparative ion–exchange chromatography.

2) Dimerization of uridine-5'-monophosphate tributylammonium salt (I) with pyrophosphoryl chloride (III) in pyridine, followed by chromatographic purification as before.

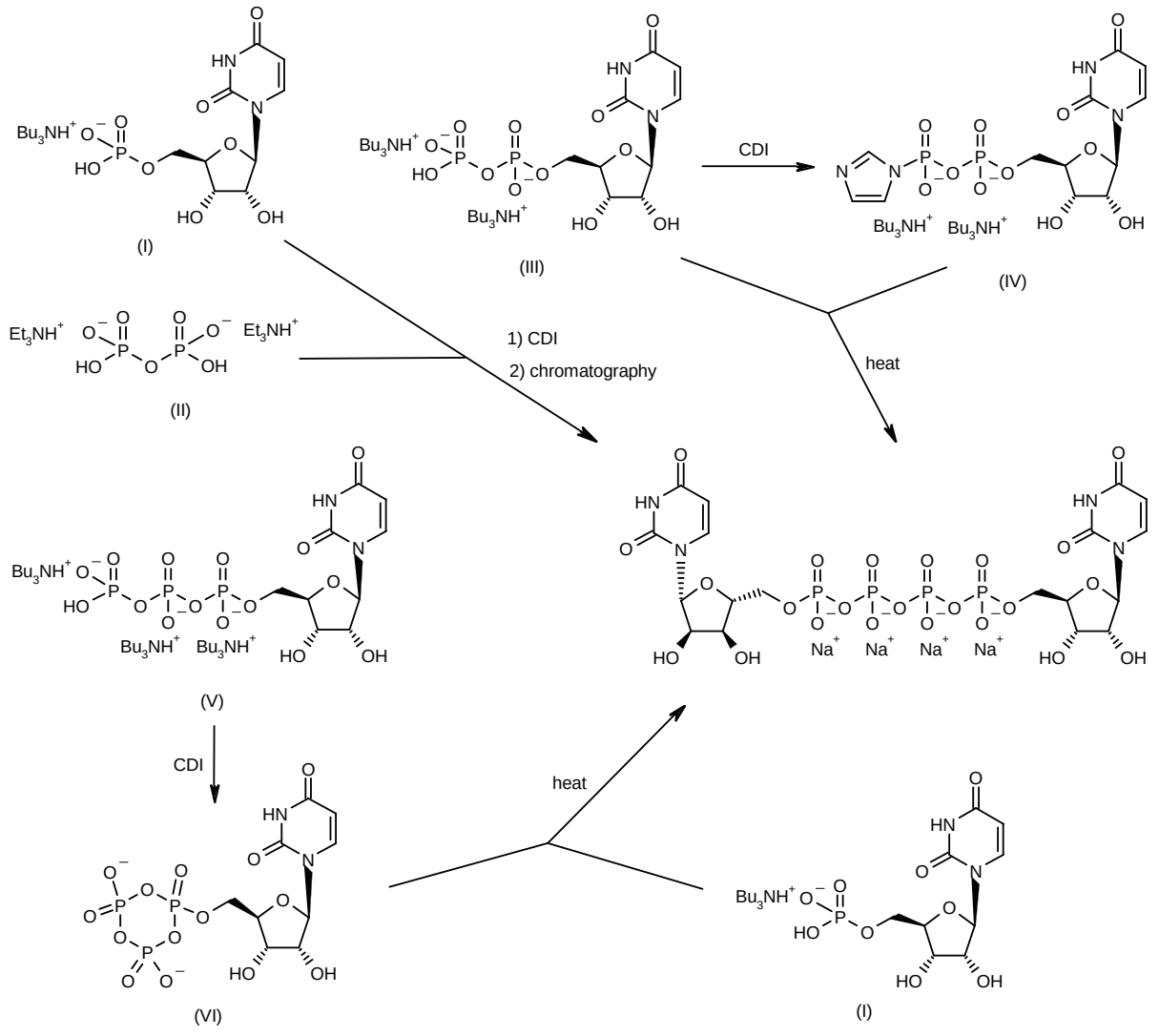
3) Condensation of uridine (IV) with $POCl_3$ and bis(tributylammonium) pyrophosphate (II) by means of tributylamine in trimethyl phosphate, followed by chromatographic purification as before.

4) Dimerization of uridine-5'-diphosphate tributylammonium salt (V) by means of CDI in DMF, followed by purification over Dowex 50Wx4 Na^+.

5) Condensation of uridine-5'-triphosphate tributylammonium salt (VI) with uridine-5'-monophosphate tributylammonium salt (I) by means of DCC in DMF, followed by chromatographic purification as before.

6) Reaction of uridine-5'-monophosphate tributylammonium salt (I) with CDI in DMF, followed by condensation with uridine-5'-triphosphate (VI) and chromatographic purification as before (2). Scheme 2.

