Drugs of the Future 2001, 26(3): 283-327

CCC: 0377-8282/2001

Information Update

Volume 1-25, Number 3

Estimated developmental phase for this month's updated products:

Preclinical

TAK-779 (anti-HIV, chemokine CCR5 antagonist; Takeda)

Phase I

Calanolide A (anti-HIV, reverse transcriptase inhibitor; Sarawak MediChem, MediChem)
CL-387626 (anti-RSV; Wyeth-Ayerst)

Phase II

Alovudine (anti-HIV, reverse transcriptase inhibitor; Medivir)
Carzelesin (oncolytic; Pharmacia)
CS-834 (carbapenem; Sankyo)
GR-205171A (tachykinin NK_1 antagonist; GlaxoSmithKline)
MKC-242 (anxiolytic, antidepressant, 5-HT_{1A} agonist; Mitsubishi Chem.)

Phase III

Cefmatilen hydrochloride hydrate (cephalosporin; Shionogi)
β-Elemene (oncolytic; Dalian Jin Gang)
Fenretinide (oncolytic; Natl. Cancer Inst., R.W. Johnson)
RWJ-270201 (anti-influenza, neuraminidase inhibitor; BioCryst, R.W. Johnson, Ortho-McNeil)
Tirapazamine (oncolytic; Sanofi-Synthélabo, SRI)
Voriconazole (antifungal; Pfizer)

Preregistered

Dutasteride (treatment of BPH; GlaxoSmithKline, Yamanouchi)
Eletriptan (antimigraine; Pfizer)
Fidarestat (treatment of diabetic neuropathy, aldose reductase inhibitor; Sanwa, Kaken, Japan Energy)
Novel erythropoiesis stimulation protein (hematopoietic, antianemic, oncolytic; Amgen, Kirin Brewery, Genesis Pharma)
Omapatrilat (antihypertensive, treatment of heart failure, NEP/ACE inhibitor; Bristol-Myers Squibb)

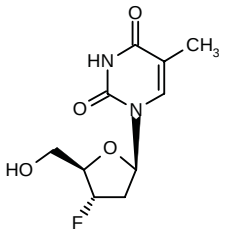
Launched/Year

Anagrelide hydrochloride (antithrombocythemic; Roberts, Yuhan, Inverni della Beffa)/1997
Azelastine hydrochloride (antihistaminic; Asta Medica, Eisai, Carter-Wallace, Bausch & Lomb)/1986
Ceftriaxone sodium (cephalosporin; Roche, Cubist)/1982
Cetrorelix acetate (treatment of female infertility, oncolytic, treatment of BPH; Asta Medica, Serono, Nippon Kayaku, Shionogi)/1999
Cyclosporin A (immunosuppressant; Novartis, SangStat, Abbott)/1983
Ciprofloxacin hydrochloride (quinolone antibacterial; Bayer, Alcon, DepoMed)/1986
Eflornithine hydrochloride (oncolytic, antitrypanosomal, treatment of hirsutism; Aventis Pharma, Bristol-Myers Squibb, Gillette)/1991
Gatifloxacin (quinolone antibacterial; Kyorin, Bristol-Myers Squibb, Schering-Plough, Grünenthal, Senju, Dainippon, Allergan)/1999
Irinotecan hydrochloride (oncolytic; Yakult Honsha, Pharmacia, Daiichi Pharm., Aventis Pharma, Almirall Prodesfarma)/1994
Lovastatin (hypolipidemic, HMG-CoA reductase inhibitor; Merck & Co.)/1987
Nifekalant hydrochloride (antiarrhythmic, potassium channel blocker; Mitsui Pharm.)/1999
Tazarotene (antipsoriatic, antiacne; Allergan, Pierre Fabre, 3M Pharm., Bioglan)/1996
Unoprostone isopropyl ester (antiglaucoma; Ueno, Novartis Ophthalmics, Fujisawa)/1994
Zafirlukast (antiallergy/antiasthmatic; AstraZeneca)/1996
Zoledronic acid monohydrate (treatment of hypercalcemia; Novartis)/2000
Zolmitriptan (antimigraine, 5-$HT_{1B/1D}$ agonist; AstraZeneca)/1997

Alovudine
MIV-310

Anti-HIV
Reverse Transcriptase Inhibitor

EN: 136724



$C_{10}H_{13}FN_2O_4$ **Medivir**

Medivir will proceed with the clinical evaluation of alovudine after a nearly 10-year hiatus in the development process. In 1991 and 1992, alovudine was tested in phase I and phase II trials in patients with AIDS. However, since multiresistant HIV had not yet appeared, the compound offered no advantages over zidovudine and development was discontinued. In recent laboratory tests of alovudine, multiresistant HIV in cell culture was as sensitive to alovudine as wild-type virus. Medivir will soon submit an application to perform phase II studies in patients with multiresistant HIV, and clinical trials are expected to begin this year (1).

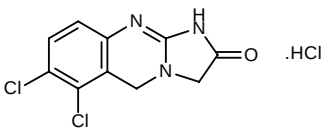
1. *Medivir reinitiates development of alovudine for AIDS.* DailyDrugNews.com (Daily Essentials) March 20, 2000.

Original monograph - Drugs Fut 1994, 19: 221.

Anagrelide Hydrochloride
Agrelin®
Agrylin®

Antithrombocythemic

EN: 090016



$C_{10}H_7Cl_2N_3O.HCl$ **Roberts; Yuhan; Inverni della Beffa**

The European Commission has granted orphan drug status to Shire's anagrelide hydrochloride for the treatment of essential thrombocythemia, covering the E.U. plus Norway and Iceland and conferring up to 10 years of market exclusivity for the product following approval. Orphan drug status was previously granted to anagrelide in the U.S., where it enjoys market exclusivity until 2004, and in Japan, where it will also have 10 years of exclusivity following marketing approval. Anagrelide is currently marketed in the U.S. and Canada under the name Agrylin®, and it is also available through distributors in South Korea, Switzerland, Israel, South Africa and Australia. The product is currently in phase III trials in Europe and in phase I in Japan (1).

1. *Anagrelide designated an orphan drug by European Commission.* DailyDrugNews.com (Daily Essentials) Jan 4, 2001.

Original monograph - Drugs Fut 1980, 5: 117.

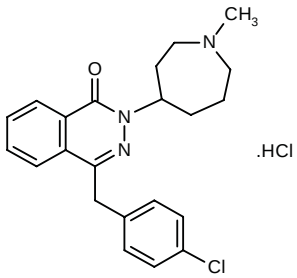
Additional Reference

Laguna, M.S. et al. *Effectiveness of anagrelide in the treatment of symptomatic patients with essential thrombocythemia.* Clin Appl Thromb-Hemost 2000, 6(3): 157.

Azelastine Hydrochloride
Optivar®
Astelin®

Antihistaminic

EN: 090028



$C_{22}H_{24}ClN_3O.HCl$ **Asta Medica; Eisai; Carter-Wallace; Bausch & Lomb**

Bausch & Lomb and Muro, an Asta Medica company, will copromote the new ocular antiallergy medicine Optivar® (azelastine hydrochloride ophthalmic solution 0.05%), which was recently approved by the FDA for the treatment of itchy eyes associated with allergic conjunctivitis in adults and children three years of age and older. The drug offers a 3-min onset of action and an 8-h duration of action with twice-daily dosing (1).

The FDA has approved Astelin® Nasal Spray, 137 μg, for the treatment of nonallergic vasomotor rhinitis in patients aged 5 years and older. This approval makes Astelin® Nasal Spray the only second-generation antihistamine indicated and proven effective for both seasonal allergic rhinitis and nonallergic vasomotor rhinitis. The product will be marketed by Wallace Laboratories, a division of Carter-Wallace (2).

1. *Bausch & Lomb and Muro to copromote Optivar.* DailyDrugNews.com (Daily Essentials) Aug 16, 2000.

2. *Astelin Nasal Spray approved in U.S. for treatment of nonallergic vasomotor rhinitis.* DailyDrugNews.com (Daily Essentials) Nov 10, 2000.

Original monograph - Drugs Fut 1980, 5: 123.

  CCC: 0377-8282/2001

Additional Reference

Beck, G. et al. *Effect of azelastine nasal spray on mediators of inflammation in patients with seasonal allergic rhinitis (SAR).* J Allergy Clin Immunol 2000, 105(1, Part 2): Abst 607.

Canonica, G.W. et al. *Multinational investigation of efficacy and safety of azelastine eye drops in the treatment of patients with perennial allergic conjunctivitis.* 17th Int Congr Allergol Clin Immunol (Oct 15-20, Sidney) 2000, Abst P-454.

Garay, R.P. et al. *Azelastine vs. placebo nasal spray in vasomotor rhinitis.* J Allergy Clin Immunol 2000, 105(1, Part 2): Abst 1146.

Golden, S. et al. *Effect of topical nasal azelastine on the symptoms of rhinitis, sleep, and daytime somnolence in perennial allergic rhinitis.* Ann Allergy Asthma Immunol 2000, 85(1): 53.

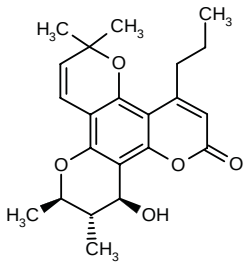
Nazarov, O.A. et al. *Azelastine eye drops in the treatment of patients suffering from perennial allergic conjunctivitis.* 17th Int Congr Allergol Clin Immunol (Oct 15-20, Sidney) 2000, Abst P-455.

Storms, W.W. et al. *Efficacy of Astelin (azelastine) nasal spray in patients with vasomotor rhinitis.* J Allergy Clin Immunol 2000, 105(1, Part 2): Abst 613.

Calanolide A
NSC-675451

Anti-HIV
Reverse Transcriptase Inhibitor

EN: 204331



$C_{22}H_{26}O_5$ **Sarawak MediChem; MediChem**

An enantioselective total synthesis of (+)-calanolide A has been reported: The silylation of 2'-hydroxy-4',6'-dimethoxybutyrophenone (I) with TIPS-Cl by means of benzylltriethylammonium chloride and NaOH in benzene gives the silyl ether (II), which is demethylated with BCl_3 in dichloromethane, yielding 2'-hydroxy-4'-methoxy-6'-(triisopropylsilyloxy)butyrophenone (III). The Wittig condensation of (III) with the phosphorane (IV) in *N,N*-diethylaniline with simultaneous cyclization affords the benzopyranone (V), which is submitted to a Friedel-Crafts condensation with the acyl chloride (VI) by means of $SnCl_4$ in dichloromethane to provide the 8-acylbenzopyranone (VII). The desilylation of (VII) by means of TBAF in THF/dichloromethane gives the 5-hydroxy compound (VIII) which is submitted to a propargylation with alcohol (IX) and DBU and then to a Claisen rearrangement with *N,N*-diethylaniline, affording the pyrano-benzopyran (X). Demethylation of (X) with MgI_2 in refluxing benzene gives the phenol (XI), which is submitted to a (–)-quinine-catalyzed asymmetric intramolecular oxo-Michael addition in chlorobenzene to yield an 80:20 mixture of the chiral *cis*- and *trans*-benzotripyrans (XII) (94% ee) and (XIII), respectively. Since the desired compound is the minor component (XIII), the preceding mixture is treated with MgI_2 in refluxing benzene to afford an equilibrated 50:50 mixture that is separated by chromatography, and the undesired *cis*-isomer can be recycled by repeating the MgI_2 treatment. The enantiomerically rich *trans*-isomer (XIII) is finally reduced with LiAlH-(O-*t*-Bu)$_3$ in THF (1). Scheme 1.

The pharmacokinetics and preliminary antiviral activity of (+)-calanolide A were evaluated in HIV-infected patients in 2 phase IB double-blind, placebo-controlled studies. Patients were randomized to receive (+)-calanolide A at doses of 200 or 400 mg b.i.d. (31 patients) or 600 mg b.i.d. (12 patients) for 14 days. C_{max} and AUC increased dose-proportionally, indicating linear pharmacokinetics. No drug accumulation was seen over the entire dosing period, although the agent did have a relatively long elimination half-life (15-20 h). The antiviral effect appeared to be dose-dependent, and there was a general trend of viral load reduction (mean reduction from baseline of –0.81 $\log_{10}$). The results suggested that further studies of (+)-calanolide A in combination with other antiretroviral agents should be carried out to evaluate the drug's long-term antiviral efficacy (2).

1. Tanaka, T. et al. *Enantioselective total synthesis of anti-HIV-1 active (+)-calanolide A through a quinine-catalyzed asymmetric intramolecular oxo-Michael addition.* Tetrahedron Lett 2000, 41(52): 10229.

2. Dutta, B. et al. *Comparative pharmacokinetics and preliminary antiviral effect of (+)-calanolide A, a novel NNRTI, when administered to HIV-1-infected subjects in US and Southeast Asia.* 13th Int AIDS Conf (July 9-14, Durban) 2000, Abst TuPeB3193.

Original monograph - Drugs Fut 1999, 24: 235.

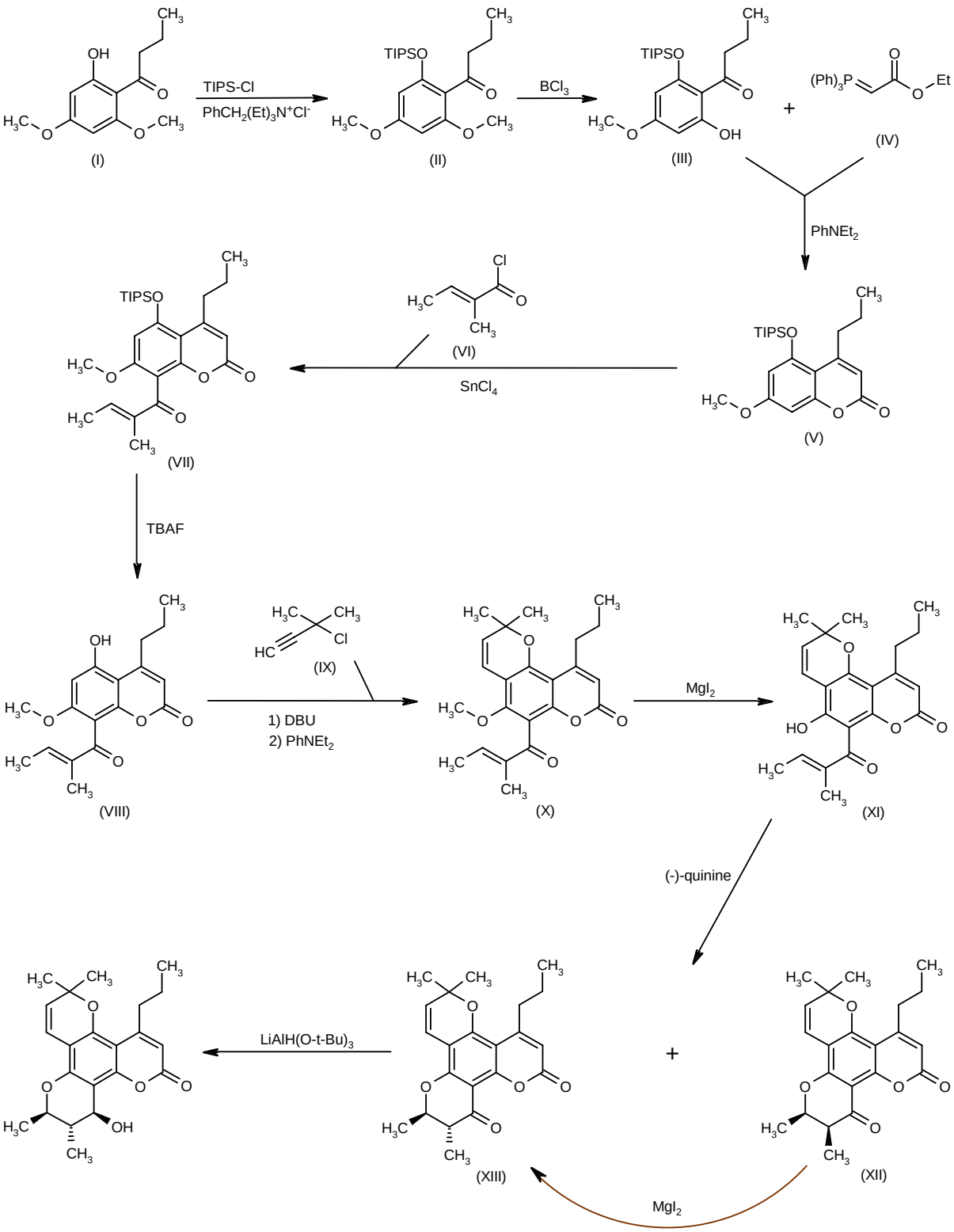
Additional References

Buckheit, R.W. Jr. et al. *Anti-HIV-1 activity of calanolides used in combination with other mechanistically diverse inhibitors of HIV-1 replication.* Antivir Chem Chemother 2000, 11(5): 321.

Xu, Z.Q. et al. *Quantification of (+)-calanolide A, a novel and naturally occurring anti-HIV agent, by high-performance liquid chromatography in plasma from rat, dog and human.* J Chromatogr B - Biomed Sci Appl 2000, 742(2): 267.

Zhang, J. et al. *Automated process research. An example of accelerated optimization of the Friedel-Crafts acylation reaction, a key step for the synthesis of anti-HIV (+)-calanolide A.* Org Process Res Dev 2000, 4(6): 577.

Scheme 1: Synthesis of Calanolide

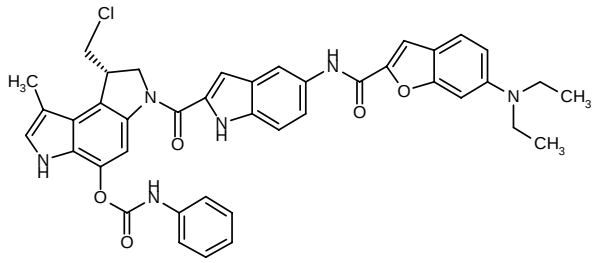


  CCC: 0377-8282/2001

Carzelesin

Oncolytic

EN: 149876



$C_{41}H_{37}ClN_6O_5$ **Pharmacia**

Carzelesin (150 μg/m^2 bolus infusion 4 times/week) was not effective as a second- or third-line chemotherapy for breast, ovarian, head and neck cancer and non-Hodgkin's lymphoma or as first-line therapy for colorectal cancer, gastric cancer or melanoma in a phase II study conducted in a total of 140 patients. The agent was generally well tolerated. The most common toxicity was myelotoxicity and grade 3 and 4 leukopenia, neutropenia, thrombocytopenia and anemia were observed in 18.6, 20.3, 16.2 and 8.7%, of the patients, respectively. Nonhematological toxicities were mild. One partial response was seen in a patient with melanoma (1).

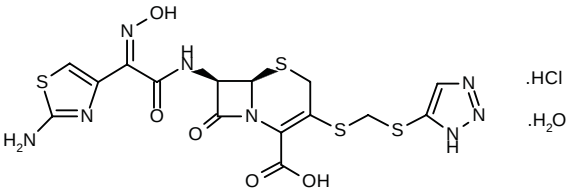
1. Pavlidis, N., Aamdal, S., Awada, A. et al. *Carzelesin phase II study in advanced breast, ovarian, colorectal, gastric, head and neck cancer, non-Hodgkin's lymphoma and malignant melanoma: A study of the EORTC early clinical studies group (ECSG).* Cancer Chemother Pharmacol 2000, 46(2): 167.

Original monograph - Drugs Fut 1996, 21: 245.

Cefmatilen Hydrochloride Hydrate S-1090

Cephalosporin

EN: 189332



$C_{15}H_{14}N_8O_5S_4.HCl.H_2O$ **Shionogi**

A double-blind study conducted in 242 adult outpatients with complicated urinary tract infections showed that S-1090 (100 mg b.i.d. after meals for 7 days) was superior to and as safe as cefdinir (100 mg t.i.d. after meals for 7 days). Patients with *Pseudomonas aeruginosa*, *Serratia marcescens* and *Stenotrophomonas maltophilia* infections were excluded. The overall clinical efficacy rate for S-1090 was significantly higher than that of cefdinir (94 *vs.* 81.7%). Drug-related adverse events (8.7 and 9.2%) and the incidence of abnormal laboratory findings (4.9 and 9.3%) were similar for both groups (1).

1. Matsumoto, T. et al. *A double-blind study to compare S-1090 and cefdinir for the treatment of complicated urinary tract infection.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst M-829.

Original monograph - Drugs Fut 1996, 21: 254.

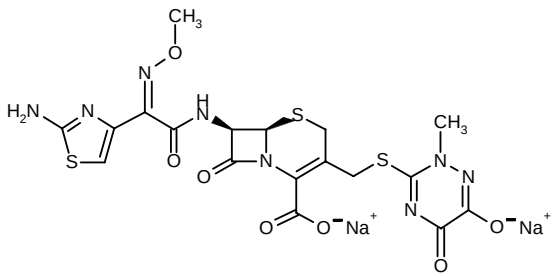
Additional Reference

Nishino, I., Fujimoto, H., Umeda, T. *Determination of a new oral cephalosporin, cefmatilen hydrochloride hydrate, and its seven metabolites in human and animal plasma and urine by coupled systems of ion-exchange and reversed-phase high-performance liquid chromatography.* J Chromatogr B - Biomed Sci Appl 2000, 749(1): 101.