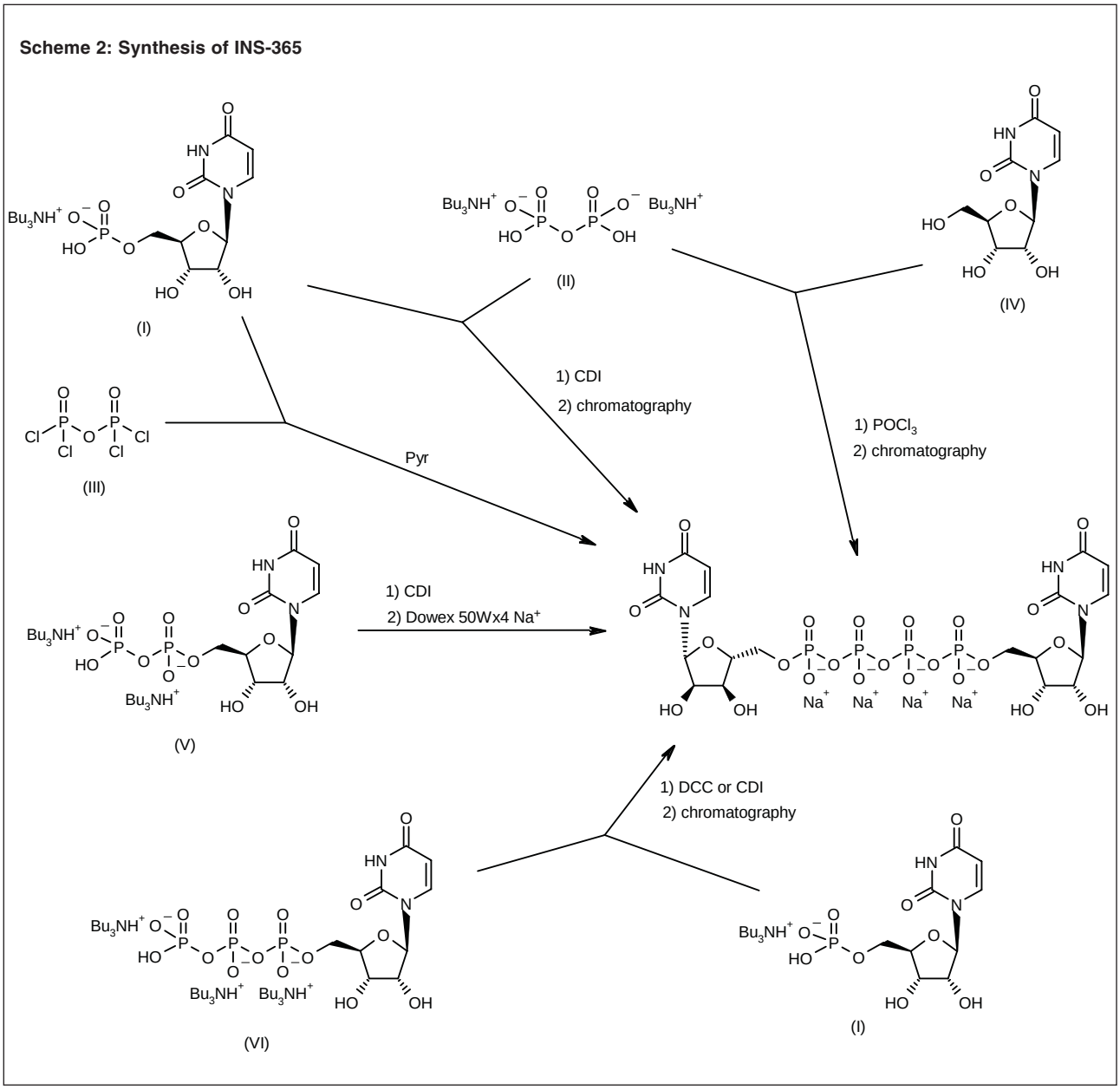
Scheme 1: Synthesis of INS-365



A double-blind, randomized, placebo-controlled trial in 12 smokers to evaluate the safety and effect of inhaled nebulized INS-365 on mucociliary clearance has been reported. Patients were treated on three different occasions with single doses of saline, INS-365 40 mg or 80 mg. Both doses of INS-365 were well tolerated, with mild to moderate adverse events which resolved spontaneously. Cough was seen in 6 of 12 patients following saline and all 12 following INS-365, transient wheezing was detected in 1 of 12 following saline and 10 of 12 following INS-365, and nasal congestion was reported by 1 of 12 subjects following saline, 10 of 12 following low-dose INS-365 and 9 of 12 following high-dose INS-365. Mucociliary clearance was similarly enhanced after both doses of INS-365 compared to saline. The investigators suggest that INS-365 may have beneficial effects in smoking-related obstructive airways disease and other conditions related to impaired mucociliary clearance such as sinusitis, and that it may be effective at even lower doses (3).

Results from a double-blind crossover, placebo-controlled study showed that mucociliary clearance was acutely improved by minimal doses of aerosolized INS-365. Clearance of [^{99}Tc]-Fe_2O_3 particles in 12 chronic smokers was measured over a 2-h period by γ camera scanning; during the inititial 20 min of scanning subjects were treated with inhaled INS-365 or vehicle. Particle clearance rates (C in %/min) increased with INS-365 doses of 40 mg (C = 0.95 ± 0.12) and 80 mg (C = 1.07 ± 0.12) as compared to placebo (C = 0.56 ± 0.11). Central

Scheme 2: Synthesis of INS-365



vs. peripheral lung regions showed the greatest increase in C (3.5-fold *vs.* 2.0-fold over baseline) with the 80 mg dose. Mild cough occurring during treatment was not found to be predictive of enhanced clearance rates (4).

Inspire has decided to temporarily suspend enrollment of new patients in the double-blind, placebo-controlled, multicenter phase II trial of INS-365 Respiratory for the treatment of chronic bronchitis, in order to further evaluate the protocol design. All patients currently enrolled in the trial will continue to receive INS-365 or placebo through completion of the study. The company is working with partner Genentech to analyze and review the protocol design and data from patients currently enrolled in the trial, in an attempt to ensure optimal design and conduct of the remainder of the phase II program. The product has also completed a phase I study for the treatment of cystic fibrosis (5).

Inspire has commenced a U.S. phase III clinical program for INS-365 Ophthalmic for the treatment of dry eye disease. Pursuant to the program, a total of approximately 1000 patients with dry eye are expected to be enrolled in 2 trials at 60 ophthalmology centers. The double-blind, placebo-controlled trials will evaluate the efficiency of two concentrations of INS-365 Ophthalmic on a chronic basis. Both objective ocular surface measurements and subjective assessments have been incorporated into the study design (6).

The ocular safety and tolerability of INS-365 (0.5, 1, 2 and 5% solution 3 times over 6 h) were shown in a

randomized, double-blind, placebo-controlled, intrasubject-paired comparison, dose-escalation study conducted in 5 cohorts of 10 healthy subjects. The incidence of ocular adverse events was similar in both treated and placebo groups. Adverse events possibly related to treatment with the 5% solution included painless blepharospasm and an increase in lacrimation. According to Schirmer testing, the agent had no acute effects on tear secretion as compared to placebo (7).

Results from a double-blind, parallel-group phase II trial of INS-365 Ophthalmic eye drops for the treatment of dry eye indicate that INS-365 showed strong and consistent trends in the improvement of both signs and symptoms of dry eye, including a statistically significant improvement over placebo on an important objective efficacy endpoint, corneal staining. Although not the aim of the study, results showed significant differences for improvement in several other important measures of efficacy, including conjunctival staining, tear breakup time and the unanesthetized Schirmer test (a test measuring tear secretion) in the INS-365 treatment groups at various time-points throughout the study. In addition, the subjective endpoints of ocular itching and burning consistently improved in drug-treated cohorts, with burning showing a statistically significant difference. Ocular tolerability was excellent over a 10-fold range of concentrations (0.5-5.0%). The dose-ranging, placebo-controlled study, involving 158 patients with moderate to severe disease, took place at 12 sites in the U.S. (8).

Based on a review of its product pipeline and related priorities, Genentech has decided to return to Inspire rights to INS-365 Respiratory for chronic bronchitis (9).

Allergan and Inspire have entered into a licensing, development and marketing agreement relating to Inspire's INS-365 Ophthalmic. Pursuant to the agreement, Allergan obtains an exclusive license to develop and commercialize INS-365 Ophthalmic worldwide, with the exception of Japan and nine other Asian countries covered by Inspire's agreement with Santen. In exchange, Inspire will receive both upfront and milestone payments, a copromotion arrangement for INS-365 Ophthalmic in the U.S. and payments based on U.S. net sales (10).

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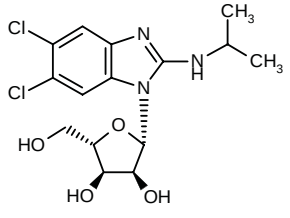
Maribavir
Benzimidavir
1263W94

Anti-CMV

EN: 233414



$C_{15}H_{19}Cl_2N_3O_4$ **GlaxoSmithKline**

A phase I trial conducted in 8 patients with AIDS and CMV retinitis examined the safety and intravitreal penetration of multiple-dose oral 1263W94 (800 mg t.i.d. or 1200 mg b.i.d. for 7 days). Seven patients completed the study and no serious drug-related adverse events were observed. The majority of drug-related adverse events were mild or moderate and included dysgeusia, diarrhea, nausea and vomiting with the exception of 1 case of grade 4 hypotony. Concentrations of the agent in the vitreous humor were found to be above the IC_{50} values required for inhibition of HCMV (0.142 ± 0.094 μg/ml). Of the 3 patients who had detectable HCMV at baseline,

  CCC: 0377-8282/2001

decreases of 1.9, 0.26 and ≥ 1.1 log_{10} HCMV DNA copies/ml, respectively, were observed by day 8 (1).

Glaxo has terminated the development of maribavir (2).

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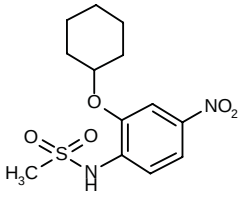
NS-398

COX-2 Inhibitor

EN: 151658



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

A study using rats with partial bladder obstruction showed that NS-398 (2 mg/kg/day by gavage for the first 48 h postsurgery) exhibited less bladder wall thickening at 2 weeks postsurgery as compared to untreated controls. Bladder weight in NS-398-treated animals was 0.10 ± 0.01 g as compared to 0.16 ± 0.01 g in untreated controls. Since all untreated animals exhibited a > 10-fold increase in COX-2 after obstruction, it was suggested that NS-398-induced inhibition of this enzyme was responsible for the reduction in bladder wall thickening (1).

The efficacy of NS-398 has been evaluated in a model of streptozotocin-induced diabetes in mice. In animals receiving the inhibitor, destruction of beta-cells was prevented; this was true even when initiation of NS-398 treatment was delayed by 3 days. These findings support the role of COX-2 in the autoimmune destruction of pancreatic β-cells that occurs in type 1 diabetes, and indicate that the COX-2 enzyme may be a valid target for the prevention of this disease (2).