Ceftriaxone Sodium Rocephin®

Cephalosporin

EN: 091136



$C_{18}H_{16}N_8Na_2O_7S_3$ **Roche; Cubist**

Cubist Pharmaceuticals has acquired worldwide rights to oral ceftriaxone from International Health Management Associates. This formulation is the first orally active version of Roche's intravenous antibiotic Rocephin®. The intravenous formulation of ceftriaxone has been successfully and safely prescribed for over 15 years in both adults and children. The drug is a third-generation cephalosporin and has demonstrated a broad spectrum of bactericidal activity against Gram-positive and Gram-negative bacteria. To date, ceftriaxone has been primarily used to treat hospital inpatients due to the lack of an oral version. If successfully developed, Cubist believes that an oral formulation could greatly expand the potential of ceftriaxone through community-based prescribing. In addition, the company believes oral ceftriaxone could also be used for the continuation of parenteral antibiotic therapy. The oral formulation of ceftriaxone is in preclinical development and is expected to begin clinical testing in 2002 (1, 2).

1. *Cubist acquires rights to oral ceftriaxone.* DailyDrugNews.com (Daily Essentials) Dec 4, 2000.

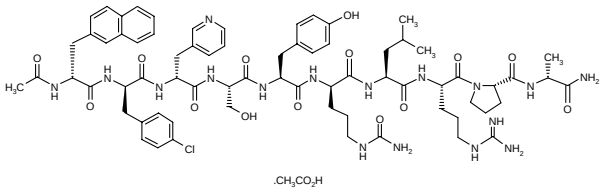
2. *Cubist reports results for fourth quarter and full year.* DailyDrugNews.com (Daily Essentials) Feb 20, 2001.

Original monograph - Drugs Fut 1981, 6: 132.

Cetrorelix Acetate
Cetrotide®

Treatment of Female Infertility
Oncolytic
Treatment of BPH

EN: 148387



$C_{70}H_{92}ClN_{17}O_{14}.C_2H_4O_2$

Asta Medica; Serono; Nippon Kayaku; Shionogi

Serono has acquired exclusive rights from Asta Medica to market, distribute and sell Cetrotide® (cetrorelix acetate for injection) in the U.S. and worldwide, with the exception of Japan, for the indication of controlled ovarian stimulation prior to assisted reproductive technologies. Serono expects to launch Cetrotide® in the U.S. in 2001 (1).

1. *Serono acquires exclusive rights to Cetrotide; U.S. launch planned.* DailyDrugNews.com (Daily Essentials) Sept 5, 2000.

Original monograph - Drugs Fut 1994, 19: 228.

Additional References

Albano, C. et al. *Ovarian stimulation with HMG: Results of a prospective randomized phase III European study comparing the luteinizing hormone-releasing hormone (LHRH)-antagonist cetrorelix and the LHRH-agonist buserelin.* Hum Reprod 2000, 15(3): 526.

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Gonzalez-Barcena, D. et al. *Long-term benefits of therapy with LH-RH antagonist cetrorelix in men with benign prostatic hyperplasia.* 82nd Annu Meet Endocr Soc (June 21-24, Toronto) 2000, Abst 2358.

Kovacs, M. et al. *Luteinizing hormone-releasing hormone (LH-RH) antagonist cetrorelix down-regulates the mRNA expression of pituitary receptors for LH-RH by counteracting the stimulatory effect of endogenous LH-RH.* Proc Natl Acad Sci USA 2001, 98(4): 1829.

Ludwig, M. et al. *Health condition of 227 children born after controlled ovarian stimulation for IVF using the LHRH antagonist cetrorelix (Cetrotide®).* Fertil Steril 2000, 74(3, Suppl. 1): Abst P-236.

Ludwig, M. et al. *No significant leukocytosis under controlled ovarian stimulation using the LHRH antagonist cetrorelix and recFSH.* Eur J Obstet Gynecol Reprod Biol 2000, 89(2): 177.

Nagaraja, N.V. et al. *Pharmacokinetic and pharmacodynamic modeling of cetrorelix, an LH-RH antagonist, after subcutaneous administration in healthy premenopausal women.* Clin Pharmacol Ther 2000, 68(6): 617.

Nagaraja, N.V. et al. *Pharmacokinetic/pharmacodynamic (PK/PD) modeling of LH suppression and LH surge delay by cetrorelix after single and multiple doses in healthy premenopausal women.* Clin Pharmacol Ther 2001, 69(2): Abst PII-99.

Nikolettos, N. et al. *Comparison of cryopreservation outcome with human pronuclear stage oocytes obtained by the GnRH antagonist, cetrorelix, and GnRH agonists.* Eur J Obstet Gynecol Reprod Biol 2000, 93(1): 91.

Olivennes, F. et al. *Prospective, randomized, controlled study of in vitro fertilization-embryo transfer with a single dose of a luteinizing hormone-releasing hormone (LH-RH) antagonist (cetrorelix) or a depot formula of an LH-RH agonist (triptorelin).* Fertil Steril 2000, 73(2): 314.

Pechstein, B. et al. *Pharmacokinetic-pharmacodynamic modeling of testosterone and luteinizing hormone suppression by cetrorelix in healthy volunteers.* J Clin Pharmacol 2000, 40(3): 266.

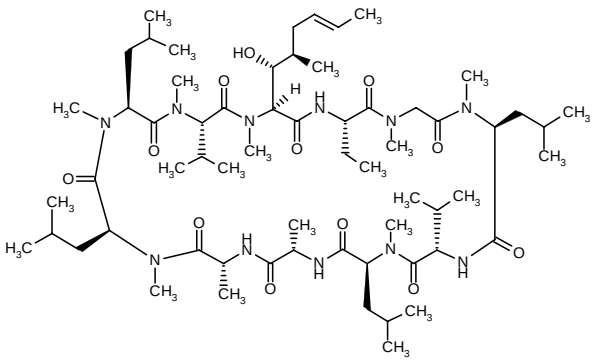
Reissmann, T. et al. *The LHRH antagonist Cetrorelix: A review.* Hum Reprod Update 2000, 6(4): 322.

Riethmüller-Winzen, H. et al. *Safety aspects of the LHRH antagonist cetrorelix (Cetrotide(R)).* Int J Gynecol Obstet 2000, 70(Suppl. 1): Abst P1.06.19.

Cyclosporin A
SangCya®
Gengraf®
Neoral®

Immunosuppressant

EN: 091277



$C_{62}H_{111}N_{11}O_{12}$

Novartis; **SangStat; Abbott**

Why the calcineurin inhibitor ciclosporin so frequently causes hypertension in organ transplant recipients was the subject of a recent study at the University of Texas Southwestern Medical Center. In mice administered ciclosporin, the drug induced high blood pressure by stimulating sensory nerve endings in the kidney which contain synapsin-positive microvesicles. Synapsins are synaptic vesicle phosphoproteins which regulate neurotransmitter

release and are also found on microvesicles in sensory nerve endings in peripheral tissues. In mice lacking synapsin I and II, ciclosporin did not stimulate sensory nerve endings and blood pressure did not increase as in the control mice. Future therapies targeting synapsins might therefore reduce the incidence of ciclosporin-induced secondary hypertension (1).

Data from 2 new studies demonstrate that a change in the procedures used for monitoring blood levels of ciclosporin (Neoral®) significantly reduces the incidence of acute rejection. Results show that measuring ciclosporin blood levels 2 h after dosing (C2), in contrast to the conventional trough monitoring (C0), improved clinical outcomes without increasing the incidence of adverse events. In one study involving 307 liver transplant recipients, acute organ rejections were reduced by 25% in the C2 monitored group, and in a second study involving 204 kidney transplant recipients, the reduction in moderate and severe acute rejections was 34% (2).

A randomized, double-blind, placebo-controlled, 2-way crossover study in 25 transplant recipients on stable ciclosporin before entry and with stable renal function showed that ciclosporin exposure significantly increased with concomitant voriconazole administration (200 mg b.i.d. for 8 days). Thus, plasma ciclosporin levels should be monitored and doses adjusted with concomitant therapy. The adjusted geometric mean AUC_{τ} values for ciclosporin alone and coadministration with voriconazole were 2733 and 4637 ng·h/ml, respectively. The C_{max} and t_{max} of ciclosporin were not significantly affected by voriconazole coadministration (3).

Preliminary data from a randomized, open-label, multicenter, 6-month trial of the new ciclosporin formulation Gengraf®, developed by Abbott as a Neoral® bioequivalent product, in 101 *de novo* renal transplant subjects have been reported. The subjects were randomized to receive either Gengraf® capsules b.i.d. or Neoral® capsules b.i.d. as part of triple immunosuppressive therapy including mycophenolate mofetil and prednisone. Data from 24 subjects, 12 in each group, who have completed the 6-month trial were available. The results suggested no differences in trough levels of ciclosporin, dose adjustments, acute rejection episodes or safety between the two groups (4).

Gengraf® was approved by the FDA for the prevention of organ rejection in kidney, liver and heart transplants. The FDA also granted an AB rating, meaning that the product is considered therapeutically equivalent to or interchangeable with the reference drug Neoral® (5).

SangStat has announced the approval of SangCya®, its ciclosporin oral solution (100 mg/ml) in Germany under the European Community's mutual recognition procedure, with the U.K. serving as the reference member state (6).

SangStat has obtained an exclusive license to technology for a novel ciclosporin capsule formulation. The company expects to use this technology to develop and market in Europe a ciclosporin capsule that is significantly smaller than any other ciclosporin capsule currently on the market. SangStat has already conducted pilot studies in healthy volunteers demonstrating the new capsule's bioequivalence to Neoral® ciclosporin capsules when taken with water. The other filing requirements, including stability testing, are under way (7).

1. Zhang, W. et al. *Cyclosporine A-induced hypertension involves synapsin in renal sensory nerve endigs.* Proc Natl Acad Sci USA 2000, 97(17): 9765.

2. *Novartis updates transplantation pipeline at ongoing congress.* DailyDrugNews.com (Daily Essentials) Aug 30, 2000.

3. Ghahramani, P., Romero, A.J., Lant, A.F., Allen, M.J. *The effect of voriconazole on the pharmacokinetics of cyclosporin.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst A-845.

4. Scandling, J., Rajagopalan, P.R., Magee, J., Conti, D., Mendez, R., Bronson, D., Awni, W., Nabulsi, A., Hoffman, R. *Clinical experience with Gengraf™ (Abbott cyclosporine) in de novo renal transplant recipients.* Transplant 2000 (May 13-17, Chicago) 2000, Abst 184.

5. *Clinical data support equivalence of Gengraf and Neoral: Gengraf approved by FDA.* DailyDrugNews.com (Daily Essentials) May 19, 2000.

6. *SangCya approved in Germany.* DailyDrugNews.com (Daily Essentials) April 12, 2000.

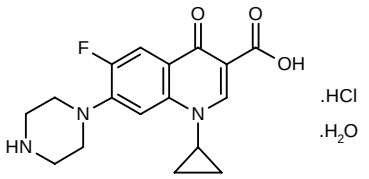
7. *SangStat obtains technology to develop smaller ciclosporin capsule.* DailyDrugNews.com (Daily Essentials) Oct 16, 2000.

Original monograph - Drugs Fut 1982, 7: 591.

Ciprofloxacin Hydrochloride
Cipro®
Ciprofloxacin GR®

Quinolone Antibacterial

EN: 090006



$C_{17}H_{18}FN_3O_3.HCl.H_2O$ **Bayer; Alcon; DepoMed**

The FDA has approved the use of ciprofloxacin (Cipro®) to reduce the incidence or progression of inhalational anthrax following exposure to aerosolized *Bacillus anthracis*, the bacterium that causes anthrax. This indication was granted under provisions of accelerated approval, based on the use of a surrogate endpoint of blood levels achieved in humans and the results of *in vitro* and animal testing. The use of the surrogate endpoint was further supported by ciprofloxacin serum concentrations in the rhesus monkey model of postexposure inhalational anthrax, which demonstrated a significantly improved survival rate for animals that received ciprofloxacin compared to animals that did not receive an

antimicrobial following exposure to aerosolized *B. anthracis*. The serum levels measured in monkeys that survived exposure to anthrax bacteria can be achieved or exceeded in humans who received the recommended doses. The recommended adult dose of ciprofloxacin for postexposure inhalational anthrax is 500 mg given orally twice a day. The recommended pediatric dose for this indication is 15 mg/kg given orally twice a day; the pediatric intravenous dose is 10 mg/kg twice a day. The most common adverse drug reactions observed include nausea, vomiting, diarrhea, abdominal pain, rash, headache and restlessness. In patients who have received ciprofloxacin for 60 days or longer, no new or unexpected adverse reactions were identified compared to patients receiving shorter approved regimens. In addition, studies are currently under way to evaluate long-term safety, including effects on cartilage, in pediatric patients (1).

DepoMed reported successful results from a phase I trial comparing Ciprofloxacin GR®, the company's Gastric Retention (GR) dosage form of ciprofloxacin hydrochloride, with Bayer's immediate-release, twice-daily ciprofloxacin hydrochloride formulation Cipro®. The single-dose trial involving 15 volunteers demonstrated that Ciprofloxacin GR® had comparable bioavailability and a significantly extended blood plasma concentration profile compared with Cipro®. DepoMed's Gastric Retention system is designed to improve the absorption and bioavailability of oral drugs through controlled release high in the gastrointestinal tract. DepoMed intends to file an IND for Ciprofloxacin GR® later this year. The study for which the company will seek approval is a multiple-dose trial for an undisclosed indication (2).

1. *FDA approves ciprofloxacin for treatment of postexposure inhalational anthrax.* DailyDrugNews.com (Daily Essentials) Sept 7, 2000.

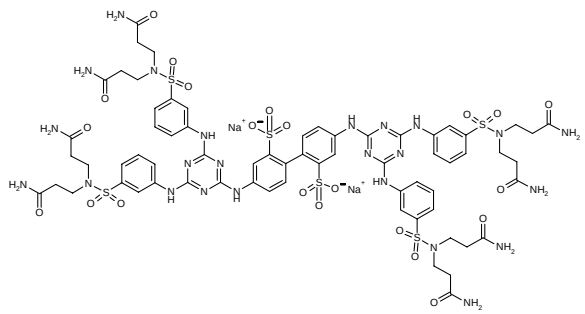
2. *Results with extended-release ciprofloxacin product promising, reports DepoMed.* DailyDrugNews.com (Daily Essentials) Jan 25, 2001.

Original monograph - Drugs Fut 1984, 9: 179.

CL-387626
RFI-641

Anti-RSV

EN: 266287



$C_{66}H_{76}N_{24}Na_2O_{22}S_6$

Wyeth-Ayerst

RFI-641 is a novel inhibitor of respiratory syncytial virus (RSV) fusion with potent *in vitro* activity against laboratory strains and clinical isolates of the virus, inhibiting 90% of clinical isolates at a concentration of 0.03 μg/ml. The compound also proved effective in yield reduction assays, with IC_{90} values for RSV A and B strains of 0.22 μg/ml and 0.12 μg/ml, respectively. In contrast, cytotoxicity was observed only at concentrations at least 100-fold higher. Moreover, only a modest reduction in antiviral activity was seen with up to 100-fold increases in multiples of infection. RFI-641 is a promising new compound for the treatment of RSV upper and lower respiratory tract infections presently in clinical trials (1).

The mechanism of action of RFI-641 against RSV was described in a recent report. The agent targets the viral fusion event without affecting attachment as seen in studies incubating wild-type RSV and mutant RSV cp52 which lacks attachment and small hydrophobic envelope proteins. The fusion glycoprotein (F protein) may therefore be the site of action. Incubation of RSV with RFI-641 *in vitro* did not inactivate the virus. However, syncytia formation was blocked with RFI-461 treatment in cells with established RSV infection. Activity was observed for the agent against both A and B groups of RSV as well as laboratory adapted strains, suggesting that the target site of the agent is highly conserved. Resistant viruses isolated using RFI-641 analogs displayed IC_{50} values 10 times greater than those obtained for wild-type viruses and showed a single point mutation in the F protein (2).

RFI-641 has been tested *in vivo* in animal models of RSV infection. Administered nasally 2 h before infection, RFI-641 at doses of 0.04-2.0 mg/kg produced reductions in lung titers in mice, and doses of 0.2-10 mg/kg were effective in cotton rats. In African green monkeys, intranasal pretreatment at doses of 0.24-6 mg reduced nasal and throat viral titers, as well as titers in bronchoalveolar lavage. RFI-641 also exhibited therapeutic efficacy when given intranasally once daily starting 24 h after infection, reducing viral loads in nasal and throat tissues at the dose of 12 mg. The new fusion inhibitor thus appears to have utility for both the prophylaxis and therapy of RSV infection (3).

1. Huntley, C.C., Feld, B., Hu, W., Quartuccio, S., Grimberg, D., O'Hara, B., O'Connell, J., Gazumyan, A. *In vitro activity of RFI-641, a potent inhibitor of RSV.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst H-187.

2. Gazumyan, A. et al. *The mechanism of action of RFI-641, a novel respiratory syncytial virus (RSV) fusion inhibitor.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst H-1159.

3. Weiss, W.J., Wyde, P., Prince, G. *Efficacy of RFI-641; A novel fusion inhibitor, in animal models of RSV infection.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst H-186.

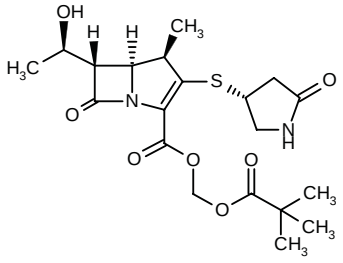
Original monograph - Drugs Fut 2000, 25: 287.

  CCC: 0377-8282/2001

CS-834

Carbapenem

EN: 233813



$C_{20}H_{28}N_2O_7S$ **Sankyo**

The *in vitro* activity of R-95867, the active metabolite of CS-834, was compared with those of other oral agents against a variety of anaerobic bacteria. R-96867 was 2- to 4-fold less active than DU-6859a but more active than cefditoren, clindamycin and ampicillin/sulbactam against strains of peptostreptococci, clostridia and fusobacteria, as well as *Bacteroides fragilis* and *Porphyromonas* spp. (1).

CS-834 has been tested for its absorption kinetics following oral (intragastric) administration of [^{14}C]-labeled compound to rats. The results showed that the drug rapidly passed, mainly in unchanged form, from the stomach to the small intestine, where it was partially metabolized to R-95867 and other unidentified compounds. On the other hand, the compound reached the systemic circulation in the form of R-95867 (2).

1. Kato, N., Tanaka, K., Kato, H., Watanabe, K. *In vitro activity of R-95867, the active metabolite of a new oral carbapenem, CS-834, against anaerobic bacteria.* J Antimicrob Chemother 2000, 45(3): 357.

2. Shibayama, T. et al. *Absorption kinetics of CS-834, an orally ester type carbapenems antibiotic in rats.* Xenobiotic Metab Dispos 2000, 15(Suppl.): Abst 11PD-38.

Original monograph - Drugs Fut 1998, 23: 261.

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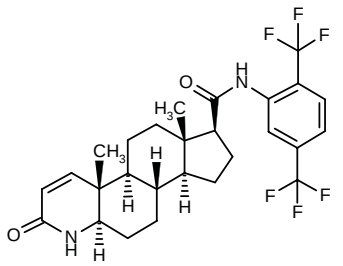
Liu, C.-X. et al. *Impact of a new quinolone, DU-6859a, and two oral carbapenems, CS-834 and L-084, on the rat and mouse caecal microflora.* J Antimicrob Chemother 2000, 46(5): 823.

Dutasteride

Treatment of BPH

EN: 222406



$C_{27}H_{30}F_6N_2O_2$ **GlaxoSmithKline; Yamanouchi**

In an open-label, crossover study, 38 healthy male subjects were given tamsulosin (0.4 mg/day) or terazosin (titrated up to 10 mg/day) for 14 days, followed by 7-day washout and subsequent treatment with dutasteride (0.5 mg/day following a 40-mg loading dose) for 21 days and then dutasteride plus tamoxifen or terazosin for another 14 days. The results showed no significant drug interactions as regards pharmacokinetics. In addition, the incidence of adverse events of headache, dizziness, musculoskeletal pain, orthostasis, nausea and emesis was lower when dutasteride was coadministered with tamoxifen (18% *vs.* 29%) or terazosin (35% *vs.* 67%) compared to either drug alone (1).

1. Clark, R.V., Haberer, L.J., Horton, J.R., Foster, C.D. *No evidence of drug interactions between GI198745, a novel dual 5α reductase inhibitor, and α_1 adrenergic antagonist.* J Urol 2000, 163(4, Suppl.): Abst 975.