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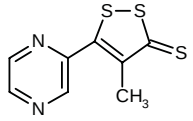
Oltipraz

Chemopreventive

EN: 090895



$C_8H_6N_2S_3$ **Aventis Pharma**

A study using *c-fos* knockout and wild-type mice examined the effects of oltipraz (1 g/kg by oral gavage) on protein expression. Results showed that genotype influenced protein expression since untreated knockout mice exhibited increased expression of Ferritin H, Ferritin L, glutathione-S-transferase (GST)Ya and GSTm by 9.4-, 2.3-, 8.9- and 1.6-fold, respectively, as compared to untreated wild-type animals. Treatment with the agent increased total hepatic GST activity by 1.8- and 2.0-fold, respectively, and GSTm activity by 2.9- and 2.2-fold, respectively, in both knockout and wild-type animals. No significant differences in kidney and lung tissue were observed between treated and untreated animals and between genotypes (1).

A phase I trial conducted in 26 patients who had previously resected colon polyps or were first-degree female relatives of breast cancer patients examined the efficacy and safety of oral oltipraz at doses of 20 (level 1 [L1]), 50 (L2) or 100 (L3) mg/day for 6 months or 125 mg twice/week for 6 months (L4). Of the total number of patients, 4/4, 4/6, 5/7 and 4/7 completed the 6 months of treatment with L1, L2, L3 and L4, respectively. Mild to severe toxicities were observed which included gastrointestinal symptoms, photosensitivity/heat intolerance and neurological symptoms. No significant differences in mean plasma oltipraz concentrations were seen for the doses or over time. One patient on L3 showed a significant increase in rectal tissue glutathione (GSH) and GSH-S-transferase (GST) activity and 3 patients given L1 and L4 showed a > 50% increase in tissue GSH. A significant correlation was found between lymphocyte GSH levels and plasma oltipraz concentrations. However, no correlations were detected between lymphocyte GST levels or tissue GSH or GST levels and plasma oltipraz concentrations. The study is ongoing (2).

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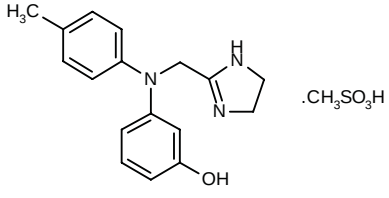
Phentolamine Mesilate

Vasomax® *Treatment of Erectile Dysfunction*

Vasofem® *Treatment of Female Sexual Dysfunction*

EN: 091428



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

Data from a clinical trial in Mexico involving phentolamine mesilate (Vasofem®) indicate its promise for the treatment of female sexual dysfunction (FSD). The randomized, double-blind, placebo-controlled, crossover study involved 42 postmenopausal women diagnosed with female sexual arousal disorder (FSAD), a subset of FSD, of whom 18 were also using hormone replacement

  CCC: 0377-8282/2001

therapy (HRT). The objective of the trial was to study the effect of phentolamine mesilate, administered as a tablet or vaginal solution, under neutral and erotic visual stimulation. Compared to placebo, the 40-mg tablet showed a 45% difference in blood flow and also statistically significant differences for the subjective recordings of arousal, lubrication, engorgement, tingling and warmth. Zonagen is currently conducting an 80-patient placebo-controlled trial in Mexico evaluating orally administered phentolamine in an at-home setting. The drug's IND has recently been upgraded by the FDA to a partial clinical hold. A complete clinical hold was imposed last year after finding brown fat proliferations in a 2-year rodent carcinogenicity study (1).

With respect to the company's phentolamine mesilate products, the FDA recently notified Zonagen that a shorter mechanistic study of brown fat proliferation may be submitted in place of the additional 2-year rodent study formerly required by the agency. Successful completion of this study showing that effects predictive of brown fat proliferation will not be expected in humans will be required before the agency lifts its partial clinical hold on the drugs or considers their approvability. Clinical studies with Vasomax® for the treatment of erectile dysfunction and Vasofem® for the treatment of female sexual arousal disorder were previously limited by the FDA to a duration of less than 3 months and a dosing frequency not to exceed 3 per week. The U.K. Medicines Control Agency lifted its clinical hold on Vasomax® in August (2).

1. *Zonagen's product for FSD shows promise in clinical trial.* DailyDrugNews.com (Daily Essentials) Sept 18, 2000.

2. *Update on U.S. status of Zonagen's sexual dysfunction products.* DailyDrugNews.com (Daily Essentials) Sept 15, 2000.

Original monograph - Drugs Fut 1998, 23: 725.

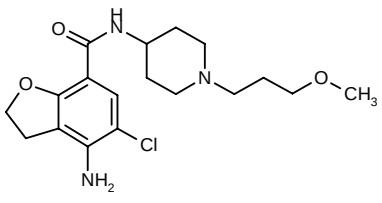
Additional Reference

Rubio, E.A. et al. *Evaluation of the effects of phentolamine mesylate on vaginal blood flow response in postmenopausal women with female sexual dysfunction.* Int J Gynecol Obstet 2000, 70(Suppl. 1): Abst FC4.23.08.

Prucalopride
Resolor®

Treatment of IBS
Treatment of Constipation

EN: 254527



$C_{18}H_{26}ClN_3O_3$ **Janssen**

The effects of prucalopride on GI and colonic transit times in patients with constipation have been evaluated. Forty patients meeting Rome I criteria for functional constipation, *i.e.*, 2 or less bowel movements per week and difficult evacuation with at least 25% of bowel movements, and without a rectal evacuation disorder were randomized to treatment with placebo or prucalopride at a daily dose of 2 or 4 mg for 7 days in a double-blind, parallel-group study. The most frequent adverse events on prucalopride were headache, diarrhea, flatulence, nausea and abdominal pain, and 2 patients withdrew due to adverse events. Prucalopride, particularly at the higher dose, accelerated overall gastric emptying and small bowel transit time compared to placebo, and it also accelerated overall colonic transit at the dose of 4 mg and significantly accelerated ascending colon emptying. These results thus confirm the prokinetic effects of prucalopride at all levels of the gastrointestinal tract and indicate that its effects are dose-dependent (1).

1. Bouras, E.P., Camilleri, M., Burton, D.D., Thomforde, G., McKinzie, S., Zinsmeister, A.R. *Prucalopride accelerates gastrointestinal and colonic transit in patients with constipation without a rectal evacuation disorder.* Gastroenterology 2001, 120(2): 354.

Original monograph - Drugs Fut 1999, 24: 729.

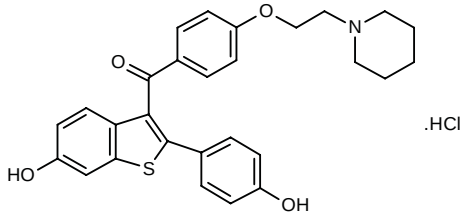
Additional References

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

Prins, N.H. et al. *M_3 cholinoceptor blockade inhibits dog colonic motility and antagonises 5-HT_4 receptor agonist-induced giant migrating contractions.* Dig Dis Week (May 20-23, Atlanta) 2001, Abst 4047.

Raloxifene Hydrochloride
Loxifen® *Treatment of Osteoporosis*
Optruma® *Prevention of Osteoporosis*
Evista® *Treatment of Postmenopausal Syndrome*

EN: 090328



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

Mounting evidence indicates that estrogen may have beneficial cognitive effects in postmenopausal women with Alzheimer's disease. The selective estrogen receptor modulator raloxifene hydrochloride is associated with

certain beneficial effects of estrogen without an increased risk of cancer. The results of a randomized, double-blind, placebo-controlled, parallel pilot trial in postmenopausal women with probable Alzheimer's disease according to NINCDS/ADRDA criteria have been reported, in which subjects were randomized to receive raloxifene at a dose of 120 mg/day or placebo for 3 months. Patients treated with raloxifene showed improvement in performance on a selective attention test and a visual-spatial memory task compared to placebo-treated patients, indicating that the agent may in fact exert beneficial effects on brain function in such patients (1).