Original monograph - Drugs Fut 1999, 24: 246.

Eflornithine Hydrochloride

Oncolytic

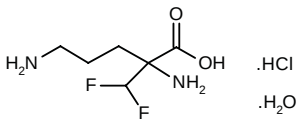
Vaniqa®

Antitrypanosomal

Ornidyl®

Treatment of Hirsutism

EN: 090024



$C_6H_{12}F_2N_2O_2.HCl.H_2O$ **Aventis Pharma; Bristol-Myers Squibb; Gillette**

A study using the hamster organ flank model examined the pharmacology of eflornithine monohydrate (10% in a hydro-alcoholic or cream vehicle). Flank organ follicle levels of ornithine decarboxylase were decreased 2- to 3-fold between 1 and 24 h of treatment with the hydro-alcoholic vehicle and putrescine levels were also reduced 2- and 3-fold within 6 and 24 h, respectively. In addition, 3 weeks of treatment with eflornithine (1-15%) in the hydro-alcoholic or cream vehicle caused dose- and vehicle-dependent hair mass inhibition of up to 85%. Follicle shrinkage and the depth of follicle penetration into the skin were also decreased with treatment. No contralateral hair mass inhibition was seen and the effects of the agent were partially reversed after discontinuation. Animals treated with the 10 or 15% formulation showed responses to treatment within 7-8 days with greater effects seen over an 18-day period; 30-40% and 65-80% decreases in hair length were observed by days 7 and 14, respectively, following treatment with the 10% formulation (1).

The efficacy and safety of eflornithine (5, 10 or 15%) as a treatment of unwanted facial hair growth in women was examined in a clinical trial. The 15% formulation resulted in significant reductions in hair growth as

compared to placebo; average hair length was decreased 47% as compared to 8% with placebo. Ferriman-Gallwey scores changed by at least –1 to –1.5 in 52% of the subjects treated with the 15% formulation as compared to 7% in the placebo group. Efficacy was observed in some subjects at 8 weeks while the majority showed efficacy after 24 weeks of treatment. Reductions in hair length of 26 and 28% were observed with the 5 and 10% formulations, respectively, although these changes were not significantly different from placebo (2).

Two randomized trials conducted in a total of 596 women with excessive, unwanted facial hair assessed the quality of life with eflornithine treatment (15% cream). The trials used a Subject Self-Assessment Questionnaire (SSAQ) which included 6 questions, the Physician Global assessment and quantitative hair assessment. A consistent response was observed, as well as a strong agreement between the parameters examined (3).

A cream formulation of eflornithine hydrochloride was launched in mid-September in the U.S. as Vaniqa™ by Bristol-Myers Squibb and Gillette for the reduction of unwanted facial hair in women. Based on studies with the oral formulation, topical eflornithine is postulated to irreversibly inhibit ornithine decarboxylase activity in the skin, resulting in inhibition of cell division and synthetic functions and the rate of hair growth. The product is available as a cream containing 13.9% anhydrous eflornithine hydrochloride as the monohydrate (150 mg/g) (4).

During 2001, Ilex plans to complete accrual to the eflornithine phase III trial in superficial bladder cancer and to initiate a phase III trial of eflornithine in combination with celecoxib in patients with familial adenomatous polyposis (5).

1. Shander, D., Funkhouser, M.G., Ahluwalia, G.S., McCallun, A.M. *Pharmacology of hair growth inhibition by topical treatment with eflornithine-HCl monohydrate (DFMO) using the hamster flank organ model.* 59th Annu Meet Am Acad Dermatol (March 2-7, Washington DC) 2001, Abst P123.

2. Shander, D., Funkhouser, M.G., Harrington, F.E., Ahluwalia, G.S., Morton, J.P., Gourley, J., Di Pasquale, L.V., Redmond, G.P. *Clinical dose range studies with topical application of the ornithine decarboxylase inhibitor eflornithine HCl (α-(difluoromethyl)-DL-ornithine; DFMO) in women with facial hirsutism.* 59th Annu Meet Am Acad Dermatol (March 2-7, Washington DC) 2001, Abst P228.

3. Jackson, J.D., Garo, G., Garfield, F.B., Huber, F., Schrode, K., Bogaerts, J., Shander, D., Caro, J.J. *The evaluation of quality of life in two studies of women treated with topical eflornithine HCl 15% cream for excessive unwanted facial hair.* 59th Annu Meet Am Acad Dermatol (March 2-7, Washington DC) 2001, Abst P259.

4. *First prescription drug to treat unwanted facial hair introduced in U.S.* DailyDrugNews.com (Daily Essentials) Oct 5, 2000.

5. *Ilex Oncology updates year-end 2000 developments, highlights plans for 2001.* DailyDrugNews.com (Daily Essentials) Feb 22, 2001.

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Elmore, E. et al. *Analysis of DFMO induced changes in cancer related gene expression in two pre-cancerous human colon polyp cell lines using RNA microarrays.* Proc Amer Assoc Cancer Res 2000, 41: Abst 4223.

Einspahr, J.G. et al. *Topical DFMO, a promising chemoprevention agent in non-melanoma skin cancer, modulates p53, polyamines, and actinic keratoses.* Proc Amer Assoc Cancer Res 2001, 42: Abst 2497.

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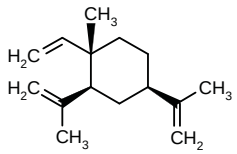
  CCC: 0377-8282/2001

Zou, C.P. et al. *Apoptosis induction by DFMO in immortalized human cervical epithelial cells and cervical cancer cells.* Proc Amer Assoc Cancer Res 2000, 41: Abst 4226.

β-Elemene

Oncolytic

EN: 257947



C15 H24 **Dalian Jin Gang**

A stereoselective synthesis of β-elemene has been reported: Reaction of 2-allylpropane-1,3-diol (I) with tosyl chloride and pyridine gives the ditosylate (II), which is treated with NaCN in refluxing DMF to yield the dinitrile (III). The methanolysis of (III) with TsOH and refluxing methanol affords the dicarboxylic acid (IV), which is reduced with $LiAlH_4$ in THF to provide 3-allyl-1,5-pentanediol (V). The reaction of (V) with CBr_4 and PPh_3 in dichloromethane gives the dibromide (VI), which is ozonolyzed with ozone and PPh_3 in dichloromethane to yield the aldehyde (VII). Condensation of (VII) with the phosphorane (VIII) in dichloromethane affords the unsaturated ester (IX), which is reduced with DIBAL in toluene to afford the alcohol (X). Condensation of (X) with triethyl orthopropionate (XI) in refluxing phenol/toluene gives the *anti*-dibromoester (XII), along with some *syn*-isomer that is easily separated. Cyclization of (XII) with LDA in THF yields the cyclohexanecarboxylate (XIII), which is treated with *t*-BuOK in THF to afford the divinylcylohexanecarboxylate (XIV). Reduction of (XIV) with DIBAL in toluene provides the carbinol (XV), which is treated with CuCl, $PdCl_2$ and O_2 in DMF/water to give the acetyl derivative (XVI). Oxidation of (XVI) with PCC and AcONa in dichloromethane gives the keto-aldehyde (XVII), which is finally submitted to a double Wittig methylenation with methylenetriphenylphosphorane (XVIII) in THF (1). Scheme 2.

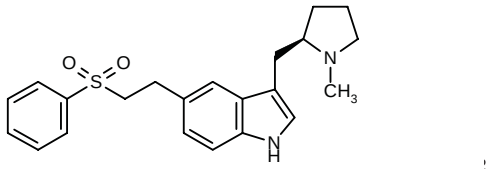
1. Kim, D., Lee, J., Chang, J., Kim, S. *Stereoselective synthesis of (±)-β-elemene by a doubly diastereo-differentiating internal alkylation: A remarkable difference in the rate of enolization between syn and anti esters.* Tetrahedron 2001, 57(7): 1247.

Original monograph - Drugs Fut 1998, 23: 266.

Eletriptan
Relpax®

Antimigraine

EN: 223823



$_2H_{26}N_2O_2S$ **Pfizer**

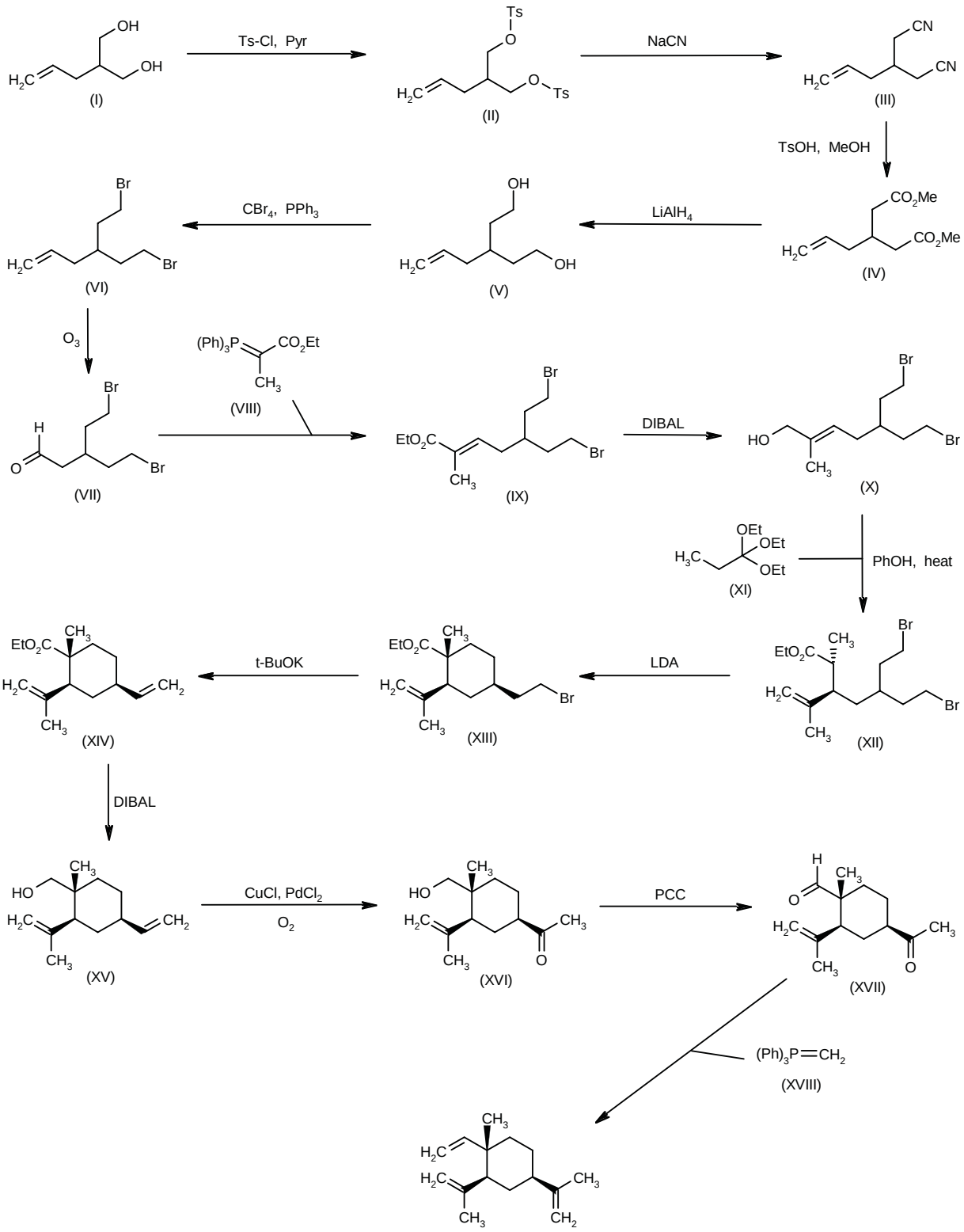
Pharmaceutical compositions for the treatment of migraine containing 5-HT_1 agonists, preferably eletriptan, and metoclopramide have been found to provide enhanced efficacy and less nausea due to the antiemetic effects of metoclopramide (1).

Eletriptan was shown to inhibit glyceryl trinitrate (GTN)-induced activation of spontaneous trigeminal neuron activity in anesthetized cats. The superior sagittal sinus and facial receptive fields of cats were stimulated and GTN (10-100 mg/kg/min) was administered via retrograde infusion from the lingual artery into the common carotid artery. GTN increased the basal discharge rate of second-order neurons receiving dural and facial sensory input by 139 ± 47% and iontophoretic administration of eletriptan (50 nA) reversed this increase in rate; GR-127935 blocked the effects eletriptan. It was concluded that eletriptan selectively blocks GTN-induced noxious sensory activity in the dura through activation of $5HT_{1B/1D}$ receptors (2).

A study using anesthetized cats showed that iontophoretic administration of eletriptan (10-50 nA) suppressed (59 ± 4%) the activity of trigeminal nucleus caudalis second-order sensory neurons receiving input from the electrically stimulated superior sagittal sinus; some second-order neurons receiving input from the electrically stimulated facial receptive field were also suppressed by administration of the agent. Administration of eletriptan (100 μg/ml i.v.) inhibited responses of neurons receiving input from the superior sagittal sinus but not those responding to facial receptive field stimulation. Maximum inhibition (51 ± 7%) was seen 75 min postinfusion and was reversed over 3 h. Results provide further evidence that eletriptan selectively acts on neurons responding to craniovascular sensory input (3).

The safety, tolerability and efficacy of long-term eletriptan (40 mg titrated to 80 mg and reduced again to 40 mg based on response and followed by a stable dose for 1 year) were examined in 2 randomized, open-label studies. Subjects participating had recently completed a double-blind trial in which they were randomized to receive eletriptan (40 mg) or Physician-Optimized Treatment (POT) to treat 3 migraine attacks. A similar incidence of drug-related adverse events was observed in groups receiving eletriptan 40 mg (14 and 9% in study 1 and 2, respectively) and 80 mg (18 and 13% in study 1 and 2, respectively) and POT (23 and 10% in study 1

Scheme 2: Synthesis of β-Elemene



and 2, respectively) and discontinuations due to adverse events were comparable in the 40 and 80 mg eletriptan groups (2-4%). Both eletriptan doses were well tolerated and good headache responses were observed with the 80 mg dose (4).

1. Sands, G.H. (Pfizer Products Inc.). *5-HT$_1$ receptor agonists and metoclopramide for the treatment of migraine.* WO 0025778.

2. Lambert, G.A., Boers, P.M., Hoskin, K., Donaldson, C., Zagami, A.S. *The activation of trigeminovascular sensory neurons by glyceryl trinitrate is suppressed by eletriptan.* Cephalalgia 2000, 20(4): Abst 23.

3. Lambert, G.A., Donaldson, C., Zagami, A.S. *Eletriptan: Selective effect on craniovascular second order secondary neurones when administered intravenously or iontophoretically.* Cephalalgia 2000, 20(4): Abst 326.

4. McKenzie, I., Pitman, V. *Safety, tolerability and efficacy of eletriptan (40-80 mg) for long-term treatment of migraine.* Cephalalgia 2000, 20(4): Abst 214.

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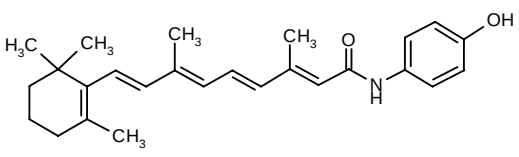
Fenretinide

Oncolytic

EN: 090670



$C_{26}H_{33}NO_2$ **Natl. Cancer Inst. (US); R.W. Johnson**

An *in vitro* study using microsomes isolated from JEG-3 human placental carcinoma cells showed that fenretinide dose-dependently inhibited aromatase. Inhibition was both competitive and noncompetitive since in the presence of the agent, the K_m of the substrate increased while the V_{max} of the reaction decreased. The agent also inhibited aromatase activity of intact human breast cancer cells (MCF-7) in the presence or absence of cAMP and inhibited cAMP-induced aromatase mRNA expression (1).

A phase I trial involving 46 patients (2-21 years) with neuroblastoma examined the tolerability and pharmacokinetics of fenretinide (100-2300 mg/m^2 p.o. once daily in 28-day cycles). So far, 142 courses have been administered and the study is ongoing to determine the maximum tolerated dose. The C_{max} values with doses of 100 and 2300 mg/m^2 were 0.6 and 2.6 μM, respectively, on day 1 and 1.3 and 13.4 mcM, respectively, on day 28. $T_{1/2}$ values were 15 and 24 h on days 1 and 28, respectively. Retinol plasma levels were reduced by about 60-80% on day 1 and by 80-95% on day 28. Of the 45 evaluable patients, 15 had tolerable toxicities which included reversible hemeralopia (8 patients), skin xerosis (1 patient), headache (2 patients), cholelithiasis (3 patients), HZV infection (3 patients) and freckles (3 patients) (2).

An ongoing randomized, placebo-controlled 1-year trial in 213 healthy postmenopausal women is comparing transdermal and oral hormone replacement therapy with fenretinide or placebo. Mean drug exposure has been 239 ± 131 days with > 90% compliance in 90% of the subjects. A low drop-out rate and no major adverse events have been seen. The most common adverse events included vaginal bleeding, decreased dark adaptation and mammary tension (3).

An ongoing, randomized, placebo-controlled, 1-year trial in 147 healthy postmenopausal women is comparing transdermal and oral hormone replacement therapy with or without fenretinide and its effects on intermediate markers of breast cancer (*e.g.*, IGF-I levels and mammographic density). The most frequent side effects seen so far were vaginal bleeding, diminished dark adaptation and mammary tension (4).

A phase III placebo-controlled trial in 426 postmenopausal estrogen or progesterone receptor-positive breast cancer patients evaluating the efficacy of 5-year treatment (with 3 drug-free days/month) with tamoxifen (20 mg/day) + fenretinide (400 mg/day, 3 drug-free days/month) as compared to tamoxifen + placebo, showed poor accrual and a high drop-out rate. It was recommended the study be terminated. Significantly more patients on fenretinide discontinued for reasons other than relapse or death as compared to placebo (21% and 30% *vs.* 14% and 15% at 1 and 2 years, respectively). Significantly higher incidences of grade I/II vision problems, leukopenia and hypercalcemia were observed in the group receiving fenretinide (5).

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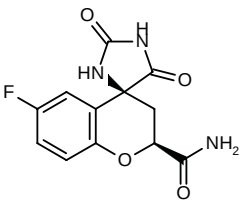

$C_{12}H_{10}FN_3O_4$ **Sanwa; Kaken; Japan Energy**

A study using STZ-induced diabetic rats showed the efficacy of long-term (15-month) fidarestat treatment (0.5, 1 and 2 mg/kg/day suspended in 5% arabic gum via gavage) in preventing the functional and structural progression of diabetic neuropathy. Dose-dependent corrections in slowed F-wave and motor and sensory nerve conduction velocities were observed with treatment and the incidence of paranodal demyelination and axonal degeneration were decreased to normal; axonal atrophy, distorted axon circularity and reductions in myelin sheath thicknesses were also inhibited with treatment. Sorbitol and fructose levels were normalized and peripheral nerve myo-inositol levels were decreased (1).

The results of a 1-year, double-blind, placebo-controlled, parallel-group phase III study evaluating fidarestat in 279 patients with diabetic neuropathy have been presented. The compound (1 mg/day) produced significant improvements in median and tibial nerve function as compared to baseline, whereas median nerve function deteriorated significantly in the placebo group as compared to baseline. Nerve symptoms of numbness, sensation of rigidity, paresthesia in the sole upon walking and hyperesthesia also improved significantly with fidarestat as compared to placebo. The study drug was safe and well tolerated, with a similar incidence of skin and subcutaneous tissue disorders in the fidarestat and placebo treatment groups, and no hepatotoxicity was reported. Thus, fidarestat was deemed effective for both treating and preventing the progression of diabetic neuropathy (2).

Sanwa Kagaku has teamed up with Kaken for the marketing of fidarestat for the treatment of diabetic complications (3).

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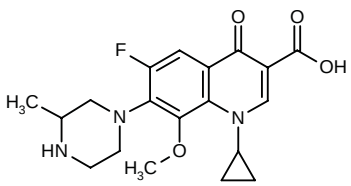

$C_{19}H_{22}FN_3O_4$ **Kyorin; Bristol-Myers Squibb; Schering-Plough; Grünenthal; Senju; Dainippon; Allergan**

The *in vitro* synergistic activity of gatifloxacin in combination with cefepime, ceftazidime, cefoperazone, imipenem, aztreonam, chloramphenicol, trimethoprim-sulfamethoxazole, ticarcillin-clavulanate, minocycline, piperacillin and amikacin was examined against *Pseudomonas aeruginosa*, *Pseudomonas stutzeri*, *Burkholderia cepacia*, *Stenotrophomonas maltophilia* and/or *Acinetobacter* spp. The MICs for gatifloxacin

against the strains were 0.5-4, 0.015-0.25, 2-8, 0.5-4 and 0.06-1 μg/ml, respectively. Synergism was observed when gatifloxacin was combined with piperacillin, aztreonam or imipenem against *P. aeruginosa*; piperacillin, aztreonam and amikacin against *P. stutzeri*; ceftazidime or aztreonam against *B. cepacia*; ceftazidime and ticarcillin-clavulanate or aztreonam against *S. maltophilia*; and ceftazidime, aztreonam or trimethoprim-sulfamethoxazole against *Acinetobacter* spp. It was concluded that synergism was more often observed with nonquinolone agents against pseudomonads and related species (1).

The *in vitro* activities of gemifloxacin and other quinolones were compared against isolates of *Borrelia burgdorferi*, *Borrelia garinii*, *Borrelia afzelii*, *Borrelia valaisiana* and *Borrelia bissettii*. Gatifloxacin, sparfloxacin and gemifloxacin showed the lowest MIC values (MIC_{90} = 1, 0.7 and 0.125 μg/ml, respectively) as compared to levofloxacin (MIC_{90} = 4 μg/ml), ciprofloxacin (MIC_{90} = 2 μg/ml) and nalidixic acid (MIC_{90} = 128 μg/ml or greater). Mean bactericidal concentrations for gemifloxacin, ciprofloxacin and nalidixic acid were 1.8, 13.8 and > 128 μg/ml, respectively (2).

An *in vitro* study examining the inhibitory activities of gatifloxacin, ciprofloxacin and other structurally related compounds against DNA gyrase and topoisomerase IV of *Staphylococcus aureus* and expressed in *Escherichia coli* found that the introduction of the methoxy group at position 8 in gatifloxacin enhances activity against gyrase. The 8-methoxy compounds were 4-fold more active than the 8-hydrogen counterparts and their activity against gyrase was about 6 times higher. The 7-substituents had little effect on inhibitory activity against gyrase. The highest gyrase inhibitory activity was seen with gatifloxacin (IC_{50} = 3.01 μg/ml) as compared to trovafloxacin (IC_{50} = 7.13 μg/ml), moxifloxacin (IC_{50} = 3.45 μg/ml), grepafloxacin (IC_{50} = 28.4 μg/ml), sparfloxacin (IC_{50} = 13.5 μg/ml) and levofloxacin (IC_{50} = 8.06 μg/ml). Equal or slightly better inhibitory activity against topoisomerase IV was observed for the 8-methoxy compounds as compared to the 8-hydrogen counterparts (3).

A study using chinchillas with *Haemophilus influenzae*-induced acute otitis media compared the efficacy of gatifloxacin (15 mg/kg/day) with ampicillin (40 mg/kg/day) and azithromycin (5 mg/kg/day). Treatment was started 2 days after inoculation and continued for 10 days. The rates of survival of animals infected with beta-lactamase negative and beta-lactamase positive *H. influenzae* and treated with gatifloxacin were 96 and 93%, respectively, as compared to 72 and 73% and 96 and 61%, respectively, for ampicillin- and azithromycin-treated animals (4).

A study using a penicillin-resistant pneumococci rabbit meningitis model compared the efficacy of gatifloxacin (15 mg/kg after inoculation) and cefepime (100 mg/kg at 0 and 4 h after inoculation) alone or in combination with ceftriaxone (125 mg/kg after inoculation) + vancomycin (20 mg/kg at 0 and 4 h after inoculation) treatment. Gatifloxacin was found to penetrate well into inflamed meninges (49%) and was more active than ceftriaxone + vancomycin. Gatifloxacin combined with cefepime was the most effective treatment. All results were confirmed *in vitro* in time-kill assays (5).

The penetration of gatifloxacin (400 mg once daily for 5-10 days) into sinus mucosa and sinus secretions was examined in a randomized study conducted in 18 patients with acute sinusitis, acute exacerbation of chronic sinusitis or chronic sinusitis. Gatifloxacin was shown to penetrate well into sinus mucosa, with high concentrations of the agent maintained longer in tissue as compared to plasma (6).

The pharmacokinetics of oral gatifloxacin suspension (5, 10 or 15 mg/kg) and tablet (10 mg/kg) formulations were examined in an ascending single-dose study conducted in 88 pediatric (< 2 up to 16 years of age) patients. The recommended dose for further studies was concluded to be 10 mg/kg/day. The agent was safe and well tolerated and the pharmacokinetics obtained were age-independent. The 10 mg/kg dose was found to result in exposure similar to that observed with a 400 mg/day dose in adults. C_{max} values for the 5, 10 and 15 mg suspensions and the 10 mg tablet were 2.1 ± 1.3, 4.1 ± 1, 5.4 ± 1.4 and 5.4 ± 1.2 μg/ml, respectively, and AUC values were 14.4 ± 4.7, 36 ± 12, 48.7 ± 15.4 and 44.7 ± 10.5 μg·h/ml, respectively; $t_{1/2}$ values were 4.8 ± 1, 5.4 ± 1.8, 4.9 ± 1.2 and 7 ± 4.1 h, respectively (7).

A multicenter, open-label, noncomparator study conducted in 6852 ambulatory outpatients with community-acquired pneumonia (CAP), acute exacerbation of chronic bronchitis (AECB) or bacterial sinusitis showed the efficacy and safety of oral gatifloxacin (400 mg/day). The rate of clinical improvement was 96%, with relapse and therapeutic failure rates of only 1.74 and 0.79%, respectively. Adverse events were generally mild and self-limiting of which the most common were nausea (3.2%), headache (2.5%), gastric complaints (1.88%) and dizziness (1.7%). Two allergic reactions possibly related to gatifloxacin were observed (8).

Results from 4166 patients suffering from AECB, bacterial sinusitis or CAP and cardiovascular disease involved in the ongoing Tequin Clinical Experience Study (TeqCES) showed the safety and tolerability of gatifloxacin (400 mg once daily for 7-14 days); 1194 of these patients also received concurrent cardiovascular medication. The most common adverse events were headache, nausea, dizziness and diarrhea and none required discontinuations or modifications in therapy. No arrhythmias were seen although 1 patient each had congestive heart failure and chest pain, both of which were unrelated to gatifloxacin (9).

Interim results from a subset of 509 patients with AECB participating in the ongoing TeqCES showed the safety and efficacy of gatifloxacin (400 mg once daily for 7-10 days). The cure rate for all AECB patients was 92%. *H. influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis* were identified in 24, 54 and 40 patients, respectively. Outcomes did not differ for patients with risk factors such as smokers and those suffering from COPD (10).

A randomized, open-label, 2-way crossover study conducted in 12 healthy volunteers showed the effects of oxycodone (5 mg p.o. every 4 h) on the bioavailability of gatifloxacin (400 mg p.o. alone or 1 h after oxycodone). No significant differences in mean AUC, C_{max} or $t_{1/2}$ values for gatifloxacin were observed with coadministration. Although the t_{max} significantly increased (1.75 ± 0.75 *vs.* 4.25 ± 1.48 h) with combination treatment, this increase was concluded to be clinically insignificant (11).

Interim results from 4166 patients with CAP, AECB or bacterial sinusitis participating in the TeqCES showed the safety and efficacy of gatifloxacin (400 mg once daily for 7-14 days). The clinical cure rate for CAP patients (n = 379) was 96%, with *H. influenzae*, *S. pneumoniae* and *M. catarrhalis* the most frequently isolated pathogens. Cure rates for patients with CAP due to *S. pneumoniae* including penicillin-resistant strains was 100%; 93 and 100% were the cure rates for infections due to β-lactamase positive strains and *M. catarrhalis*, respectively (12).

Bristol-Myers Squibb and Schering-Plough have established an agreement to copromote gatifloxacin (Tequin™) in the U.S. The agreement between the companies is for an undisclosed period of time and financial details were not divulged. Schering-Plough will begin immediate promotion of the drug. Separately, Bristol-Myers Squibb announced that Tequin™ has been selected for use in the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) trial, the first head-to-head statin trial to examine the role played by infection in heart disease and the atherosclerotic process. PROVE IT will compare the effects of pravastatin sodium versus atorvastatin calcium in reducing the risk of heart attacks and other cardiac events, as well as examining the role of gatifloxacin in reducing the risk of these cardiovascular events by suppressing the growth of *Chlamydia pneumoniae*. Increasing evidence points to a role for infectious agents, particularly *C. pneumoniae*, in the development of cardiovascular disease and atherosclerosis. The PROVE IT trial is a double-blind, randomized study that will enroll 4000 patients at about 500 U.S. and international sites who have had an acute coronary syndrome within the previous 10 days. Patients will be given either 40 mg of pravastatin or 80 mg of atorvastatin and an initial daily regimen of either gatifloxacin 400 mg or placebo; additional courses of gatifloxacin or placebo will be given throughout the trial. Patients will be followed for an average of 2 years (13).

Allergan and Kyorin have entered into a license agreement for the development and commercialization of gatifloxacin for the treatment of ocular infections. In conjunction with a license agreement with Kyorin, Bristol-Myers Squibb currently commercializes the oral and injectable forms of gatifloxacin in the U.S. for the treatment of a broad spectrum of infections. The European development and marketing rights for the oral and injectable forms of gatifloxacin were licensed by Gruenenthal from Kyorin. Under the terms of the agreement, Kyorin will grant Allergan rights to develop and commercialize the topical ophthalmic formulation of gatifloxacin in all territories except Japan, Korea, China and Taiwan (14).

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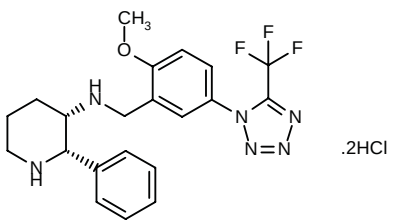
GR-205171A *Tachykinin NK_1 Antagonist*
Vofopitant Hydrochloride

EN: 235944



$C_{21}H_{23}F_3N_6O.2HCl$ **GlaxoSmithKline**

Evidence exists supporting the idea that substance P and NK_1 receptors localized in corticolimbic structures may play a role in the control of mood. In a recent experimental study, the activities of the NK_1 antagonists GR-205171 and CP-99994 were compared to those of fluoxetine in models predictive of antidepressant activity. Both substances reduced marble-burying behavior in mice and diminished aggressive behavior in isolated mice when administered at doses that also exhibit antinociceptive properties in the formalin test. These doses were lower than those which elicited motor disturbances, as determined by the induction of ataxia in the rotarod test in mice. In a forced swimming test in mice and rats, none of the drugs reduced immobility. GR-205171 administration led to increases in dialysate levels of noradrenaline and dopamine in the frontal cortex of freely moving rats. Fluoxetine, however, led to elevation of noradrenaline, dopamine and 5-HT levels. As seen from the data, NK_1 antagonists cause significant effects in rodent models sensitive to the antidepressant fluoxetine. Nevertheless, these NK_1 antagonists may act by modulating states other than depression, such as anxiety or impulsiveness. Finally, the activity of the NK_1 antagonists was independent of 5-HT, but may be linked to dopaminergic and/or adrenergic mechanisms (1).

Vofopitant hydrochloride is the proposed international nonproprietary name for GR-205171A (2).

1. Brocco, M., Dekeyne, A., Gobert, A., de Nanteuil, G., Millan, M.J. *Actions of the neurokinin1 antagonists, GR205,171 and CP99,994, in behavioural and neurochemical models of potential antidepressant activity.* Int J Neuropsychopharmacol 2000, 3(Suppl. 1): Abst P.19.33.

2. *Proposed international nonproprietary names (Prop. INN): List 82*. WHO Drug Inf 1999, 13(4): 291.

Original monograph - Drugs Fut 1999, 24: 254.

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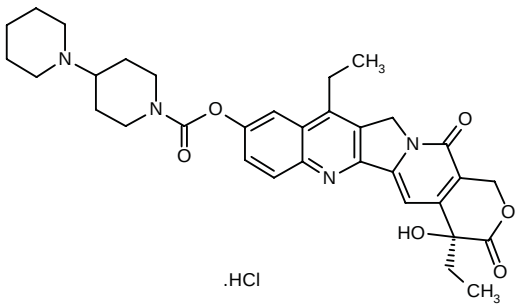
Irinotecan Hydrochloride *Oncolytic*

Campto®
Topotecin®
Camptosar®

EN: 103766



$C_{33}H_{38}N_4O_6.HCl$

Yakult Honsha; Pharmacia; Daiichi Pharm.; Aventis Pharma; Almirall Prodesfarma

Health Canada has approved Pharmacia's irinotecan hydrochloride (Camptosar®) in combination with 5-fluorouracil (5-FU) and leucovorin as a new first-line treatment for patients with metastatic colorectal cancer. Clinical data from 2 large, prospective, multicenter, international trials were recently reported. The 2 phase III studies compared patients who received irinotecan combined with 5-FU and leucovorin to those receiving the current standard of 5-FU and leucovorin alone. Irinotecan patients lived 20% longer, on average, than those who received the traditional therapy. The irinotecan combination also led to significant improvements in tumor response, and a reduction in the speed at which tumors worsened, in comparison with the traditional first-line treatment. The FDA approved the combination as a first-line treatment in April 2000 (1).

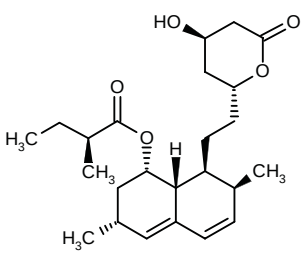
1. *Camptosar approved in Canada as first-line treatment of metastatic colorectal cancer.* DailyDrugNews.com (Daily Essentials) March 29, 2001.

Original monograph - Drugs Fut 1987, 12: 207.

Lovastatin *Hypolipidemic*

Mevacor® *HMG-CoA Reductase Inhibitor*

EN: 090077



$C_{24}H_{36}O_5$

Merck & Co.

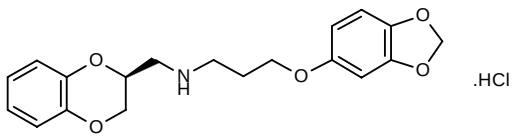
Members of the Nonprescription Drug and Endocrinologic and Metabolic Drug Advisory Committees have voted against approval of an over-the-counter (OTC), low-dose formulation of lovastatin (Mevacor®, 10-mg tablets). The joint advisory committee has requested that Merck provide additional information to demonstrate consumers' ability to use the product with minimal instructions. The committee unanimously agreed that the drug showed significant clinical benefit by reducing LDL cholesterol levels and was safe in the OTC-eligible population. Merck will continue to work with the FDA to discuss criteria for approval of an OTC medication to lower cholesterol. In the clinical program Merck conducted to establish the benefits of a 10-mg OTC formulation of lovastatin, it was shown that this dose lowered total cholesterol by 10-13%, lowered LDL cholesterol levels by 15-22% and increased HDL cholesterol levels by 5-7% (1).

1. *FDA advisory committee recommends against approval of OTC Mevacor.* DailyDrugNews.com (Daily Essentials) July 17, 2000.

Original monograph - Drugs Fut 1984, 9: 197.

MKC-242

Anxiolytic
Antidepressant
EN: 176577 *5-HT$_{1A}$ Agonist*



$C_{19}H_{21}NO_5$.HCl **Mitsubishi Chem.**

MKC-242 was shown to reduce isolation-induced aggressive behavior in mice in a recent study. In this study, aggressive behavior, including biting attacks, wrestling, lateral threat and tail rattle, was videotaped after 2 mice who had been isolated for a 6-week period were placed together in a new cage. Videotaping of DOI-induced behavior was also performed and the head twitch response was determined. A dose-dependent decline in total fighting time (TFT) was observed with MKC-242 at oral doses of 0.1-1.0 mg/kg, doses which also produce anxiolytic effects. WAY-100635, a 5-HT$_2$ receptor antagonist, blocked the activity of MKC-242 but did not affect TFT when administered alone, and the antiaggressive effect of MKC-242 was not altered by pretreatment with 5,7-dihydroxytryptamine. Flumazenil antagonized the effect of MKC-242. The DOI-induced head twitch response was attenuated by MKC-242, which was antagonized by WAY-100635. MKC-242 therefore clearly exhibits antiaggressive activity, effects which may be mediated by postsynaptic 5-HT$_{1A}$ receptors, as well as by a possible interaction with 5-HT$_2$ and GABA receptors (1).

Mitsubishi-Tokyo Pharmaceuticals is evaluating MKC-242 in phase II clinical trials for the treatment of depression and anxiety (2).

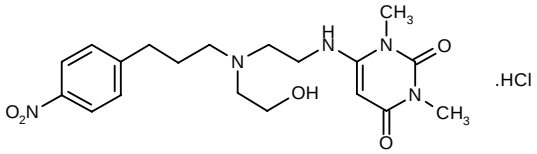
1. Matsuda, T., Sakaue, M., Baba, A. *Potent anti-aggressive effect of MKC-242, a 5-HT$_{1A}$ receptor agonist, in isolated mice.* Int J Neuropsychopharmacol 2000, 3(Suppl. 1): Abst P.03.153.

2. Mitsubishi-Tokyo Pharmaceuticals Product Pipeline 2000, March 31.

Original monograph - Drugs Fut 1997, 22: 225.

Nifekalant Hydrochloride *Antiarrhythmic*
Shinbit® *Potassium Channel Blocker*

EN: 162601



$C_{19}H_{27}N_5O_5$.HCl **Mitsui Pharm.**

The efficacy and safety of nifekalant hydrochloride, a class III antiarrhythmic agent, for suppressing ventricular arrhythmias associated with extensive anterior acute myocardial infarction were assessed in 4 hospitalized male patients. All patients developed severe ventricular arrhythmias by the third day, which did not respond to class I agents or magnesium, and were treated with nifekalant, initially at a dose of 0.05-0.3 mg/kg i.v., followed by 0.05-0.3 mg/kg/h by continuous infusion for 2-18 days. The QTc interval was prolonged by 17-37% with nifekalant administration and ventricular arrhythmias were suppressed. No adverse effects on hemodynamics were seen during drug administration. Thus, at low doses nifekalant was safe and effective in suppressing ventricular tachycardia/ventricular fibrillation in acute myocardial infarction patients (1).

1. Takenaka, K. et al. *Efficacy of nifekalant against ventricular arrhythmia accompanied by extensive anterior acute myocardial infarction.* J Cardiol 2000, 36(Suppl. 1): Abst P143.

Original monograph - Drugs Fut 1993, 18: 226.

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Yoshizawa, N. et al. *Effects of class III antiarrhythmic agent, MS-551 on the postrepolarization refractoriness in cardiac muscle - Evaluation utilizing atrial conduction block model.* Jpn Circ J 2001, 65(Suppl. I-A): Abst PJ059.

Novel Erythropoiesis Stimulating Protein

NESP *Hematopoietic*
Darbepoetin Alfa *Antianemic*
ARANESP® *Oncolytic*

EN: 236400

[30-L-Asparagine,32-L-threonine,87-L-valine,88-L-asparagine,90-L-threonine]erythropoietin (human)

Amgen; Kirin Brewery; Genesis Pharma

An open-label, randomized, dose-escalation study in patients with nonmyeloid malignancies and anemia secondary to chemotherapy compared the pharmacokinetics, safety and efficacy of novel erythropoiesis stimulating protein (NESP; s.c. once/week) with recombinant human erythropoietin (rHuEPO; 3 times/week). Results showed that NESP should be administered less frequently than the latter agent. Following single-dose NESP (0.5 μg/kg s.c.), the C_{max}, t_{max}, $t_{1/2}$ and relative clearance values obtained were 1.77 ng/ml, 72 h, 49.7 h and 2.79 ml/h/g, respectively. Mean concentrations at week 1, 48 h after dosing with 0.5 and 1 μg/kg, were 1.6 ± 0.77 and 3.3 ± 0.81 ng/ml, respectively. Adverse events were similar in both treatment groups (1).

The results from a randomized, controlled phase I/II trial comparing NESP and rHuEPO in solid tumor patients with anemia receiving chemotherapy have been reported. In this study, patients were randomized to receive rHuEPO (150-300 IU/kg 3 times weekly) or NESP at escalating doses of 0.5, 1.0 1.5, 2.25 and 4.5 μg/kg/week. So far, 288 patients have been randomized, 205 of whom were evaluable at the time of reporting. The results showed a dose-dependent increase in hemoglobin and a dose-dependent reduction in red blood cell transfusions on NESP. Higher doses of NESP were comparable to rHuEPO as regards effects on hemoglobin, but it appeared to be more effective than the standard in reducing the need for RBC transfusions. No dose-limiting toxicity was observed and pharmacokinetics were dose- and time-proportional (2).

In a double-blind, placebo-controlled phase I/II dose-finding study in 163 anemic cancer patients with solid tumors, NESP demonstrated a dose-dependent effect on hemoglobin and red blood cell transfusions when given just once every 3 weeks. In contrast, standard therapy requires that patients be given injections 3 times per week. NESP appeared to increase hemoglobin more rapidly and to a greater extent than placebo in this study and was well tolerated (3).