The cognitive effects of raloxifene hydrochloride have been assessed in women receiving this agent as a treatment for osteoporosis. A total of 7478 postmenopausal women with osteoporosis and a mean age of 66 years were randomized to 60 or 120 mg/day of raloxifene or placebo for 3 years. Several different tests were administered to evaluate cognitive function at baseline, 6 months and 1, 2 and 3 years. Decline in cognitive function was defined in relative terms as a change in cognitive score from baseline to 3 years that was in the worst 10%. All three study groups showed slight improvements in cognitive function during the study. The risk of cognitive decline did not differ significantly among groups, although a trend towards less decline in verbal memory and attention was observed in the combined raloxifene groups as compared to placebo (2).

Lilly's landmark global clinical trial, Raloxifene Use for The Heart (RUTH), has reached full enrollment and has been expanded to include reduction in risk of invasive breast cancer as one of two primary objectives. RUTH was originally designed to determine whether raloxifene hydrochloride (Evista®) can reduce the risk of heart attack and heart-related death in postmenopausal women. However, based on encouraging data from previous clinical trials, reduction in risk of invasive breast cancer has been elevated from a secondary objective to a main objective of the trial. In addition, RUTH will also assess the effect of raloxifene hydrochloride on a variety of other important measures, including all-cause death, acute coronary syndromes treated in the hospital, coronary angioplasty, bypass surgery, surgical and nonsurgical treatment of peripheral artery disease, stroke, fractures and all-cause hospitalization. Outcomes in women taking the agent will be compared with those in women taking placebo. Enrollment in the trial included more than 10,000 women at nearly 200 sites in 26 countries. Early results may be available in approximately 5 years (3).

1. Baker, L.D., Cholerton, B.A., Gleason, C.E., Watson, S. *Raloxifene: Cognitive-enhancing effects for post-menopausal women with AD.* Neurobiol Aging 2000, 21(15): Abst 417.

2. Yaffe, K., Krueger, K., Sarkar, S. et al. *Cognitive function in postmenopausal women treated with raloxifene.* New Engl J Med 2001, 344(16): 1207.

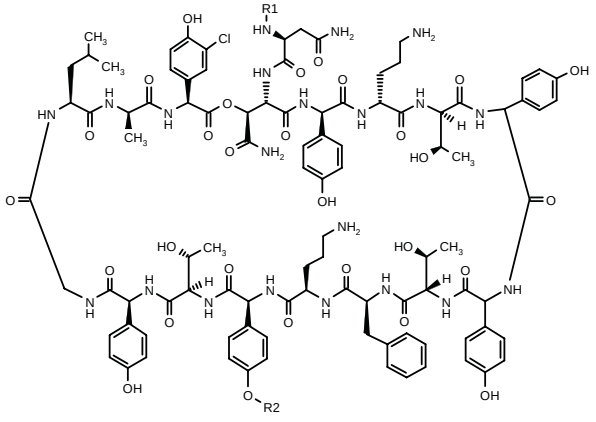
3. *RUTH trial expanded to include invasive breast cancer prevention as main objective.* DailyDrugNews.com (Daily Essentials) Dec 7, 2000.

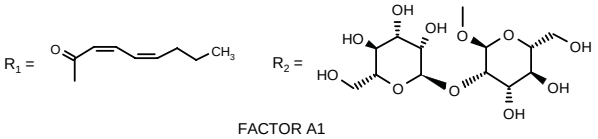
Original monograph - Drugs Fut 1984, 9: 516.

Ramoplanin

Glycopeptide Antibiotic

EN: 091144





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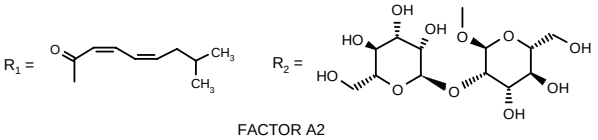

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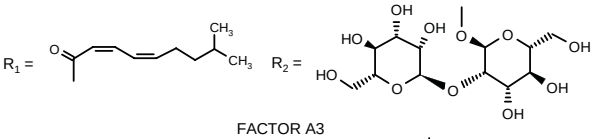

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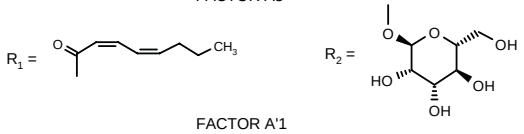
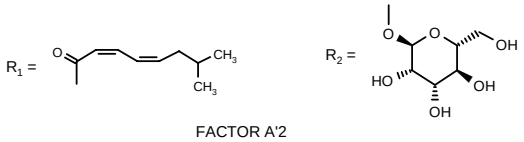
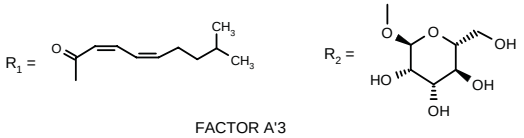


FACTOR A'1



FACTOR A'2



FACTOR A'3

Biosearch Italia; IntraBiotics

A quantification method for the quantitative analysis of the major component (A_2) of ramoplanin in human blood,

  CCC: 0377-8282/2001

urine and feces has been developed: A_2 and the internal standard (tetrahydrogenated A_2) were extracted from plasma or urine by automated solid phase extraction using a Zymark Rapid Trace workstation. The extracts were dried, reconstituted and injected on a HPLC/MS/MS with a C18 column and a PE Sciex mass spectrometer using a Turbolon spray interface. For fecal samples, 20% homogenate in water was diluted with mobile phase before injection. The standard calibration curve was linear in the range 10-1000 ng/ml for plasma and urine, and 2-200 μg/ml for fecal samples. Interassay precision and accuracy were 8.5% (1).

The steering committee for IntraBiotics' phase III trial of oral ramoplanin has advised the company that the rate of patient enrollment in the trial is not sufficient to complete the study by the end of 2001, the previously anticipated timeframe for reporting data from the trial. The clinical study is designed to demonstrate whether treatment with ramoplanin reduces the incidence of bloodstream infections due to vancomycin-resistant enterococci (VRE) in cancer patients known to carry VRE bacteria in their intestines. The study has enrolled 104 of the planned 950 patients at 20 of the targeted 51 sites in the U.S. The company expects the completion of the trial to be delayed a year or more (2).

Biosearch Italia and IntraBiotics have amended their collaborative agreement for the development and commercialization of ramoplanin in North America, for topical and oral pharmaceutical uses. Pursuant to the agreement, Biosearch Italia will provide funding to IntraBiotics in order to continue a phase III trial for a transition period ending on August 31, 2001, which may be extended by mutual agreement. At the end of the transition period, Biosearch will reacquire all rights to the drug in North America for all indications except topical applications of the drug, which will be retained by IntraBiotics unless certain clinical milestones are not met. In compensation for its clinical development expenses thus far for ramoplanin, IntraBiotics will receive a royalty on future net sales of ramoplanin in North America, if it is successfully developed.

If, at the end of the transition period, IntraBiotics can demonstrate that it can and wants to continue full development of ramoplanin, the companies may agree to maintain the license to IntraBiotics for the drug in North America in which case Biosearch will receive a refund of the development costs it has incurred, plus a premium of 25%. If IntraBiotics has not started clinical development for topical indications of ramoplanin by the end of March 2002, all relevant rights will also revert to Biosearch (3).

Ramoplanin has been granted orphan drug status by the European Commission for the prevention of invasive infections caused by VRE in patients carrying this microorganism and at risk of infection. These patients include cancer patients undergoing chemotherapy or patients having received transplants. In the U.S., ramoplanin has been granted fast track designation by the FDA (4).

1. Petersen, M.E. et al. *Development and validation of an LC/MS/MS method for the quantitation of ramoplanin, a glycolipodepsipeptide antibiotic, in human plasma, urine and feces.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 3547.

2. *Phase III trial of IntraBiotics' oral ramoplanin experiences delay.* DailyDrugNews.com (Daily Essentials) March 14, 2001.

3. *Biosearch Italia may reacquire rights to ramoplanin: IntraBiotics focuses on iseganan.* DailyDrugNews.com (Daily Essentials) May 31, 2001.