Amgen is seeking approval of NESP for the management of anemia in patients with chronic renal insufficiency (CRI) and patients with chronic kidney disease requiring dialysis, with less frequent dosing than rHuEPO. Clinical data have shown that NESP was safe and effective in managing the anemia of patients with end-stage renal disease (ESRD) or CRI. The NESP oncology program is in phase II studies and is progressing well. Preliminary results from a phase I/II study involving 130 patients with solid tumors compared 4 different dose levels of NESP administered once weekly to rHuEPO administered 3 times weekly and demonstrated that hemoglobin levels rose in a dose-dependent manner, as expected. The drug was found to be safe and well tolerated. Results from a 24-week phase II/III study involving 166 patients with CRI randomized to receive either NESP or rHuEPO have also been reported. NESP administered once weekly at a starting dose of 0.4 μg/kg treated anemia comparably to rHuEPO administered twice weekly. Both treatment groups exhibited similar safety profiles and similar increases in hemoglobin levels. Similar findings were observed in another phase II/III trial involving 122 patients on dialysis who had not received prior rHuEPO therapy. It was reported that NESP achieved target hemoglobin levels using the same starting dose as in the previous study. In this study, NESP dosed once weekly was well tolerated in the treatment of anemia as compared with rHuEPO administered three times weekly. In a third study, a pivotal, double-blind, 28-week phase III trial, 501 patients undergoing dialysis were randomized either to switch from rHuEPO 3 times weekly to NESP once weekly or to remain on rHuEPO. Despite the reduced dose frequency, NESP enabled dialysis patients to maintain target hemoglobin levels. Both treatment groups exhibited similar safety profiles. Another study involving 703 patients with ESRD reported that ESRD patients can be switched from rHuEPO 2 or 3 times weekly to NESP once weekly, or from rHuEPO once weekly to NESP treatment once every other week, while maintaining target hemoglobin concentrations (4).

Regulatory reviews of NESP in nephrology are on schedule and Amgen anticipates receiving approvals during the first half of 2001 in the U.S. and Europe. The company reported that the first pivotal trial of NESP in treating

oncology patients with anemia was successful and that it plans to file for U.S. regulatory approval of this indication this year (5).

Amgen and Genesis Pharma have signed an agreement granting Genesis certain exclusive rights to distribute, market and sell NESP in Greece and Cyprus. NESP is currently under review by the FDA and the EMEA for the treatment of anemia resulting from chronic renal failure. The drug may treat anemia with less frequent dosing than rHuEPO, thereby simplifying anemia management (6).

The European Committee on Proprietary Medicinal Products (CPMP) has recommended approval of Amgen's NESP for the treatment of anemia associated with chronic renal failure. The CPMP's recommendation for approval will be forwarded to the European Commission for marketing authorization, after which Amgen could obtain a single license for marketing throughout the E.U. Launch schedules for each country will vary according to each nation's pricing and reimbursement procedures (7).

Kirin Brewery has begun clinical trials of NESP for the treatment of renal-failure associated anemia. Kirin holds the manufacturing, development and marketing rights to NESP in China, Korea, Japan and several other Asian countries (8).

Darbepoetin alfa is the United States Adopted Name for NESP (9).

1. Glaspy, J., Colowick, A.B., Heatherington, A. *Novel erythropoiesis stimulating protein (NESP) exhibits a prolonged serum half life ($t_{1/2}$) in oncology patients (pts).* Proc Am Soc Clin Oncol 2000, 19: Abst 210.

2. Glaspy, J., Tchekmedyan, S., Jadeja, J., Richards, D. *Randomized, active-controlled, phase I/II, dose-escalation study of ARANESP™ in solid tumor patients.* Blood 2000, 96(11, Part 1): Abst 1278.

3. *ARANESP effective given once weekly, and possibly less frequently, in treating anemia.* DailyDrugNews.com (Daily Essentials) Dec 11, 2000.

4. *Amgen reviews third quarter developments.* DailyDrugNews.com (Daily Essentials) Nov 17, 2000.

5. *Amgen highlights Q4 and full-year 2000 developments.* DailyDrugNews.com (Daily Essentials) Jan 29, 2001.

6. *Amgen and Genesis Pharma sign distribution agreement for ARANESP.* DailyDrugNews.com (Daily Essentials) Jan 23, 2001.

7. *Amgen's ARANESP recommended for approval by CPMP.* DailyDrugNews.com (Daily Essentials) March 20, 2001.

8. *Kirin accelerates development of NESP in Asia.* DailyDrugNews.com (Daily Essentials) Feb 26, 2001.

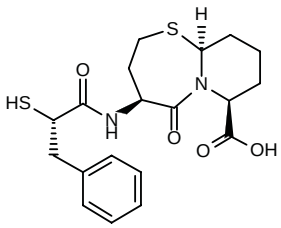
9. *USAN Council. List No. 432.* Clin Pharmacol Ther 2000, 68(5): 581.

Original monograph - Drugs Fut 2000, 25: 246.

Omapatrilat
Vanlev®

Antihypertensive
Treatment of Heart Failure
NEP/ACE Inhibitor

EN: 218551



$C_{19}H_{24}N_2O_4S_2$ **Bristol-Myers Squibb**

Vasopeptidase inhibitors have been reported to be useful for the treatment of angina pectoris. A preferred vasopeptidase inhibitor is omapatrilat that is undergoing clinical evaluation for the treatment of hypertension and heart failure. The antianginal activity of omapatrilat was demonstrated in a rat heart model of low flow ischemia and in a canine model of exertional myocardial dysfunction with an improvement in exercise performance and an increase in peak exercise capacity accompanied by an increase in wall thickening (1).

A study compared the *in vitro* and *in vivo* inhibition of 2 active sites (N- and C-domains) of angiotensin converting enzyme by omapatrilat and fosinopril. A double-blind, placebo-controlled crossover study conducted in 9 mildly sodium-depleted normotensive subjects showed that fosinopril (20 mg) was more specific for the N-domain over the C-domain since plasma and urine AcSDKP were significantly higher than those observed in patients treated with omapatrilat (10 mg). Similarly, *in vitro* results showed that omapatrilat was 5 times more active than fosinopril in inhibiting angiotensin I hydrolysis and inhibited both N- and C-domain hydrolysis; fosinopril was slightly more specific in inhibiting N-domain hydrolysis (2).

An *in vitro* study using ventricular membranes prepared from hearts from normal (n = 7) donors and patients with ischemic (n = 11) or dilated (n = 12) cardiomyopathy showed the cardioprotective effects of omapatrilat (61 nM) over ramiprilat (36 nM) on bradykinin metabolism. Ramiprilat significantly increased the bradykinin half-life in all tissue types in a similar manner (297 ± 104, 267 ± 157 and 407 ± 146 s for normal, ischemic and dilated tissue, respectively). In contrast, omapatrilat was significantly more effective in cardiomyopathic tissue (544 ± 249 and 811 ± 349 s for ischemic and dilated tissue, respectively) as compared to normal tissue (478 ± 210 s) (3).

Researchers compared the cardioprotective effects of the vasopeptidase inhibitor (VPI) omapatrilat and the angiotensin-converting enzyme (ACE) inhibitor captopril to determine whether, due to its additional inhibition of neutral endopeptidase (NEP), omapatrilat would have better cardioprotective effects after myocardial infarction (MI) than captopril. Rats underwent coronary

ligation-induced MI, and those surviving 4 h post-MI were assigned to omapatrilat (40 or 80 mg/kg/day), captopril (160 mg/kg/day) or placebo for 56 days. Survival, hemodynamic measurements and ventricular dilatation showed similar improvements with both agents. Moreover, similar reductions in ventricular weights were observed, although the pattern of ventricular modeling caused by each drug was different. Both omapatrilat and captopril reduced the expression of the profibrotic cytokine TGF, but neither affected the antiinflammatory cytokine interleukin-10. Moreover, only captopril reduced the proinflammatory cytokine TNF-α, which was expressed in cardiomyocytes. Both drugs caused a decrease in endothelin-1 levels, but only omapatrilat increased natriuretic peptides. Based on the findings of this study, both omapatrilat and captopril were shown to markedly improve post-MI survival, cardiac function and cardiac remodeling. Furthermore, although the two classes of drugs had some different activities, the addition of NEP inhibition to ACE inhibition, as occurs in vasopeptidase inhibitors such as omapatrilat, did not appear to enhance its cardioprotective activity in this model (4).

In Dahl salt-sensitive rats fed a high-sodium diet, omapatrilat provided better control of systolic blood pressure (SBP) and more favorable effects on endothelial function than the ACE inhibitor captopril. In rats fed a low-sodium diet, in contrast, omapatrilat affected neither SBP nor endothelial function to a significant degree (5).

A study using spontaneously hypertensive rats (SHR) showed the antihypertensive and antihypertrophic efficacy of omapatrilat (10 and 40 mg/kg/day p.o. for 10 days). After 10 days of treatment, a dose-dependent decrease in blood pressure (212 ± 4 and 197 ± 4 mmHg, respectively, *vs.* 237 ± 4 mmHg with vehicle) was observed and left ventricular hypertrophy was significantly decreased (2.71 ± 0.02 and 2.55 ± 0.02 mg/g, respectively, *vs.* 2.76 ± 0.03 mg/g). Omapatrilat-treated SHR also showed significant increases in kidney weight, decreases in plasma ACE and increases in plasma renin activity as compared to vehicle-treated SHR (6).

A study using stroke-prone spontaneously hypertensive rats (SPSHR) showed that omapatrilat (40 mg/kg/day p.o. for 10 weeks) significantly decreased systolic blood pressure (145 ± 3 *vs.* 230 ± 2 mmHg) and improved acetylcholine-induced endothelium-dependent relaxation of resistance arteries; the agent had no effect on sodium nitroprusside-induced endothelium-independent relaxation or on vascular stiffness. Resistance arteries from omapatrilat-treated animals had significantly decreased median width/lumen ratios and lumen diameter tended to be larger (7).

A study using ApoE–/– mice showed that omapatrilat (38 mg/kg p.o. for 12 weeks) inhibited development of atherosclerosis, possibly through reduction in blood pressure and/or effects on the vessel wall. Omapatrilat-treated animals had significantly reduced blood pressure (71.5 ± 4.8 mmHg) as compared to untreated controls (100.9 ± 3.9 mmHg). The omapatrilat group also displayed significantly higher plasma total cholesterol (536 ± 19.3 *vs.* 433 ± 29.4 mg/dl) and free fatty acids (67.3 ± 4.7 *vs.* 48 ± 3.9 mg/dl) levels and significantly lower HDL levels (26.5 ± 3.4 *vs.* 38.1 ± 2.5 mg/dl). Treatment with omapatrilat significantly reduced the percent of total aorta covered by lesion (1.14 ± 0.16 *vs.* 3.16 ± 0.44%) (8).

Omapatrilat was shown to be more effective than enalapril in providing protection against nephropathy in 5/6 nephrectomized rats. After 20 weeks of treatment, both agents lowered SBP to normal levels. However, significantly greater decreases in proteinuria (22 ± 3 *vs.* 40 ± 9) and significantly less development of focal glomerulosclerosis (14 ± 2% *vs.* 22 ± 6%) were observed in omapatrilat-treated animals as compared to enalapril-treated animals (9).

A study using unilaterally nephrectomized obese diabetic Zucker rats showed that omapatrilat (40 mg/kg/day) significantly decreased systolic (120 ± 12 *vs.* 201 ± 62 mmHg in controls) and diastolic (84 ± 15 *vs.* 141 ± 13 mmHg) blood pressure and provided renal protection. Glomerulosclerosis was significantly reduced to 4 ± 3% in omapatrilat-treated animals as compared to 57 ± 9% in controls; urinary albumin excretion was also significantly decreased (7 ± 3 *vs.* 195 ± 58 mg/day) (10).

A study using SHR showed that omapatrilat (100 μmol/kg/day for 12 weeks) treatment significantly lowered blood pressure (127 ± 15 *vs.* 194 ± 12 mmHg in untreated controls), improved cardiac index (72.63 ± 6.83 *vs.* 50.30 ± 4.05 ml/min/100 g), improved stroke index (217.12 ± 21.56 *vs.* 153.75 ± 16.69 ml/beat/100 g), improved total peripheral resistance index (0.134 ± 0.016 *vs.* 0.351 ± 0.038 mmHg/ml/min), caused regression of the left ventricle (2.42 ± 0.09 *vs.* 2.89 ± 0.065 mg/g) and increased insulin sensitivity (15.9 ± 5.6 *vs.* 11.7 ± 6.5 ml/min/mU) (11).

A study using Dahl salt-sensitive rats treated with 4% NaCl for 8 weeks showed that omapatrilat (35 mg/kg/day for 8 weeks) prevented structural and functional changes of small mesenteric arteries. Treatment with either omapatrilat or captopril (100 mg/kg/day) significantly lowered systolic blood pressure (163 ± 5 and 165 ± 8 mmHg *vs.* 200 ± 5 mmHg). Ompatrilat tended to increase plasma ANP levels (1016 ± 240 *vs.* 644 ± 97 pg/ml) while captopril caused a further significant decrease (351 ± 67 pg/ml). Both ompatrilat and captopril decreased the cross structural area of small mesenteric arteries (23.9 ± 1.6 x 10^3 and 25.9 ± 1.1 x 10^3 μm^2 *vs.* 29.4 ± 1.5 x 10^3 μm^2). Omapatrilat more potently normalized the reduction in acetylcholine-induced endothelium-dependent relaxation as compared to captopril (98 ± 1 *vs.* 90 ± 2%) (12).

A study using dogs with ventricular pacing (180 bpm for 10 days)-induced early left ventricular dysfunction showed the efficacy of omapatrilat (1 mmol/kg i.v. bolus) as compared to fosinoprilat (1 mmol/kg i.v. bolus) and furosemide (40 mg i.v. bolus) in improving cardiorenal and neurohormone effects. A larger reduction in mean arterial pressure was observed in omapatrilat-treated dogs as compared to treatment with the other agents. Similar decreases in pulmonary arterial pressure and

pulmonary capillary wedge pressure were seen in all treatment groups and no changes in renal blood flow or renal vascular resistance were observed. While omapatrilat prevented changes in cardiac output, a significant decrease in this parameter was observed with the other agents (3 ± 0.3 to 1.8 ± 0.2 l/min). Systemic vascular resistance increased with the other agents (39 ± 3 to 58 ± 6) although omapatrilat-treated animals showed a significant decrease (36 ± 3 to 20 ± 2). Glomerular filtration was lower in animals treated with the other agents as compared to omapatrilat. All treatments increased sodium excretion. No changes in renin activity or aldosterone were observed in the omapatrilat group as compared to other treatments, which increased both parameters markedly (13).

In a dog model of evolving (tachycardia-induced) heart failure, omapatrilat monotherapy produced more significant reductions in ventricular dilatation, leading to reduced diastolic wall stress, than either fosinopril alone or fosinopril plus a diuretic (14).

A study conducted in 12 subjects showed that omapatrilat undergoes extensive metabolism in humans. Subjects were administered a single dose of [^{14}C]-omapatrilat (50 mg p.o.; 2 μCi/ml). The major metabolites detected in plasma were *S*-methyl omapatrilat and its acyl glucuronide and *S*-methyl (*S*)-2-thio-3-phenylpropionic acid with omapatrilat accounting for < 3% of plasma radioactivity. Although 40-43% of plasma radioactivity was unextractable, all was extractable following dithiothreitol reduction in which omapatrilat and the hydrolysis product (*S*)-2-thio-3-phenylpropionic acid were identified and appeared to be bound to plasma proteins by reversible disulfide bonds. No omapatrilat was found in urine. Urinary metabolites detected were: 3 metabolites responsible for 56% of the radioactivity that resulted from the hydrolysis of the exocyclic amide bond of the parent compound (2 diastereomers of *S*-methyl (*S*)-2-thio-3-phenylpropionic acid and the acyl glucuronide of *S*-methyl (*S*)-2-thio-3-phenylpropionic acid; a L-cysteine mixed disulfide of omapatrilat responsible for 8% of the urinary radioactivity; and 5 omapatrilat-derived metabolites accounting for 30% of the radioactivity (2 were mixtures of diastereomers of *S*-methyl sulfoxide of omapatrilat; 1 was the *S*-methyl omapatrilat ring sulfoxide, 1 was *S*-methyl omapatrilat and the last was its acyl glucuronide) (15).

In a small clinical study, single-dose omapatrilat (25 mg p.o.) was shown to increase the native vasodilator atrial natriuretic peptide (ANP) and its second messenger cGMP by 20% and 30%, respectively, indicating inhibition of vasopeptidase, and to decrease the activity of ACE. Omapatrilat had no effect on levels of the native vasoconstrictor endothelin in either normal volunteers or subjects with mild to moderate heart failure (16).

The pharmacokinetics of single-dose omapatrilat (10 mg i.v. and 25 mg p.o.) and its metabolites were examined in a 2-way crossover study in 17 NYHA class II or III congestive heart failure (CHF) patients and 17 control subjects. Following oral administration, AUC and C_{max} values of omapatrilat were significantly higher in CHF patients as compared to controls. No significant difference was found in the absolute bioavailability of omapatrilat between population groups (29% in CHF patients and 22% in controls). High AUC ratios of BMS-196087 and BMS-225308 to omapatrilat were observed in control subjects as compared to CHF patients after oral dosing. The pharmacokinetics of omapatrilat were similar in both populations following i.v. dosing. It was concluded that differences in systemic exposure between the study populations were not clinically significant (17).

An open-label, repeated-dose study in 10 normal subjects and 10 subjects with hepatic cirrhosis (Childs-Pugh A/B) given omapatrilat (25 mg/day for 14 days) showed that dose adjustments are not required in patients with mild hepatic cirrhosis. The geometric mean C_{max} and AUC values for the unchanged compound were 92 and 12% higher on day 1, respectively, and 68 and 20% higher on day 14, respectively, in subjects with cirrhosis. Similarly, the geometric mean C_{max} and AUC values for total reducible omapatrilat were 61 and 37% higher on day 1, respectively, and 70 and 51% higher on day 14, respectively, in subjects with cirrhosis. However, these differences were not significant (18).

The pharmacokinetics and pharmacodynamics of omapatrilat (40 mg p.o.) and atenolol (50 mg p.o.) following coadministration were examined in a double-blind, 3 way crossover study in 15 male and 9 female volunteers. Omapatrilat did not alter atenolol's reducing effects on average resting and minimum heart rates. Although atenolol did not alter the pharmacokinetics of omapatrilat, omapatrilat significantly reduced the C_{max} and AUC values of atenolol by 30%. Both agents were well tolerated (19).

Omapatrilat's effects on volume homeostasis were evaluated in 19 patients with chronic, symptomatic heart failure (NYHA class II or III, left ventricular ejection fraction of 40% or less). Patients were administered doses of 2.5, 5, 10, 20 or 40 mg of omapatrilat for 12 weeks. Diuretic dose was not increased during the treatment period. Blood volume, venous blood ANP and left ventricular volume were analyzed at baseline and after 12 weeks, and 24-h urine volume and sodium excretion were compared at baseline and on day 83. Treatment with the two higher doses of omapatrilat produced beneficial reductions in left ventricular and circulatory blood volume, as well as potentiation of natriuretic peptides in this group of patients with chronic heart failure (20).

A substudy conducted in 15 salt-sensitive, low-renin, hypertensive subjects participating in a multicenter, randomized, double-blind, parallel 4-week trial examined the effects of omapatrilat (40 mg) on angiotensin (Ang)-(1-7) and compared it to lisinopril (20 mg) given to 25 other subjects. Ompatrilat significantly increased peak and 24-h urinary Ang-(1-7) 5 times more than lisinopril. On day 28, urinary Ang-(1-7) and ANP were increased at 0-12, 12-24 and 20-24 h postdosing; urinary and plasma ANP were not altered by lisinopril. Twenty-four hour ambulatory systolic/diastolic pressure was decreased by

–15.4/–9.3 mmHg in the omapatrilat groups as compared to 7.2/–5.1 mmHg in the lisinopril group. It was concluded that the antihypertensive renal efficacy of omapatrilat also involves effects on Ang-(1-7) (21).

Results from a 12-week, double-blind randomized trial in 41 patients with chronic heart failure (NYHA II-III, left ventricular ejection fraction [LVEF] > 40%) showed the long-term efficacy of omapatrilat (5-40 mg once daily). At 12 weeks, patients treated with 20-40 mg omapatrilat showed a significant 67% increase in ANP at 3 h postdosing, indicating neutral endopeptidase inhibition. SBP decreased by –3.6 ± 4.6, –16.8 ± 6.1 and –25 ± 4.5 mmHg in groups treated with 2.5 mg, 5-10 mg and 20-40 mg, respectively, and mean arterial pressure decreased by –0.2 ± 3, –10.6 ± 4.2 and –14 ± 3 mmHg, respectively. Wave reflection was also improved with the higher doses and increases in the maximum vasodilator capacity were observed (22).

A double-blind, randomized 48-week study in 341 patients with mild to moderate hypertension and left ventricular hypertrophy showed significant improvement in hypertension and left ventricular function with omapatrilat (20 mg force titrated to 40 and 80 mg every 8 weeks) as compared to losartan (50 mg force-titrated to 100 mg and 100 mg [mock titrated] every 8 weeks). Left ventricular mass index significantly decreased (–7.2 g/m^2 for omapatrilat and -3.4 g/m^2 for losartan) in both treatment groups at 24 weeks. However, blood pressure decreased significantly more in the omapatrilat group (–28/–14 *vs.* –22/-11 mmHg). Treatment with omapatrilat also significantly increased the ratio of E-wave/atrial diameter, an effect not seen with losartan (23).

Two double-blind, placebo-controlled single-dose (2.5-500 mg) and multiple-dose (10-125 mg/day for 10 days) studies in a total of 109 healthy subjects maintained on a 6 g sodium and 4 g potassium diet (starting 4 days prior to and continuing throughout the studies) showed that omapatrilat had no effect on urinary sodium excretion. Increases (4- to 5-fold) in daily urinary ANP and cGMP and decreases in ACE activity (to 10% of baseline) were observed following multiple dosing. In addition, supine systolic (by 8-15 mmHg) and diastolic (by 6-16 mmHg) blood pressure decreased following 10-day dosing with 10-75 mg (24).

Results from a substudy involving 41 patients participating in a randomized study in 57 salt-sensitive hypertensive patients showed that 28-day treatment with omapatrilat (40 mg) significantly increased mean predose (0 h) plasma adrenomedullin levels by about 50% at 4 h postdosing. Lisinopril (20 mg) had no effect on these levels (25).

A randomized, placebo-controlled, parallel-group study in 26 healthy subjects given furosemide (20 mg/day for 15 days) showed that omapatrilat (10 mg on days 6-10 and 25 mg on days 11-15) did not affect furosemide-induced diuresis. Coadministration was well tolerated. No additional diuresis or natriuresis was observed with omapatrilat coadministration. The small (20-27%) reduction in daily urinary ANP excretion rates observed after 15 days of furosemide alone significantly increased more than 2-fold with coadministration of omapatrilat. Coadministration was well tolerated. Furosemide did not alter omapatrilat-induced effects on vasodilator peptides (26).

Results from a multicenter, randomized, double-blind, 3-week study (with a 1-week lead-in dose of 10 mg) in 57 salt-sensitive hypertensive patients showed the efficacy of omapatrilat (40 mg) over lisinopril (20 mg) in controlling blood pressure. Treatment with omapatrilat resulted in significantly greater decreases in 24-h ambulatory diastolic (–9.3 *vs.* –5.1 mmHg) and systolic (–15.4 *vs.* –7.2 mmHg) blood pressure on day 28. Omapatrilat significantly increased urinary ANP excretion by 42.6 ± 2.6 ng/24-h and plasma ANP from 54.05 pg/ml at trough (0 h) to 63 ± 7 pg/ml at peak (4 h); lisinopril had no effect on urinary ANP excretion but increased plasma ANP from 49.6 ± 4.4 to 51.6 ± 3.9 pg/ml. Similar significant suppression of ACE activity was observed with both agents 4 h postdosing on day 28 (–98.4 ± 0.53 and –97.9 ± 0.49% substrate hydrolyzed/min for omapatrilat and lisinopril, respectively) (27).

A multicenter, randomized, double-blind, placebo-controlled study with a 4-week placebo lead-in period involving 429 elderly patients (mean age = 67 years) with isolated systolic hypertension (seated systolic blood pressure [seSBP] of 160-199 mmHg; seated diastolic BP [seDBP] of < 90 mmHg) showed the efficacy and tolerability of omapatrilat (10 or 20 mg or 20 mg force-titrated to 40 mg at week 1). Treatment with 20 mg and 40 mg omapatrilat resulted in significant dose-dependent decreases in seSBP (–23.4 and –26.1 mmHg *vs.* –14.2 mmHg in placebo) and pulse pressure (–20.6 and –21.4 mmHg *vs.* –13.6 mmHg in placebo) at week 9. Adverse events were higher in the 3 omapatrilat groups as compared to placebo (28).

Results from a subset of 122 patients participating in a multicenter, randomized, double-blind, placebo-controlled study with a 4-week placebo lead-in period conducted in a total of 429 elderly patients with isolated systolic hypertension showed that omapatrilat (10 or 20 mg or 20 mg force-titrated to 40 mg at week 1) increased urinary ANP excretion. The changes in urinary ANP excretion rates from baseline were 25.4, 32.4 and 50.5 pg/ml creatinine for the 10, 20 and 40 mg omapatrilat groups, respectively, as compared to 0.9 pg/ml creatinine in placebo. The 20 and 40 mg doses resulted in sustained increases in ANP excretion lasting for at least 24 h (29).

The safety and tolerability of omapatrilat (10 mg titrated to 20, 40 or 80 mg) was shown in a 16-week, open-label trial in 89 hypertensive (seSBP of 90-110 mmHg) subjects with impaired renal function (creatinine clearance of ≤ 60 ml/min). Treatment reduced seSBP and seDBP in subjects with creatinine clearance rates of ≥ 30 ml/min (by 28 ± 2 and 161 mmHg, respectively) and in subjects with rates of < 30 ml/min (by 24 ± 5 and 12 ± 2 mmHg, respectively). Mean 24-h urinary protein excretion was decreased in 20% of the subjects. A modest increase in mean serum creatinine was observed although creatinine clearance rates were not affected by treatment. Mild

and transient increases in serum potassium were occasionally observed (30).

Results of a 10-week, randomized, double-blind, parallel-group study in 430 mild to moderate hypertensive subjects (DBP of 95-110 mmHg) showed the efficacy of omapatrilat (20 and 40 mg o.d. for 2 weeks each followed by 80 mg for weeks) over amlodipine (5 mg for 2 weeks followed by 10 mg for 8 weeks) in reducing ambulatory BP parameters. At 10 weeks, reductions in mean 24-h ambulatory SBP (–20.4, *vs.* –14.5 mmHg), DBP (–13.6 *vs.* –9.3 mmHg) and BP (–15.9 *vs.* –11 mmHg) were significantly greater in the group receiving 80 mg omapatrilat as compared to amlodipine. Overall adverse event and discontinuation rates were lower in the omapatrilat groups as compared to amlodipine (31).

A randomized, double-blind, 10-week study in 347 hypertensive subjects (SBP of 150-180 mmHg) compared the antihypertensive efficacy of omapatrilat (20 mg force titrated to 40 and 80 mg at week 2 and 8, respectively) with lisinopril (10 mg force titrated to 20 and 40 mg at week 2 and 8, respectively). Both treatments were well tolerated. Omapatrilat (80 mg) reduced 24-h mean ambulatory SBP (–19 *vs.* –12.2 mmHg), diastolic BP (–10.5 *vs.* –7.5 mmHg) and BP (–13.3 *vs.* –9.1 mmHg) significantly more than lisinopril (40 mg) at 10 weeks. Neither treatment affected heart rate (32).

The OPERA trial, a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in approximately 12,600 antihypertensive therapy naive subjects (seSBP of ≥ 140 mmHg and < 160 mmHg; seDBP of < 90 mmHg) is designed to evaluate the efficacy of once-daily omapatrilat in reducing cardiovascular morbidity and mortality in individuals with enhanced risk for atherosclerotic events due to Stage I isolated systolic hypertension and other factors (33).

Results were reported from an ongoing, long-term (3 years), open-label study involving 83 subjects with mild to moderate hypertension who were given omapatrilat (≥ 20 mg once daily) for more than 6 months and then randomized to receive in a double-blind manner either continued omapatrilat or placebo. Reductions in blood pressure were maintained in those patients continuing on omapatrilat while patients switched to placebo displayed significant increases in systolic (16.5 mmHg) and diastolic (9.6 mmHg) pressure as compared to omapatrilat; 5 of the 41 patients on placebo showed an increase in seDBP of > 100 mmHg and were discontinued, returning to open-label omapatrilat. The switch to placebo was also accompanied by new or worsening headache (22% *vs.* 2.4% in continued omapatrilat). Continued omapatrilat was better tolerated than withdrawal to placebo since the overall rate of adverse events was 31% as compared to 54% in placebo (34).

Results from a randomized, placebo-controlled study in 348 elderly hypertensive (seSBP of 95-110 mmHg) subjects showed the efficacy and tolerability of omapatrilat (10 or 20 mg/day or 20 mg force-titrated to 40 mg at week 1). Treatment with 10, 20 and 40 mg omapatrilat resulted in significant dose-dependent decreases in seSBP (–11.5, –17 and –19.3 mmHg, respectively, *vs.* –6.3 mmHg in placebo) at week 9; the 40 mg omapatrilat dose also significantly decreased pulse pressure as compared to placebo (–6.1 *vs.* +2.1 mmHg). Dose-dependent increases in peak urinary ANP excretion were observed at week 7 (7 ± 1 h postdosing) with the 3 omapatrilat doses (26.7, 33.9 and 42.6 pg/mg creatinine, respectively) as compared to placebo (0.4 pg/mg creatinine). Adverse events were similar in the 3 omapatrilat groups (35).

The safety and efficacy of omapatrilat (10 mg titrated to 20, 40 or 80 mg as needed to achieve seDBP of < 85 mmHg) monotherapy were demonstrated in a 16-week, open-label study in 89 subjects with hypertension (trough seDBP of 90-110 mmHg) and renal disease (creatinine clearance 60 ml/min or less). Significant decreases in seSBP and seDBP were observed at the end of treatment and mean 24-h urine protein excretion was decreased by 20% in patients with baseline values of 1 g/24 h or more. A modest increase in serum creatinine and a few cases of mild, transient serum potassium level increases were observed that did not require discontinuation (36).

The efficacy and safety of omapatrilat (10 or 20 mg titrated to 20 or 40 mg, respectively, at week 4 if seSBP = 90 mmHg or more) combined with hydrochlorothiazide (HCTZ; 25 mg) were demonstrated in a multicenter, double-blind, placebo-controlled study in 274 mild to severe hypertensive (seSBP = 95-120 mmHg) subjects unresponsive to HCTZ monotherapy. The study included a 2-week placebo lead-in and a 4-week HCTZ filter period. Significantly greater reductions in seSBP and seDBP were seen at week 8 in subjects receiving HCTZ + 10/20 mg (–14.4 and –11.9 mmHg, respectively) or 20/40 mg (–17.9 and –12.8 mmHg, respectively) omapatrilat as compared to HCTZ + placebo (–8 and –7.5 mmHg, respectively). Treatments were well tolerated with similar rates of discontinuations due to adverse events and similar frequency and type of serious adverse events were seen in all groups (37).

A randomized study conducted in 57 salt-sensitive hypertensive patients showed that omapatrilat (40 mg) and not lisinopril (20 mg) increased plasma adrenomedullin concentration, possibly contributing to the antihypertensive effects of the former agent. On day 28 at 4 h postdosing, the mean plasma adrenomedullin concentration was increased by 50% (101 to 152 pg/ml) with omapatrilat treatment as compared to no increase observed following lisinopril (102 to 98 pg/ml) (38).

A randomized study conducted in 24 salt-sensitive hypertensive subjects showed that omapatrilat (40 mg for 3 weeks) significantly reduced mean 24-h ambulatory diastolic (–9.3 *vs.* –5.1 mmHg) and systolic (–15.4 *vs.* –7.2 mmHg) blood pressure more effectively than lisinopril (20 mg for 3 weeks following a 1-week lead-in period with 10 mg). Lisinopril had no effects on urinary ANP excretion while omapatrilat significantly increased ANP excretion by 42.6 ± 2.6 ng/24 h. Omapatrilat also significantly increased plasma ANP levels from 54 ± 5.4 at trough to 63 ± 7.2 pg/ml at 4 h. ACE activity was

suppressed by both agents on day 28 at 4-h postdosing (–98 ± 2% substrate hydrolyzed/min for both agents), indicating that hypertensive effects of omapatrilat occur via a non-ACE inhibitory mechanism (39).

Results from a multicenter, randomized, double-blind, parallel-group, 4-week study in 57 salt-sensitive hypertensive patients showed the efficacy of omapatrilat (40 mg) as compared to lisinopril (20 mg) in controlling blood pressure without affecting excretory renal function. Mean 24-h ambulatory blood pressure changes were –15.4/–9.3 and –7.2/5.1 mmHg in the omapatrilat and lisinopril groups, respectively. No changes in renal function were seen with either agent and no hyperkalemia or azotemia were reported (40).

Two randomized, double-blind, lisinopril (20 mg)-controlled trials in 1242 patients with heart failure (NYHA II-IV, left ventricular ejection fraction 28%) showed the long-term safety of omapatrilat (20 mg for 52 weeks; 40 mg for 24 weeks). The combined endpoint of death or hospitalization for worsening heart failure was significantly improved with omapatrilat treatment in both the 24- and 52-week trials. Both agents were well tolerated. A lower incidence of elevated serum creatinine was observed with omapatrilat treatment (5.5 *vs.* 9%), although more cases of hypotension were seen in the omapatrilat group (11 *vs.* 6.5%). Increased incidence of syncope was seen with lisinopril (5.1 *vs.* 1.4%) (41).

The safety, tolerability and efficacy of omapatrilat (titrated to 80 mg) were assessed at 24 weeks as part of a 1-year randomized, comparator (losartan titrated to 100 mg) trial examining left ventricular hypertrophy (LVH) regression in 341 subjects with mild to moderate hypertension and LVH. Subjects receiving omapatrilat displayed significantly greater mean reductions in diastolic (–12.9 mmHg) and systolic (–26.2 mmHg) blood pressure as compared to those receiving losartan (–8.4 and –17.2 mmHg, respectively). Similar discontinuations due to adverse events were seen in both treatment groups (1.8 *vs.* 2.9% in the losartan group) (42).

The beneficial cardiovascular effects and safety of omapatrilat were retained over the long term in a large study. The Omapatrilat Heart Failure Program invoved 1242 patients with NYHA class II-IV heart failure and ejection fraction of 28%. Patients were randomized to treatment for 24 or 52 weeks with omapatrilat (40 and 20 mg, respectively) or lisinopril (20 mg in both studies) in a double-blind fashion. In both the 24- and the 52-week trial, omapatrilat improved the combined endpoint of death or hospitalization for worsening heart failure; in a pooled analysis, this reduction reached a level of statistical significance. Both active drugs were well tolerated, and the incidence of serious adverse events (renal dysfunction, elevated creatinine levels) was lower with omapatrilat than with lisinopril. Hypotension was more frequent with omapatrilat, while syncope occurred in a greater number of patients on lisinopril (43).

A randomized, double-blind, placebo-controlled, multicenter study in 278 patients with hypertension (seDBP = 95-110 mmHg) reported neurohormonal changes indicating marked vasopeptidase inhibition with omapatrilat treatment (starting with 10 mg [schedule A] or 20 mg [schedule B] for 8 weeks with elective titration at week 2 and 4 to 40 and 80 mg, respectively). Results from analysis of 73 patients showed significant changes in plasma ACE activity (–70% and –62% with schedule A and B, respectively, *vs.* -3% in placebo), plasma renin activity (425% and 480% *vs.* 11%), mean urinary (362% and 452% *vs.* 5%) and plasma (46% and 39% *vs.* 19%) ANP levels and mean urinary aldosterone levels (–40% and –42% *vs.* –10%) as compared to placebo. Trough seated systolic BP/DBP was decreased by 18.5/12.7 mmHg and 1.5/13.7 mmHg in groups receiving schedules A and B, respectively, as compared to 6/5.7 mmHg in placebo (44).

A study examining the disposition and safety of omapatrilat (10 mg/d for 8-9 days) in 30 subjects with either normal, mild to moderate or severe renal impairment or on hemodialysis concluded no dose adjustments are required in subjects with reduced renal function or on hemodialysis. The t_{max} values for omapatrilat (1.5-2 h) and its metabolites phenylmercaptopropionic acid (2-3 h), *S*-methylomapatrilat (2.5-3.5 h) and *S*-methylphenylmercaptopropionic acid (7-10 h) were unaffected by renal function. Minimal accumulation of omapatrilat and phenylmercaptopropionic acid and moderate accumulation of the *S*-methylated metabolites were seen in all subjects (45).

Patient enrollment in the ongoing OCTAVE (Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril) hypertension study was completed in January of this year. Approximately 25,000 people will be randomized to a specific arm of the OCTAVE study. OCTAVE compares the efficacy and safety of omapatrilat to enalapril. Pending positive results from an OCTAVE data analysis anticipated in mid-2001, Bristol-Myers Squibb expects to refile an NDA with the FDA for omapatrilat for the treatment of hypertension (46).

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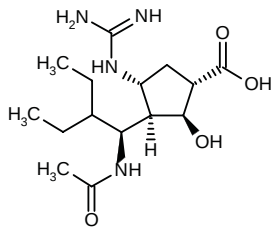
RWJ-270201
BCX-1812

Anti-Influenza
Neuraminidase Inhibitor

EN: 273549

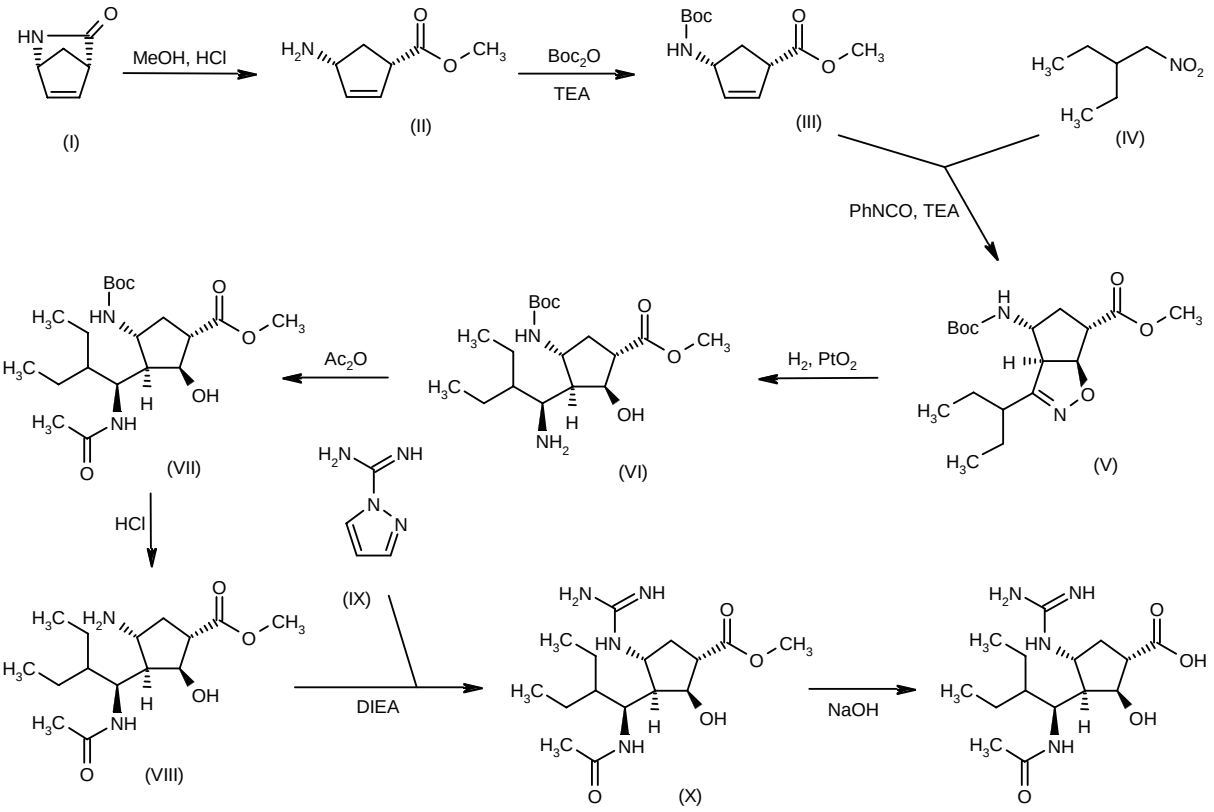


$C_{15}H_{28}N_4O_4$

BioCryst; R.W. Johnson; Ortho-McNeil

The stereospecific synthesis of RWJ-270201 has been reported: Ring opening of (–)-2-azabicyclo-[2.2.1]hept-5-en-3-one (I) with methanolic HCl gives the methyl ester (II), which is *N*-protected with Boc_2O and TEA to yield the carbamate (III). Cyclization of (III) with 2-ethyl-1-nitrobutane (IV) by means of phenyl isocyanate and TEA affords the bicyclic compound (V) and other isomers. Compound (V) is isolated from the mixture and then hydrogenated with H_2 over PtO_2 in MeOH and a catalytic amount of HCl to provide the amine (VI). Reaction of (VI) with acetic anhydride gives the acetamide (VII), which is Boc-deprotected with ethereal HCl to yield the amine (VIII). The guanylation of (VIII) with pyrazolecarboxamidine hydrochloride (IX) and DIEA affords the guanidino derivative (X), which is finally hydrolyzed with NaOH to the desired (1*S*,2*S*,3*R*,4*R*,1'*S*)-diastereomer (1). Scheme 3.