4. *Ramoplanin granted orphan drug status in Europe.* DailyDrugNews.com (Daily Essentials) July 13, 2001.

Original monograph - Drugs Fut 1990, 15: 689.

Recombinant Human Thrombopoietin MGDF®

Antithrombocythemic

EN: 213238

Genentech; ZymoGenetics; Amgen; Kirin Brewery; Pharmacia

An open-label phase I study conducted in 33 patients who had undergone high-dose chemotherapy followed by autologous bone marrow transplantation examined the safety and tolerability of recombinant human thrombopoietin (rhTPO; 0.3-4.8 μg/kg/day bolus injection every 3 days or 0.6 μg/kg/day). Treatment started the day after marrow infusion and was continued until platelets recovered to > 20,000/μl; patients also received G-CSF concomitantly. No serious adverse events or antibodies to rhTPO were observed. The median time to platelet recovery after transplantation was 19 days which was unaffected by rhTPO dose or dosing schedule (1).

1. Wolff, S.N., Herzig, R., Lynch, J. et al. *Recombinant human thrombopoietin (rhTPO) after autologous bone marrow transplantation: A phase I pharmacokinetic and pharmacodynamic study.* Bone Marrow Transplant 2001, 27(3): 261.

Original monograph - Drugs Fut 1996, 21: 711.

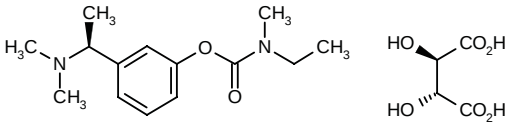
Additional Reference

Pawlowski, D. et al. *CD34+ subgroups and thrombopoietin (TPO) and flt-3 ligand (FL) serum levels in patients (pts) receiving high dose chemotherapy (HJDC) and peripheral blood stem cell (PBSC) transfusion: Impact on engraftment.* Ann Oncol 2000, 11(Suppl. 4): Abst 58P.

Rivastigmine Tartrate
Exelon®
Prometax®

Cognition Enhancer

EN: 145089



$C_{14}H_{22}N_2O_2.C_4H_6O_6$ **Novartis; Esteve**

Study results indicate that rivastigmine tartrate is associated with significant improvement in behavioral disturbances in patients with with Lewy bodies dementia. Based on the cholinergic deficit characterizing the disease, a double-blind, placebo-controlled, multicenter trial explored the use of rivastigmine in 120 patients with Lewy bodies dementia. The patients were given either placebo or rivastigmine up to 12 mg/day for 20 weeks, followed by a 3-week drug-free period. Approximately twice as many patients (63%) taking rivastigmine showed at least a 30% improvement in psychiatric symptoms (apathy, anxiety, delusions; assessed on the Neuropsychiatric Inventory) compared to those receiving placebo (30%). Significant improvement was also seen on objective measures of cognitive functioning, particularly as regards attention. During the 3-week drug-free follow-up period, the differences between rivastigmine and placebo tended to disappear. The treatment was considered acceptable as regards safety and tolerability, drug-related side effects being mostly cholinergic in nature, *i.e.*, nausea and vomiting, anorexia and somnolence. It was concluded that cholinesterase inhibitors such as rivastigmine may represent a more rational treatment option for Lewy bodies dementia than neuroleptics in terms of both efficacy and safety (1).

Novartis, in a letter to healthcare professionals through the FDA, has reported changes to the "Warnings, Precautions and Dosage and Administration" sections of the prescribing information for Exelon® (rivastigmine tartrate), which provide guidelines to reduce the risk of severe vomiting in patients who are reinitiating the drug following an interruption in therapy. According to the company, there is limited experience related to restarting rivastigmine after an interruption in therapy at doses higher than the recommended starting dose. However, to reduce the possibility of severe vomiting in patients who have interrupted therapy for longer than several days, treatment should be reinitiated at the lowest daily dose. After reinitiating therapy, patients should be titrated back to their maintenance dose as described in the "Dosage and Administration" section of the prescribing information. One case of severe vomiting with esophageal rupture has been reported following reinitiation of treatment at an inappropriate single dose of 4.5 mg following an 8-week interruption of treatment (2).

1. McKeith, I. et al. *Efficacy of rivastigmine in dementia with Lewy bodies: A randomised, double-blind, placebo-controlled international study.* Lancet 2000, 356(9247): 2031.

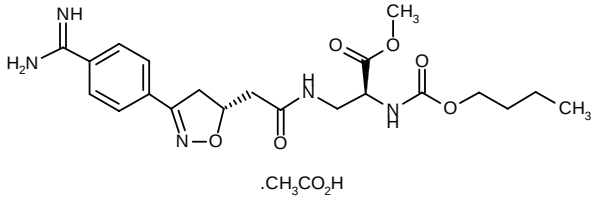
2. *Changes to Exelon product labeling announced by Novartis.* DailyDrugNews.com (Daily Essentials) Feb 5, 2001.

Original monograph - Drugs Fut 1994, 19: 656.

Roxifiban Acetate
Lumaxis®

Platelet Antiaggregatory
gpIIb/IIIa Antagonist

EN: 224676



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

A study has reported the metabolism of roxifiban. The agent was rapidly hydrolyzed to the zwitterion XV-459 *in vivo* and in *in vitro* experiments using rat, mouse and human liver slices and dog intestinal cores; XV-459 was further metabolized only to a small extent both *in vivo* and *in vitro*. Roxifiban had limited oral absorption following oral dosing of dogs with the radiolabeled parent compound and the majority of the radioactivity was excreted in feces. Following i.v. administration of [^{14}C]-roxifiban, radioactivity was detected in urine of the rat and bile and urine of dogs. XV-459 was metabolized extrahepatically by dog gut flora resulting in an isoxazoline ring-opened metabolite and hepatic metabolism *in vitro* resulted in hydroxylation of the isoxazoline ring. These hydroxylated metabolites were not found in urine or plasma of roxifiban-treated human subjects. Characterization of metabolites following administration of the agent to rats was described (1).

A study that examined the platelet gpIIb/IIIa binding profiles for the active form of roxifiban (XV-459) found that the drug binds to the same binding site(s) as other RGD mimetics as evidenced by the competitive inhibition of binding to human platelets. XV-459 competed with the FITC-labeled gpIIb/IIIa antagonist cyclic RDG peptidomimetic XL-086. XV-459 had the highest potency in inhibiting [^{3}H]-XV-459, [^{3}H]-DMP-728, [^{125}I]-echistatin and [^{125}I]-fibrinogen from binding to human platelets as compared to other RGD mimetics. The α-carbon next to the carboxy terminal was found to be an exosite for binding of members of the isoxazoline roxifiban series to human platelets. Thus, roxifiban displayed a distinct binding profile as compared to other mimetics exhibiting high-affinity binding to activated and resting platelets with a relatively slow dissociation rate (2).

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Researchers assessed the safety and efficacy of combined administration of the gpIIb/IIIa antagonist roxifiban and the low-molecular-weight heparin tinzaparin sodium in a guinea pig model of arterial thrombosis and in a guinea pig cuticle bleeding model. A prolongation of the occlusion time was observed in animals receiving i.v. roxifiban (0.8 mg/kg) or tinzaparin (150 IU/kg). Tinzaparin also caused a prolongation of clotting time, whereas roxifiban had no effect on this parameter. Tinzaparin led to a 30% peak inhibition of ADP-induced platelet aggregation, as compared to the 10% peak inhibition caused by roxifiban. In the thrombosis model, combined administration of roxifiban and tinzaparin caused an increase in occlusion time, and in the bleeding model, combined administration of the two drugs caused an additive effect in bleeding time. These data demonstrate that the combined administration of this gpIIb/IIIa antagonist and low-molecular-weight heparin offer an improved efficacy/safety ratio as compared to the agents used alone (3).

The pharmacokinetics and pharmacodynamics of roxifiban (0.5-1.25 mg/day for 7-10 days) were reported from a study conducted in 41 healthy volunteers. Moderate intersubject variability was observed for all parameters measured except V2/2 which was highly variable (54.8%). The mean EC_{50} value for inhibition of platelet aggregation in response to ADP (10 μM) was 12 ng/ml. Platelet counts influenced both EC_{50} and CL/F values due to platelet binding of roxifiban. Results indicated that a concentration of the active metabolite (XV-459) of 10-20 ng/ml would result in a 40-80% inhibition of ADP-induced platelet aggregation (4).

The dose-response effect of roxifiban was determined in patients with stable coronary artery disease. A total of 120 patients received either placebo or roxifiban (0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0 or 2.5 mg) daily for up to 30 days. At the 0.75 mg dose, platelet inhibition of over 40% was achieved and sustained throughout the study period. No significant major bleeding events were observed. Minor bleeding occurred in 4.7% of the placebo group, 14.8% of the group receiving roxifiban up to 1.5 mg daily and 31.1% of those receiving 2.0 or 2.5 mg. Thrombocytopenia developed in 1 patient and 1 patient experienced a platelet drop of more than 30% from baseline. Overall, roxifiban therapy dose-dependently sustained platelet aggregation inhibition and was not associated with major bleeding at therapeutically effective doses (5).

DuPont Pharmaceuticals has reported that the design of an ongoing phase III trial (the PURPOSE trial) of roxifiban will be changed from once-daily administration to the same total daily dose given twice a day. Twice-daily dosing will provide a level of gpIIb/IIIa receptor inhibition more similar to that achieved with intravenous compounds, which demonstrate a clear benefit to patients. The aim of the trial is to evaluate the long-term safety and efficacy of roxifiban plus aspirin in patients with moderate to severe peripheral arterial disease. While the protocol changes are being implemented, new patient enrollment will be deferred and all patients will continue their prescribed dose of aspirin and their current visit schedule. Patients who had been randomized to receive roxifiban will maintain their original assignment after the amendment is executed, with the double blinding of assignment maintained throughout. All patients will reconsent to participate in the study as part of the amendment process (6).

1. Mutlib, A.E., Diamond, S., Shockcor, J., Way, R., Nemeth, G., Gan, L., Christ, D.D. *Mass spectrometric and NMR characterization of metabolites of roxifiban, a potent and selective antagonist of the platelet glycoprotein IIb/IIIa receptor.* Xenobiotica 2000, 30(11): 1091.

2. Mousa, S.A., Bozarth, J.M., Naik, U.P., Slee, A. *Platelet GPIIb/IIIa binding characteristics of small molecule RGD mimetic: Distinct binding profile for roxifiban.* Br J Pharmacol 2001, 133(3): 331.

3. Racanelli, A.L., Schlingmann, K., Lauver, D.A., Reilly, T. *Combined administration of a low molecular weight heparin and a GPIIb/IIIa receptor antagonist results in increased efficacy safety ratio.* J Am Coll Cardiol 2001, 37(2, Suppl. A): 276A.

4. Fossler, M.J., Ebling, W.F., Kornhauser, D. et al. *Pharmacokinetics (PK) and pharmacodynamics (PD) of roxifiban (DMP754) in healthy male volunteers.* J Clin Pharmacol 2000, 40(9): Abst 59.

5. Gussak, I., Murphy, J., Daly, R., Wright, R.S., Cornwell, K., Williams, B., Wilcox, R.A., Kopecky, S.L. *The use of roxifiban, a novel oral IIb/IIIa platelet inhibitor, in patients with stable coronary artery disease.* Eur Heart J 2000, 21(Suppl.): Abst P3545.

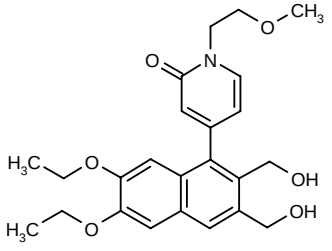
6. *DuPont Pharmaceuticals' roxifiban study amended.* DailyDrugNews.com (Daily Essentials) March 26, 2001.

Original monograph - Drugs Fut 1998, 23: 707.

T-440

Antiasthmatic
PDE4 Inhibitor

EN: 237395

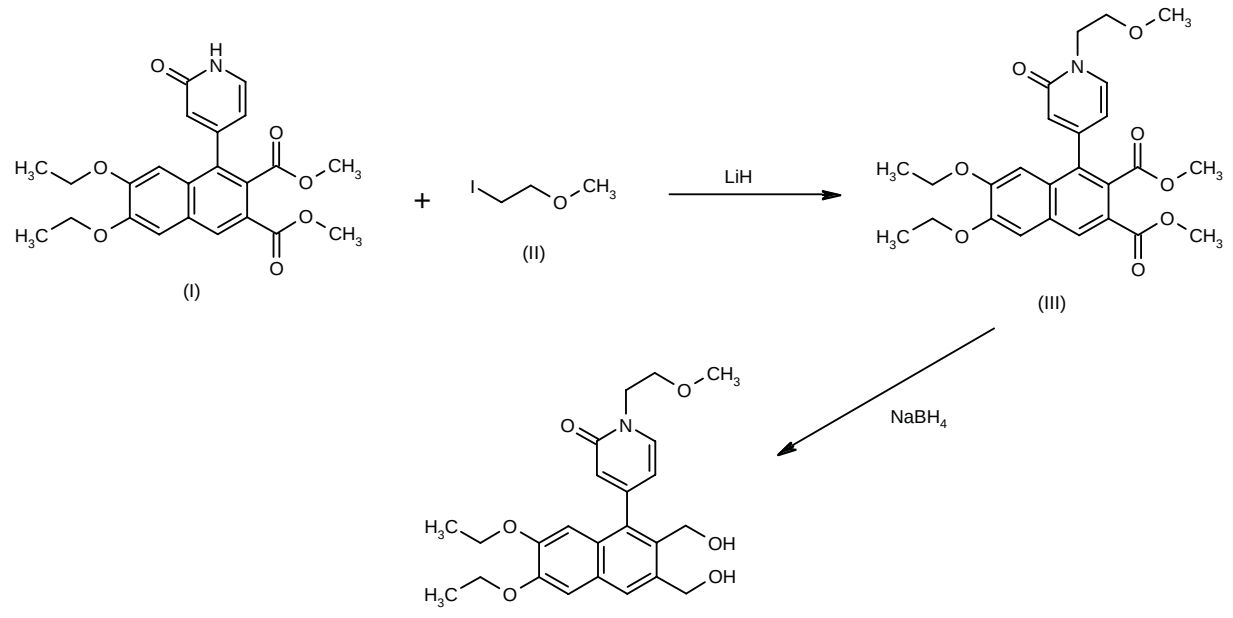


$C_{24}H_{29}NO_6$ **Tanabe Seiyaku**

An efficient *N*-alkylation process suitable for the large-scale synthesis of T-440 has been reported: Alkylation of the previously reported pyridone (I) with 2-methoxyethyl iodide (II) by means of LiH in hot DMF gives the *N*-alkylated pyridone (II) purified by crystallization. Finally, this compound is reduced with $NaBH_4$ and MeOH in refluxing THF (1) Scheme 3.

1. Sugahara, M., Moritani, Y., Kuroda, T., Kondo, K., Shimadzu, H., Ukita, T. *An efficient synthesis of the anti-asthmatic agent T-440: A selective N-alkylation of 2-pyridone.* Chem Pharm Bull 2000, 48(4): 589.