Scheme 3: Synthesis of RWJ-270201



The *in vitro* and *in vivo* efficacy of RWJ-270201 was examined against all neuraminidase (NA) subtypes (N1-N9) of avian influenza viruses. The agent inhibited viral replication in MDCK cells with an EC_{50} value of 3-13.5 μM and the NA activity IC_{50} values obtained were 5-10 nM. Balb/c mice treated for 5 days with RWJ-270201 (1 and 10 mg/kg/day by oral lavage b.i.d.) were protected from lethal challenges with A/Hong Kong/156/97 (HSN) and A/quail/Hong Kong/G1/97 (H9N2). Treatment with the agent decreased viral titers in lungs and blocked the spread of the virus into the brain (2).

A study showed that resistance development to RWJ-270201 is due to mutations in hemagglutinin (HA) and/or neuraminidase (NA). The study examined resistance development of A/Shangdong/09/93 (H3N2) and A/Singapore/1/57 (H2N2) after 10 passages through cells *in vitro* and their virulence in mice. Resistance of the A/Shangdong virus was due to only 1 amino acid change in HA (Lys189Glu) while the resistant A/Singapore virus was due to mutations in both HA and NA. Both resistant viruses were > 3000-fold more resistant to RWJ-270201 than the wild-type viruses *in vitro*. The A/Shangdong virus was more than 50-fold less virulent to mice than the wild-type virus. Treatment of mice infected with the wild-type A/Shangdong virus with RWJ-270201 did not result in recovery of drug-resistant viruses from the lungs (3).

The inhibition of neuraminidases by RWJ-270201 was examined *in vitro* and compared to inhibition by zanamivir and GS-4071 in a study using purified neuraminidase, hemagglutinin-neuraminidase complex (HANA) and whole influenza A and B strain viruses. RWJ-270201 displayed competitive inhibition with the substrate (2'-(4-methylumbelliferyl)-α-D-*N*-acetylneuraminic acid) for HANA from B/Lee/40 strain. Median IC_{50} and IC_{90} values for 9 influenza A strains were 0.2 and 1 nM for RWJ-270201, respectively, 0.8 and 5.5 nM for zanamivir, respectively, and 0.2 and 2.3 nM for GS-4071, respectively. The agents were less effective against the 4 influenza B strains tested with respective IC_{50} and IC_{90} values of 1 and 20 nM for RWJ-270201, 1.6 and 22 nM for zanamivir and 9 and 150 nM for GS-4071 (4).

An *in vitro* study has reported emergence of a mutant influenza A virus from A/Singapore/1/57 virus passaged in the presence of increasing concentrations (up to 1 mM) of RWJ-270201. The RWJ-270201 IC_{50} values against the mutant virus were unchanged as compared to the wild-type strain after the 5th and 11th passages, indicating no change in the active site of the neuraminidase

enzyme. However, after 15 passages in the presence of RWJ-270201, the IC_{50} value for the agent against the mutant strain was 300 μM as compared to < 1 nM for the wild-type strain. The IC_{50} values for GG-167 and GS-4071 were also increased 10- to 20-fold and 5000-fold, respectively. The mutant virus was found to have changes in residues in the active site (Arg 292 → Lys) and in the hemagglutinin receptor site (Gly 130 → Asp) (5).

The *in vivo* efficacy of RWJ-270201 (1-100 mg/kg/day p.o.) was examined in mice infected with influenza A/NWS/33 (H1N1), A/Bayern/07/95 (H1N1), A/Shangdong/09/93 (H3N2), A/Victoria/3/75 (H3N2), B/Hong Kong/05/72 or B/Lee/40. All doses given up to 60 h postinfection significantly prevented or increased the mean day to death, attenuated the decrease in arterial oxygen saturation, inhibited lung consolidation and decreased lung titers. RWJ-270201 showed efficacy at least equal to that of oseltamivir. In addition, treatment of mice and rats with up to 3000 mg/kg was well tolerated with no adverse effects seen with 1000 mg/kg/day given to rats for up to 5 days (6).

The efficacy of RWJ-270201 (1-10 mg/kg every 8, 12 or 24 h) was shown in a study using A/Shangdong/09/93 (H3N2)-infected BALB/c mice. RWJ-270201 significantly and dose-dependently reduced the time to death assessed using a Cox Proportional Hazards model. Schedule had no significant effects. It was concluded that once-daily dosing would be effective in humans (7).

The results from a double-blind, randomized, placebo-controlled trial in 90 subjects with experimental influenza A/Texas/36/91 infection were reported. Subjects received placebo or RWJ-270201 at doses of 100, 200 or 400 mg once daily or 200 mg b.i.d. for 5 days starting 24 h after nasal inoculation. Dose-dependent virological efficacy was seen for daily doses of 100-400 mg RWJ-270201 in infected subjects, the dose of 400 mg once daily being associated with highly significant reduction in viral AUC, peak titers and viral shedding; mean viral titers in this group decreased during the first 12 h of the study, nearing zero within 48 h. A slight but nonsignificant reduction in composite symptom scores was seen for RWJ-270201, but significantly fewer RWJ-270201-treated subjects had fever (3% *vs.* 25% on placebo). Adverse events were similar on RWJ-270201 and placebo (8).

Results from 2 randomized, double-blind, placebo-controlled studies conducted in 90 and 56 healthy subjects inoculated with human influenza A or B viruses, respectively, showed the efficacy and tolerability of oral RWJ-270201 (100, 200 or 400 mg once-daily, 200 mg b.i.d., 800 mg followed by 400 mg once daily or 800 mg once daily). Treatment with the agent began 24 h following nasal inoculation and continued for 5 days. Dose-dependent antiviral effects were observed with treatment. Treatment with 400 mg once daily, 800 mg loading dose + 400 mg once daily or 800 mg once daily significantly decreased viral AUC values by 73, 49 and 61%, respectively, as compared to placebo. Symptom scores only tended to be lower in the RWJ-270201-treated group as compared to placebo due to the minimal illness observed in both groups. Incidence of adverse events was similar for both groups (28 *vs.* 44% and 33 *vs.* 37% in the first and second study, respectively) (9).

A double-blind, randomized, placebo-controlled study in 90 volunteers experimentally infected with influenza A/Texas/36/91 (H1N1) compared drug exposure with time to viral clearance (TVC) following multiple dosing with RWJ-270201 (100, 200, 400 mg/day or 200 mg every 12 h p.o. for 5 days starting 24 h after nasal inoculation). Results from the 70 evaluable subjects showed that TVC was not affected by the RWJ-270201 dosing schedules. TVC values for 50% of the population were 78.5, 70, 64.5, 63 and 85.5 h for the respective doses and placebo. TVC was significantly influenced by baseline viral titer and peak and trough RWJ-270201 concentrations and AUC values (10).

R.W. Johnson has reported that it will not initiate the anticipated North American phase III clinical trial of RWJ-270201 (formerly known as BCX-1812) during the current flu season. RWJ-270201, an influenza neuraminidase inhibitor for the treatment and prevention of viral influenza, is licensed to R.W. Johnson and Ortho-McNeil, both Johnson & Johnson companies, by BioCryst. In recent discussions with the FDA, additional monitoring requirements were requested that would require amending the study protocol for the phase III trial. In order to respond to these requests, a delay in the commencement of the trial would impact R.W. Johnson's ability to enroll sufficient numbers of influenza patients during this influenza season. However, phase III studies with RWJ-270201 in Europe are ongoing (11).

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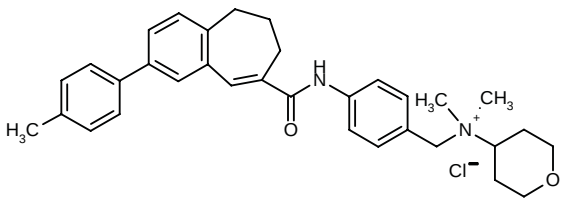
TAK-779

Anti-HIV
Chemokine CCR5 Antagonist

EN: 275823



$C_{33}H_{39}ClN_2O_2$ **Takeda**

A new large-scaleable synthesis of TAK-779 has been developed: The reduction of 4'-methylbiphenyl-4-carbonitrile (I) with sodium bis(2-methoxyethoxy)aluminum hydride (SBMEA) in THF gives the corresponding aldehyde (II), which is submitted to a Wittig condensation with the phosphonium bromide (III) by means of NaOMe in methanol to yield the pentenoic acid derivative (IV). Reduction of the double bond of (IV) with H_2 over Pd/C in THF, followed by cyclization with hot PPA, affords the benzocycloheptanone (V), which is treated with refluxing dimethyl carbonate and NaOMe to provide the β-ketoester (VI). The reduction of (VI) with $NaBH_4$ in THF gives the hydroxyester (VII), which is dehydrated with Ms-Cl and DBU and hydrolyzed with NaOH to yield 8-(4-methylphenyl)benzocyclohept-1-ene-2-carboxylic acid (VIII). Condensation of (VIII) with 4-aminobenzyl alcohol (IX) by means of $(COCl)_2$ and TEA in THF affords the corresponding amide (X), which is treated with $SOCl_2$ in THF to provide the chloromethyl derivative (XI). Finally, this compound is condensed with 4-(dimethylamino)tetrahydropyran (XII) in hot DMF to furnish the target ammonium salt. The tertiary amine (XII) has been obtained by reductive condensation of tetrahydropyran-4-one (XIII) with dimethylamine by means of H_2 over Pd/C in THF (1). Scheme 4.

A study has reported the 3-dimensional structure of the HIV-1 coreceptor CCR5 using the 3-dimensional structure of frog rhodopsin as a template and has described its interaction with TAK-779. Results showed that the binding pocket of the receptor occurred in transmembrane helices 3, 5, 6 and 7 and is composed of the following conserved or varied residues: Tyr108, Gly111, Ser114, Glu283, Gly286, Cys20, Thr105, Leu107, Phe112, Gly115, Lys197 and Met287. The active center of TAK-779 was determined to be O1, N7, N17 and O19, with the pyran cycle and aminium group of the agent interacting with the binding pocket residues of the CCR5 receptor; the remaining portion of TAK-779 interacted with the extracellular loops of CCR5 (2).

A study examined the *in vitro* sensitivity of primary HIV-1 subtype C viruses (isolated from 9 acutely infected individuals and 18 AIDS patients) to anti-CCR5 agents including TAK-779 (1 and 5 μM), RANTES (0.1 and 0.5 μg/ml) and the monoclonal antibody, PA14/PRO (33 and 168 nM). All 3 agents inhibited 20 R5 isolates by 100%. Two R5 and four R5X4 isolates were inhibited by less than 80% with the lower concentrations and by 100% with the high concentrations of the agents. One R5X4 isolate was not affected by any of the agents. Additional results showed that 5/6 isolates from acutely infected individuals were inhibited with serum antibodies from subtype B infected individuals (3).

TAK-779 was shown to have potent antiviral activity *in vitro* in a study using a newly established CCR5-expressing T-lymphoblastoid cell line (MOLT-4/CCR5) infected with R5 HIV-1. The cell line is highly susceptible to R5 HIV-1 with syncytium formation and production of high levels of HIV-1 p24 antigen observed in cells infected with Ba-L and JR-FL strains of R5 HIV-1. Progeny viruses produced by cells were shown to be R5 HIV-1 following analysis of coreceptor use and identification of gp120V3 nucleotide sequence. In contrast, the parent cell line MOLT-4 was less susceptible to Ba-L and resistant to JR-FL (4).

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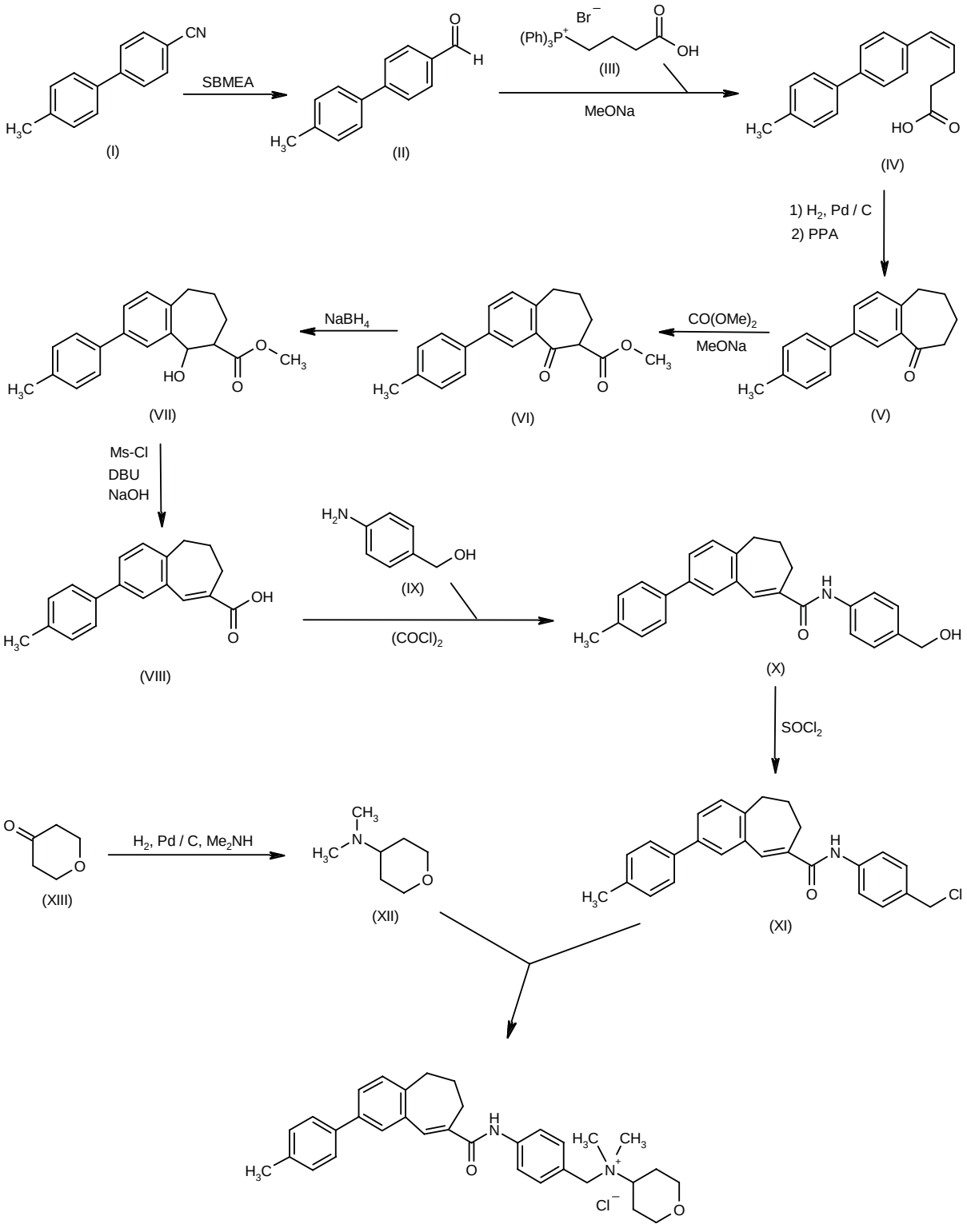
Scheme 4: Synthesis of TAK-779



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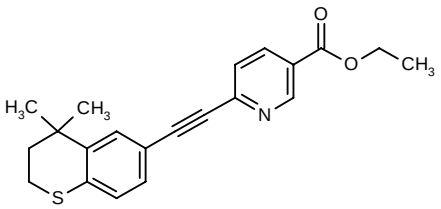
Tazarotene *Antipsoriatic*
Zorac® *Antiacne*
Tazorac®

EN: 145711



$C_{21}H_{21}NO_2S$ **Allergan; Pierre Fabre; 3M Pharm.; Bioglan**

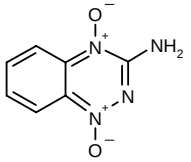
Allergan has received FDA approval to market Tazorac® (tazarotene) cream 0.05% and 0.1% for the treatment of plaque psoriasis (1).

1. *FDA approves cream formulation of Allergan's Tazorac.* DailyDrugNews.com (Daily Essentials) Oct 4, 2000.

Original monograph - Drugs Fut 1997, 22: 249.

Tirapazamine *Oncolytic*
Tirazone®

EN: 125078



$C_7H_6N_4O_2$ **Sanofi-Synthélabo; SRI**

A new metabolite of tirapazamine has been characterized. It results from bioreductive metabolism and its structure was identified using independent chemical synthesis, NMR spectroscopy and X-ray crystallography (1).

Results from a phase I trial in 25 pediatric patients with solid tumors refractory to conventional therapy showed that the maximum tolerated dose of tirapazamine in combination with cyclophosphamide (1500 mg/m^2) with MESNA was 325 mg/m^2 (30-min infusion) once every 3 weeks. The dose-limiting toxicity was any grade 3 or 4 nonhematological toxicity or an ANC of < 500/µl or a platelet count of < 50,000/µl for more than 7 days. One patient developed prolonged neutropenia at 420 mg/m^2 and was not evaluable for toxicity. Three others developed grade III reversible ototoxicity at this dose. A complete response of 12+ months was seen in 1 patient with neuroblastoma and 2 partial responses of 3 and 11 months were seen in patients with neuroblastoma and rhabdomyosarcoma, respectively. Four patients had stable disease (2).

A randomized phase II trial in 47 patients with stage IV head and neck squamous cell carcinoma showed the tolerability of adding tirapazamine to induction chemotherapy (300-330 mg/m^2 day 1 and 22) including cisplatin (100 mg/m^2 days 1 and 22) and fluorouracil (10000 mg/m^2/day continuous infusion on days 1-5 and days 22-26) and to simultaneous chemoradiotherapy (160-260 mg/m^2 days 43, 45, 47, 71, 73 and 75) including cisplatin (20 mg/m^2 days 43, 45, 47, 71, 73 and 75) and fluorouracil (600 mg/m^2/day 96-h continuous infusion on days 43-46 and 71-74). The toxicity profile observed when tirapazamine was added was similar to that seen with the same treatment regimen without tirapazamine. Evaluation of the 20 patients available for toxicity showed that granulocytopenia was the most common toxicity seen during induction therapy. Grade 3 or 4 granulocytopenia was seen in 8/16 and 4/4 patients treated with 300 and 390 mg/m^2 tirapazamine, respectively; grade 3 granulocytopenia was seen during chemoradiotherapy in 1/4, 3/12 and 2/4 patients receiving 160, 220 and 290 mg/m^2 tirapazamine, respectively. Mucositis (9 cases of grade 3 and 2 cases of grade 2) was the most frequent toxicity seen during chemoradiotherapy. Mild toxicities included skin reactions, weight loss, fatigue, muscle cramps and tinnitus. It was concluded that tirapazamine can be added to induction therapy (300 mg/m^2) and simultaneous chemoradiotherapy (220 mg/m^2), both involving cisplatin and fluorouracil (3).

The efficacy and safety of tirapazamine (159 or 260 mg/m^2 i.v. 3 times/week for 12 treatments) combined with radiation therapy (60 Gy in 2-Gy fractions) were examined in a phase II, single-arm, open-label trial in 124 patients with glioblastoma multiforme. Tirapazamine did not provide any survival advantages. The median time to survival was 10.8 months in patients given 159 mg/m^2 and 9.5 months in patients given 260 mg/m^2. Survival of patients according to classes assigned after recursive partitioning analysis was 27.4, 10.8, 7.9 and 3.8 months for class III, IV, V and VI, respectively, for patients given

159 mg/m^2 and 16.2, 10.3, 5.1 and 1.3 months, respectively, for patients given 260 mg/m^2. When compared to historical controls, results showed that class III patients given 159 mg/m^2 combined with radiation tended to survive longer although statistical significance was not reached. Grade 3 and 4 toxicities were more frequent with the higher dose level (4).

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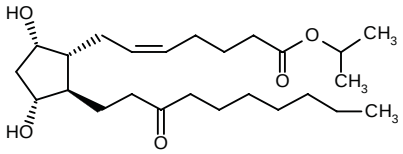
Unoprostone Isopropyl Ester Rescula®

Antiglaucoma

EN: 157908



$C_{25}H_{44}O_5$ **Ueno; Novartis Ophthalmics; Fujisawa**

The U.S. market launch of Rescula® (unoprostone isopropyl ester ophthalmic solution, 0.15%) for the treatment of open-angle glaucoma or ocular hypertension was announced by Ciba Vision, the eye care unit of Novartis, in October 2000. Rescula® is the only ocular therapy available that is a docosanoid, synthetic or naturally occurring metabolite of the 22-carbon essential fatty acids, and has proven to consistently and safely lower intraocular pressure when used as monotherapy or in combination with other drugs. Rescula® at a concentration of 0.12% is currently marketed in over 25 countries. It was licensed from Ueno Fine Chemicals (1).