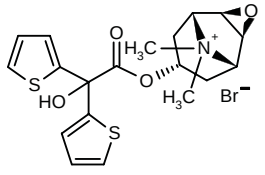
Scheme 3: Synthesis of T-440



Tiotropium Bromide
BA-679-BR
Spiriva®

Treatment of COPD
Bronchodilator

EN: 193167



$C_{19}H_{22}NO_4S_2.Br$ **Boehringer Ingelheim; Pfizer**

Tiotropium bromide has been evaluated in a multicenter, randomized, double-blind, parallel-group, placebo-controlled study enrolling 162 patients with chronic obstructive pulmonary disease (COPD), FEV_1 between 30% and 65% of the predicted normal (mean FEV_1 = 1.08 l) and FEV_1-to-FVC ratio of < 70%. Patients were randomized to once-daily treatment with tiotropium bromide (4.5, 9, 18 or 36 mcg as dry powder for inhalation) or placebo for 4 weeks. Spirometry was performed before dosing and once hourly for 6 h postdosing; efficacy was defined in terms of trough, peak and average FEV_1 responses. FEV_1 improved significantly and in a dose-related fashion, accompanied by significant improvements in FVC, within 1 h of tiotropium administration as compared to placebo. On day 29 of the study, all doses of the active drug produced significant increases in trough, peak and 6-h postdose average FEV_1 as compared to placebo; there was no significant difference between dose groups. During the 3-week period after drug discontinuation, peak expiratory flow rate (PEFR) gradually returned to baseline levels. The overall safety profile of the study drug was similar to that for placebo. A once-daily dose of 18 μg was recommended for use in long-term safety and efficacy studies (1).

A double-blind, randomized, parallel group study showed that tiotropium has a marked effect on aerosol distribution patterns in COPD. Controlled inhalation of 5 mcM inert ^{99m}Tc-radioaerosol particles was followed by radioaerosol imaging in 37 COPD patients. Patients were given either tiotropium (18 μg once daily) or placebo for 3 weeks at which time inhalation and imaging were repeated. The percentage of improvement produced by tiotropium compared to placebo was significant in 3 aerosol indices: FEV_1 (11.8 ± 12.5 *vs.* –6.1 ± 16.5), penetration index (29.3 ± 47.8 *vs.* –16.2 ± 37) and alveolar deposition at 48 h (24 ± 41 *vs.* –13.1 ± 28.7) (2).

Results from a double-blind, placebo-controlled study showed that tiotropium inhaled daily for 1 year influenced FEV_1 levels in 921 COPD patients. Common baseline mean FEV_1 for both treatment and control groups was 1.01 ± 0.42. Results from spirometry performed at baseline and again at the end of the 12-month study yielded FEV_1 values of 0.11 l (+10.9%) and -0.04 l (–4%), respectively. Day 8 predose FEV_1 values compared to last predose values were –0.01 l (–0.9%) and –0.04 l (–4%), respectively, and the 3-h postdose values on day 8 were –0.04 l (–3.2%) and –0.5 l (–4.9%) for tiotropium and placebo, respectively (3).

A 1-year, placebo-controlled study of tiotropium (10 μg once daily) in 846 patients with COPD found that long-term improvements can occur despite nonsignificant short-term improvements in FEV_1. Patients with acute improvements in FEV_1 (≥ 12% and 200 ml) following bronchodilator inhalation of tiotropium demonstrated lower BDI values and superior long-term improvements over the course of the year regardless of whether they received further tiotropium treatment or not. However, the long-term improvement in FEV_1 for groups who continued drug treatment was greater than for placebo, whether they had shown early acute improvements (11.7%) or not (11.2%) (4).

A randomized, placebo-controlled, double-blind trial in COPD patients showed that tiotropium once daily (AM or PM) improves sleep-related oxygen desaturation (SaO_2) during rapid eye movement (REM) sleep without impairing sleep quality. Sleep disturbance was observed in all patients (n = 94) with no significant differences between morning and evening groups. Patients in both treatment groups demonstrated higher morning spirometry values and fewer exacerbations (1/64) than placebo patients (3/30). Of the 49 patients with acceptable sleep data, both AM and PM groups showed significantly higher SaO_2 levels during REM sleep (+2.31 and +2.13%, respectively) as compared to placebo (5).

The efficacy of tiotropium *versus* placebo in both male and female COPD patients was shown in a 1-year, placebo-controlled study. The changes in baseline FEV_1, dyspnea and health status (assessed by SGRQ scores) as compared to last predose (12 months later) were significantly different and consistent across gender: FEV_1 (+11.8% *vs.* –3.7% for men; +10.7% *vs.* –4.8% for women); dyspnea (+1.2 *vs.* +0.5 for men; +1.3 *vs.* –0.1 for women); SGRQ (–2.9 *vs.* 0 for men; –4.3 *vs.* –1.3 for women) (6).

The effects of tiotropium on regional ventilatory responses in COPD patients were shown to be greater than those detectable by standard spirometry in a double-blind, randomized, parallel-group study. Patients received either tiotropium (18 μg) once daily for 3 weeks (n = 18) or placebo (n = 19). Quantitative analysis did not show a statistically significant overall enhancement from drug treatment, although patients with poor peak flow experienced significant improvement as compared to those with higher peak flow (7).

Results from a 1-year, placebo-controlled study in 921 COPD patients showed that PEFRs prior to an exacerbation were unchanged in patients administered tiotropium (18 μg once daily) and only moderate changes were observed in the placebo group. Although the PEFR results indicated that tiotropium improved lung function, the agent appears to have only limited use in detecting exacerbations (8).

A 1-year study in patients with COPD exacerbations has shown that tiotropium (18 μg once daily) was effective in increasing FEV_1. The frequencies of exacerbations (0, 1, 2, >2) at baseline for tiotropium and placebo were 1.06 and 1.05, 0.96 and 0.95, 0.90 and 0.88 and 0.88 and 0.88 l, respectively. Patients treated with tiotropium demonstrated mean changes in FEV_1 of +134, +115, +19 and +78 ml, as compared to –36, –32, –50 and –59 ml in placebo patients, in the respective frequency subgroups. Results indicate that the increasing frequency of exacerbations is associated with a higher rate of FEV_1 decline over time (9).

A series of double-blind, randomized studies in COPD patients showed that the impact of exacerbations on health related quality of life (HRQL) improved in tiotropium-treated patients as compared to controls. The frequency of exacerbations (0, 1, 2, >2) was associated with a decline in HRQL scores as measured on the St. George's Respiratory Questionnaire (SGRQ) for both tiotropium and control groups. In subgroups with no exacerbations, tiotropium patients showed a greater improvement in SGRQ than placebo patients (63.2% *vs.* 54.0%); tiotropium patients also showed greater benefit than placebo patients in the most frequent exacerbations groups (6.8% *vs.* 7.1%) (10).

Data from 1-year, double-blind, placebo-controlled studies in COPD patients on tiotropium 18 μg once daily showed that nocturnal symptoms (lower FEV_1, increased dyspnea and lower HRQL scores) were associated with disease severity and that tiotropium helped to improve symptoms as compared to placebo (11).

Results from a randomized, multicenter, double-blind, placebo-controlled, 1-year study conducted in 470 patients with stable COPD (mean baseline FEV_1 = 1.03 l) showed that tiotropium (18 μg) improved lung function, dyspnea and HRQL. Mean trough FEV_1 significantly improved with treatment on day 8 (0.12 *vs.* 0.0 l) and for the entire treatment period (0.11 *vs.* –0.05 l) as compared to placebo. At 1 year, mean trough FVC significantly improved in treated patients by 0.25 l as compared to a 0.03 l decrease in placebo. Treatment significantly improved dyspnea as reflected in the improved mean TDI focal score (0.86 *vs.* –0.29) and improved HRQL according to the SGRQ total scores (3.0 *vs.* –0.4 in placebo) (12).

According to scores from the SGRQ administered to a total of 535 patients with stable COPD in 2 multicenter, randomized, double-blind, parallel-group, ipratropium bromide-controlled, 1-year studies, treatment with tiotropium (18 μg once daily) significantly improved the quality of life as compared to ipratropium (40 μg q.i.d.). The mean FEV_1 for the tiotropium and ipratropium groups were 1.25 and 1.18 l, respectively. The improvements observed in the tiotropium group were significantly sustained over the study period, with greater differences observed between the two groups towards the end of the year (13).

Results from 2 multicenter, randomized, double-blind, parallel-group, 1-year studies in a total of 535 patients with stable COPD showed the superior efficacy of tiotropium (18 μg once daily) over ipratropium (20 μg 2 puffs q.i.d.). Trough and average FEV_1 and FVC were significantly superior and sustained in the tiotropium group as compared to ipratropium over the 1-year treatment period. Treatment was well tolerated (14).

A double-blind, placebo-controlled, randomized trial in 121 stable COPD patients showed that tiotropium (18 μg once daily at 9 AM or 9 PM) resulted in sustained 24-h bronchodilation and attenuated the decrease in FEV_1 observed at night, independently of the time of daily dosing. The mean FEV_1 in the tiotropium-treated group was significantly improved over 24 h in patients administered the agent in the morning (1.11 ± 0.03) or evening (1.06 ± 0.03) as compared to the placebo group (0.09 ± 0.03). The mean changes in FEV_1 from baseline from 9 AM to 3 AM were –2.8 and –1% in the groups receiving tiotropium in the AM or PM respectively, as compared to –12.8% for placebo (15).

Results from a 1-year, double-blind, randomized, placebo-controlled trial in 895 patients with COPD showed that tiotropium (18 μg once daily) decreased the need for rescue medication but had no effects on the pattern of use for symptom relief. Requirements for symptomatic relief were similar from 6 AM to midnight but lower from midnight to 6 AM in placebo and treatment groups and this pattern was not altered by severity of the disease (16).

A double-blind, randomized, multicenter trial has compared the long-term efficacy and safety of tiotropium at its apparently optimal dose of 18 μg and placebo in 470 patients with stable COPD. In this 13-week study, patients were given either treatment once daily using a dry powder inhaler and pulmonary function testing was conducted on day 1 and after 1, 7 and 13 weeks of therapy, including trough FEV_1 and FVC and average response over 3 h after dosing. Patients treated with tiotropium showed a significantly greater improvement in both trough and average FEV_1 and FVC responses compared to placebo, trough FEV_1 and FVC being about 12% greater than predose baseline values at 1 week, an effect maintained throughout the treatment period. Average postdose FEV_1 and FVC were 16-17% greater than baseline on day 1 and 19-20% greater on day 92 in tiotropium-treated COPD patients. Furthermore, significant improvement in daily morning and evening PEFR and reductions in supplemental albuterol use (about 30%) were also seen on tiotropium, and tiotropium was superior to placebo in terms of physician global evaluation and symptom (wheezing, shortness of breath) scores. Tiotropium treatment was associated with a low incidence of adverse events, the most common drug-related side effect being generally mild dry mouth (9.3% *vs.* 1.6% on placebo). In conclusion, tiotropium may represent a useful once-daily bronchodilator maintenance therapy for patients with COPD (17).

Boehringer Ingelheim and Pfizer have entered into a long-term worldwide agreement to jointly market tiotropium bromide (Spiriva®), a novel once-a-day inhaled treatment for COPD, including chronic bronchitis and emphysema. Boehringer Ingelheim has filed for marketing approval with regulatory authorities in Europe, where the drug could be available as early as mid-2002. An NDA for the product is expected to be filed with the FDA later this year. Discovered and developed by Boehringer Ingelheim, tiotropium bromide would be the first once-a-day inhaled bronchodilator treatment for COPD (18).

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Tolterodine Tartrate

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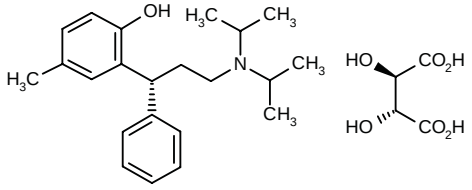

$C_{22}H_{31}NO.C_4H_6O_6$ **Pharmacia; Almirall Prodesfarma**

A U.K. study comparing two antimuscarinic treatments for overactive bladder in subjects aged 50 and over has shown that while tolterodine tartrate has similar efficacy to oxybutynin chloride, it is associated with significantly fewer adverse events. The multicenter, double-blind, randomized trial enrolled 379 patients with symptoms of urinary frequency with urgency and/or urge incontinence. Patients received either tolterodine 2 mg twice daily or oxybutynin initially at 2.5 mg twice daily, increased after 2 weeks to 5 mg twice daily. A significant difference from baseline was observed in both groups for all efficacy variables and there were no significant between-group differences. At least 1 adverse event was, however, reported by a significantly higher proportion of those taking oxybutynin (81%) compared with those on tolterodine (69%), and significantly more of those on oxybutynin (28% *vs.* 13%) had adverse events classified as severe in intensity. The authors concluded that the superior side effect profile of tolterodine makes it the pharmacotherapy of choice for the long-term management of overactive bladder symptoms (1).

A multicenter, randomized, double-blind, placebo-controlled trial was conducted to compare the efficacy and safety of extended-release (ER) and immediate-release (IR) formulations of tolterodine tartrate in 1529 patients (81% women) with overactive bladder. Patients with urinary frequency and urge incontinence received either extended-release tolterodine capsules 4 mg once daily (507 patients), immediate-release tolterodine capsules 2 mg twice daily (514 patients) or placebo (508 patients) for 12 weeks. As measured by micturition diary variables at the end of the treatment period, both tolterodine formulations significantly reduced the mean number of urge incontinence episodes per week. Median reduction compared to baseline was 71% for extended-release tolterodine, 60% for immediate-release tolterodine and 33% for placebo. Both formulations of tolterodine also improved micturition frequency, pad usage and mean volume voided per micturition as compared to placebo. Dry mouth occurred in 23% of patients receiving extended-release tolterodine, 30% of those receiving immediate-release tolterodine and 8% of those receiving placebo. Comparison of the two tolterodine formulations demonstrated that the extended-release formulation was 18% more effective and led to 23% less dry mouth of any severity than the immediate-release formulation. Moreover, only 1.8% of patients in the extended-release group experienced severe dry mouth (2).

The FDA has approved Pharmacia's Detrol® LA (tolterodine tartrate) extended-release capsules, a once-daily therapy for the treatment of overactive bladder with symptoms of urinary urge incontinence, urgency and frequency. Extended-release tolterodine was evaluated in the largest ever placebo-controlled clinical trial involving more than 1500 men and women at 167 sites worldwide. After 12 weeks of treatment, more patients taking once-daily extended-release tolterodine (4 mg daily) reported improvements in their bladder condition than patients treated with placebo, including statistically significant improvements for incontinence episodes and decreases in urinary frequency compared to placebo. Patient perception of urgency also showed improvement from baseline with treatment. In the trial, the drug was well tolerated. The first worldwide approval of the once-daily formulation was received earlier this month in Switzerland, where the product will be marketed as Detrusitol® SR (3).

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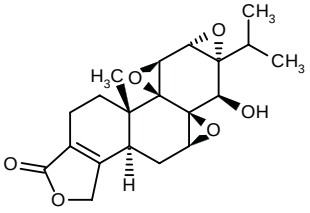
Triptolide

Immunosuppressant

EN: 090968



$C_{20}H_{24}O_6$

Kunming Inst. Botany (CN); Pharmagenesis

An *in vivo* study using a model of contact dermatitis (dorsal surfaces of the ears of BALB/c mice sensitized to oxazolone) showed that topical triptolide (0.1% during 2-day oxazolone challenge 2 weeks after sensitization) significantly decreased (> 50%) the number of cells infiltrating lymph nodes and completely suppressed the cutaneous inflammatory response. Further analysis revealed a decrease (27-35%) in CD69 expression on CD8 cells and Ia+ cells (18-52%) in lymph nodes (1).

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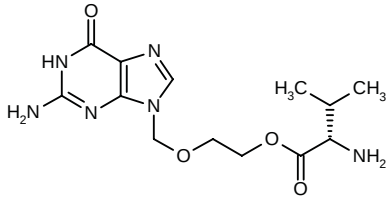

$C_{13}H_{20}N_6O_4$

GlaxoSmithKline; Theraplix; Aventis Pharma

The FDA has approved GlaxoSmithKline's sNDA for a shorter course of therapy for Valtrex® (valaciclovir hydrochloride) caplets for the treatment of recurrent episodes of genital herpes. The new dosing regimen consists of one 500-mg caplet twice daily for 3 days rather than the current 5 days (1).

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