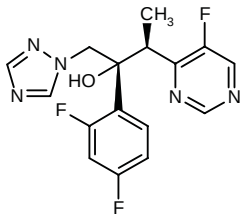
1. *October launch for Rescula, a new docosanoid for glaucoma, in U.S.* DailyDrugNews.com (Daily Essentials) Nov 3, 2000.

Original monograph - Drugs Fut 1992, 17: 193.

Voriconazole Vfend®

Antifungal

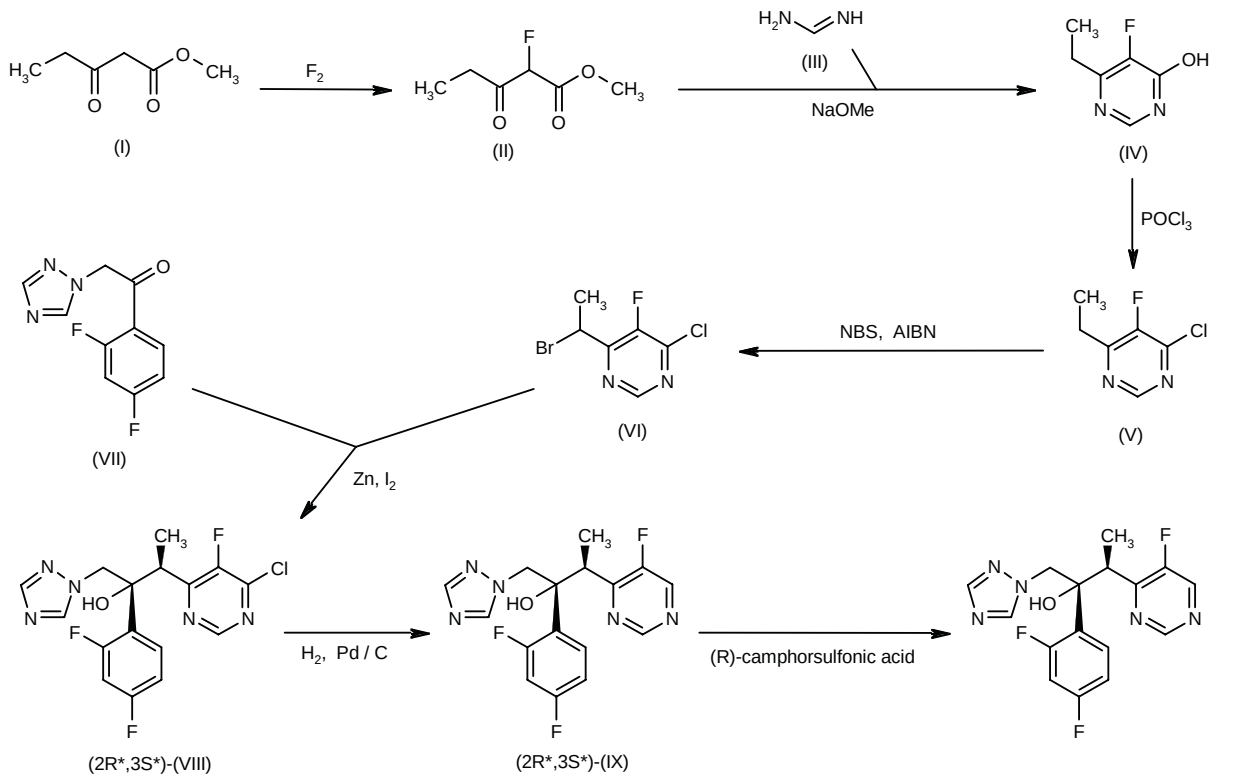
EN: 179738



$C_{16}H_{14}F_3N_5O$ **Pfizer**

A study directed to the selection and development of the preferred commercial route to voriconazole has been reported: The fluorination of 3-oxopentanoic acid methyl ester with F_2 gas gives 2-fluoro-3-oxopentanoic acid methyl ester (II), which is cyclized with formamidine (III) by means of NaOMe to yield 6-ethyl-5-fluoropyrimidin-4-ol (IV). Reaction of (IV) with $POCl_3$ and TEA in dichloromethane affords 4-chloro-6-ethyl-5-fluoropyrimidine (V), which is brominated with NBS and AIBN in dichloromethane to provide 6-(1-bromoethyl)-4-chloro-5-fluoropy-

Scheme 5: Synthesis of Voriconazole



rimidine (VI). Compound (VI) is condensed with 1-(2,4-difluorophenyl)-2-(1,2,4-triazol-1-yl)ethanone (VII) by means of I_2 and Zn in THF to furnish a mixture of the diastereomeric racemates (2*R**,3*R**)- and (2*R**,3*S**)-3-(6-chloro-5-fluoro-4-pyrimidinyl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (VIII) in a 1:10.3 molar ratio. The reductive dechlorination of (2*R**,3*S**)-(VIII) with H_2 over Pd/C gives the (2*R**,3*S**)-racemate (IX), which is submitted to optical resolution by means of crystallization with (1*R*)-10-camphorsulfonic acid (1). Scheme 5.

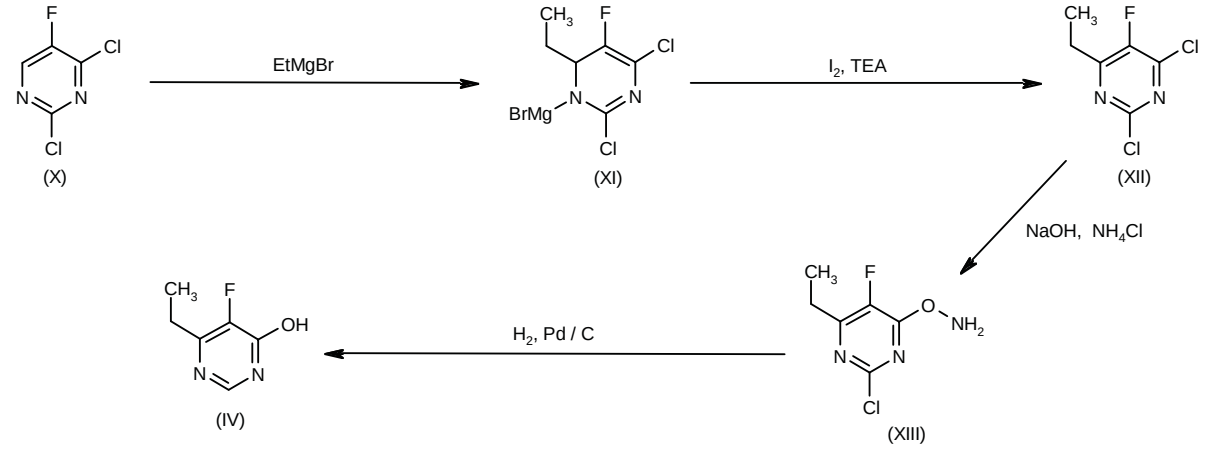
Alternatively, 6-ethyl-5-fluoropyrimidin-4-ol (IV) can be obtained by reaction of 2,4-dichloro-5-fluoropyrimidine (X) with ethylmagnesium bromide in THF to give the dihydropyrimidine derivative (XI), which is aromatized by reaction with I_2 and TEA in THF to yield 2,4-dichloro-6-ethyl-5-fluoropyrimidine (XII). The reaction of (XII) with NaOH and NH_4Cl affords the aminooxy derivative (XIII), which is finally submitted to a reductive dechlorination and deamination with H_2 over Pd/C in ethanol/water (1). Scheme 6.

The *in vitro* activities of voriconazole, itraconazole and fluconazole were compared against 58 *Candida* species isolated from ICU, oncology and surgical ward patients and transplant recipients. Of all bloodstream infections, 56.8% were due to *C. albicans*, 1.7% to *C. tropicalis*, *C. glabrata*, *C. parapsilosis*, *C. famata*, *C. pelliculosa* and *C. pulcherrima* and 3.4% to *Clavispora lusitaniae*. The MIC values for voriconazole against *C. glabrata* strains were 0.01-0.25 μg/ml (2).

The antifungal activity of voriconazole was examined *in vitro* against 300 vaginal yeast isolates from HIV-infected Ugandan patients and compared to activities of clotrimazole, fluconazole, miconazole and nystatin. All agents were effective against all the *C. albicans* isolates (83% of all isolates) with the lowest MIC obtained for voriconazole (< 0.06-1 μg/ml). MIC_{90} values for clotrimazole, fluconazole, miconazole, nystatin and voriconazole against *C. albicans* were 0.25, 1, 0.125, 2 and 0.125 μg/ml, respectively. Variable susceptible was seen with *C. glabrata* (7%), *C. tropicalis* (3%), *C. krusei* (1%) and *C. lipolytica* (0.6%), although voriconazole showed low MICs for all strains (3).

A study examined the *in vitro* activity of voriconazole against 205 *C. albicans* and *C. krusei* isolates including fluconazole-resistant strains (3 *C. albicans* and 26 *C. krusei*) and compared it to the activities of amphotericin B, 5-flucytosine, itraconazole, ketoconazole and fluconazole. While only 1 fluconazole-resistant *C. krusei* strain was relatively resistant to voriconazole (MIC = 5 mg/l), 28 resistant strains were susceptible to ≤ 2.5 mg/l voriconazole (mean MIC = 0.78 mg/l); the mean MIC for amphotericin B for these strains was 0.98 mg/l. All of the 10 amphotericin-resistant *C. krusei* strains (MIC > 2 mg/l) identified were susceptible to ≤ 2.5 mg/l voriconazole (4).

Scheme 6: Synthesis of Intermediate (IV) of Voriconazole



The *in vitro* activity of voriconazole was compared to itraconazole, SCH-56592, terbinafine, amphotericin B and 5-fluorocytosine (5-FC) against 40 clinical zygomycetes strains including *Rhizopus* spp., *Mucor* spp., *Absidia* spp., *Rhizomucor* spp., *Cunninghamella* spp. and *Apophysomyces elegans*. All strains were resistant to 5-FC and the MIC values obtained for voriconazole for all strains were high (2-64 μg/ml). The MICs for amphotericin B against *Cunninghamella* spp. and *A. elegans* were ≥ 2 mcg/ml. *Rhizopus* spp. were less susceptible than *Absidia* spp. and *Mucor* spp. to itraconazole, SCH-56592, terbinafine and amphotericin (5).

An *in vitro* study examined and compared the activity of voriconazole and fluconazole against a total of 317 *Candida* isolates, including *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. krusei*, *C. tropicalis* and *C. guilliermondii*. In contrast to fluconazole which had MIC_{50} values between 2 and > 64 μg/ml against about one-third of the isolates, all but 1 isolate of *C. glabrata* were inhibited by concentrations of < 0.03-1 μg/ml voriconazole; the one strain had an MIC_{50} of 2-8 μg/ml (6).

An *in vitro* study examined the time-kill methods of voriconazole (0.0625-16 times the MIC) against several fungal species including fluconazole-susceptible and -resistant *Candida* species and *Cryptococcus neoformans*. The EC_{50} and EC_{90} values were reported at 8, 12 and 24 h after exposure to the agent and showed that a concentration of about 3 times the MIC resulted in maximum activity at each time point. Since the EC_{50} and EC_{90} values did not change with time, it was concluded that the agent produced concentration-independent pharmacodynamics *in vitro* (7).

The *in vitro* activities of voriconazole, ketoconazole, itraconazole and terbinafine were shown against 55 strains of 7 species of *Malassezia* (authentic or ex-type). Strains of *M. furfur*, *M. sympodialis*, *M. slooffiae*, *M. pachydermatis*, *M. globosa*, *M. obtusa* and *M. restricta* were the most susceptible to ketoconazole and itraconazole (MIC values of ≤ 0.03-0.125 μg/ml). The MIC values for voriconazole were 0.063 μg/ml for 80% of all strains. *M. furfur*, *M. globosa* and *M. obtusa* strains showed the least susceptibility to terbinafine while *M. sympodialis* was very susceptible (8).

An *in vitro* study examined the interaction of voriconazole with multidrug transporters from *C. albicans* and several cytochrome P450 (CYP) mutants. Expression of the ABC-transporters CDRa and CDR2 and the major facilitators CaMDR1 and FLU1 conferred resistance to voriconazole and fluconazole in *Saccharomyces cerevisiae* and *C. albicans* deletion mutants of these genes showed increased susceptibility. Different affinities for azoles (fluconazole, itraconazole) were observed in *S. cerevisiae* expressing mutant CYP51A1; similar results were obtained with fluconazole and voriconazole (9).

The *in vitro* activity of voriconazole was compared to posaconazole, ravuconazole, FK-463, fluconazole, itraconazole and amphotericin B against 73 invasive fungemic yeasts (including *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *C. krusei*) isolated from cancer patients. The most active agent was ravuconazole. $MIC_{50/90}$ values (mg/l) for voriconazole, posaconazole, ravuconazole and FK-463 were 0.38/> 8, 1/> 8, 0.25/> 8 and 0.38/1, respectively, against fluconazole and/or itraconazole resistant strains (10).

A study in mice examined the effect of grapefruit juice (once daily by gavage or continuous as a drinking water substitute) on serum voriconazole (once daily) levels. Serum voriconazole levels in mice treated with voriconazole alone were < 3 μg/ml at all time points in contrast to levels of 0.4-2.6 and 1.8-5.8 μg/ml seen in mice also administered grapefruit juice by gavage or in drinking water, respectively. Serum voriconazole levels were

found to increase over the 10-day period in mice receiving grapefruit juice (11).

The activity of voriconazole was examined in a study using an immunosuppressed guinea pig model of invasive aspergillosis. The agent was more effective in clearing tissular *Aspergillus* as compared to amphotericin B or itraconazole. Treatment with voriconazole also significantly improved survival (12).

The activities of voriconazole and amphotericin B were examined in guinea pigs infected with a susceptible isolate of *Aspergillus fumigatus*. Significantly better survival and decreased lung fungal burden were observed in voriconazole-treated animals as compared to controls. No significant differences were observed between treatment groups although a trend toward better activity was seen with voriconazole (13).

A randomized, double-blind, placebo-controlled, 2-way crossover study in 17 healthy males showed that coadministration of voriconazole potentiated the warfarin-induced prolongation of prothrombin time. Subjects received voriconazole (300 mg b.i.d. p.o.) or placebo for 12 days with a single dose (30 mg) of warfarin on day 7; a washout period of a minimum of 7 days was included between dosing periods. The area under the time-effect curve (AUEC) value for prothrombin time during voriconazole and placebo dosing periods were 3211 and 2282 sec.h, respectively. The maximum increase in prothrombin time from baseline with coadministration of voriconazole was 16.6 s as compared to 8.4 s during the placebo period. The C_{max}, AUC_{τ} and t_{max} for voriconazole were 3736 ng/ml, 25733 ng·h/ml and 1.7 h, respectively (14).

The pharmacokinetic profile of voriconazole was reported. The agent was well absorbed after oral dosing with maximum plasma concentrations seen 1-2 h post-dosing; bioavailability was > 80%. Systemic exposure to the agent decreased by 22% during multiple dosing in the fed state, indicating that the agent should not be taken within 1 h of food intake. The pharmacokinetics of voriconazole following multiple i.v. (3 mg/kg b.i.d.) and oral (200 mg b.i.d.) dosing were nonlinear. The mean terminal $t_{1/2}$ was about 6 h and steady state with both routes of dosing was reached within 6 days. The agent was widely distributed through body fluids (volume of distribution = 2 l/kg). The agent was metabolized extensively into 1 major and other minor metabolites and elimination was predominantly via metabolic clearance. Results from *in vitro* studies using human liver microsomes showed that voriconazole was metabolized by the cytochrome P-450 isoenzymes CYP2C9, CYP3A4 and CYP2C19, and thus may inhibit the activity of these isoenzymes (15).

A double-blind, placebo-controlled trial conducted in 12 healthy males examined whether voriconazole (200 mg b.i.d. or 250 mg once daily on days 4-33) affected prednisolone (60 mg/day on days 1 and 24) disposition. C_{max} and AUC_{τ} values for voriconazole were not significantly different on days 13, 23 and 33. Voriconazole reached steady state after day 5. The mean AUC for prednisolone significantly increased in the presence of steady-state voriconazole. A 13 and 24% increase was seen with 250 mg once daily and 200 mg b.i.d. dosing, respectively (16).

Results from a randomized, double-blind, placebo-controlled, parallel-group study conducted in 25 healthy male volunteers showed that voriconazole (200 mg b.i.d. on days 11-22) did not affect the pharmacokinetics of oral digoxin (0.5 and 0.25 mg b.i.d. on days 1 and 2, respectively, and 0.25 mg once daily on days 3-22). The C_{max}, AUC_{τ}, t_{max} and renal clearance were not significantly affected by concomitant administration of the two agents (17).

Results from 2 randomized, placebo-controlled trials conducted in healthy males found no significant drug interactions between voriconazole and indinavir. The first study was open with parallel groups in which 18 subjects received voriconazole (200 mg b.i.d) on days 1-17 and either indinavir (800 mg t.i.d.) or placebo on days 8-17. The second study was a double-blind crossover trial in which 16 subjects were given indinavir with voriconazole or placebo for 7 days. The pharmacokinetics of indinavir and voriconazole were not affected by coadministration (18).

Results from 2 single-blind, placebo-controlled trials on the pharmacokinetics of voriconazole were presented. In the first study, 12 healthy volunteers were administered placebo or voriconazole 3 mg/kg i.v. once daily on days 1 and 12 and b.i.d. on days 3-11, and in the second study 18 subjects received placebo or voriconazole as a loading dose of 6 mg/kg b.i.d. on day 1 followed by 3 mg/kg b.i.d. on days 2-10. Steady-state trough concentrations of voriconazole (800 ng/ml) exceeded the MIC_{90} values for most fungal pathogens. Pharmacokinetics were dose-dependent and the use of a loading dose resulted in earlier achievement of steady state; in the second study steady state was reached within 48 h compared to about 6 days in the first study (19).

A study determined the efficacy of voriconazole as a treatment for patients with either chronic granulomatous disease (CGD; 22 patients) or those undergoing solid organ (lungs and liver the most common) transplant (SOT; 58 patients) who were involved in phase II and III and compassionate-use trials. Most of the patients had failed or could not tolerate previous antifungal treatment. Patients received i.v. loading doses of 6 mg/kg every 12 h followed by a maintenance dose of 4 mg/kg every 12 h; patients were switched from i.v. to oral dosing (200 or 100 mg b.i.d. if over or under 40 kg, respectively) when possible. Seventeen of the CGD patients had aspergillosis and 5 had infections due to other fungi. Of all the CGD patients, 54.5% had success on voriconazole, 13.6% discontinued due to intolerance and 31.9% failed. Out of the SOT population, 70% had aspergillosis and 12% had invasive *Candida* infections; 71% of the patients with aspergillosis and 39% with candidiasis had complete or partial success. Voriconazole was well tolerated with a reversible increase in liver function tests, skin rash and transient visual disturbances the most common adverse events (20).

Results from 2 open, randomized, placebo-controlled, parallel-group studies conducted in a total of 48 healthy males (18-45 years) showed that phenytoin (300 mg once daily days 8-28) decreased plasma voriconazole levels. However, an increase in voriconazole dosing from 200 to 400 mg b.i.d. compensated for the decreases in C_{max} and AUC_{τ} observed during coadministration. In the first study subjects received voriconazole on day 1 (400 mg b.i.d.), days 1-7 and 8-14 (200 mg b.i.d.) and on days 22-28 (400 b.i.d.) and phenytoin (300 mg once daily) on days 8-28. In the second study, subjects were given voriconazole (400 mg b.i.d.) or placebo on days 8-17 and a loading dose of phenytoin on days 1 and 300 mg once daily on days 2-17. Both studies showed that phenytoin decreased the C_{max} and AUC_{τ} of voriconazole with no effects on t_{max} (21).

The efficacies of oral voriconazole (200 mg b.i.d.) and fluconazole (400 mg on day 1 followed by 200 mg/day) for 2-6 weeks against esophageal candidiasis were shown from results of a multicenter, randomized, double-blind trial conducted in around 400 immunocompromised adult patients (all patients except 23 had AIDS). The success rates for voriconazole and fluconazole were 98.3 and 95%, respectively. Adverse events were seen in 79.5 and 73.5% of the patients in the voriconazole and fluconazole groups, respectively. Mild and reversible abnormal vision was the most common voriconazole-related adverse event (15.5%). Discontinuation rates due to lack of clinical response were 2 and 2.6% for the voriconazole and fluconazole groups, respectively (22).

The efficacy and safety of voriconazole (6 mg/kg i.v. every 12 h on day 1 followed by 4 mg/kg i.v. every 12 h) were shown in a compassionate-use trial conducted in 72 children (1-15 years) with invasive fungal infections. When possible, i.v. dosing was switched to oral dosing (100 or 200 mg b.i.d. for < 40 and ≥ 40 kg, respectively). Fungal infections were probable or definite in 63 cases and included 44 cases of aspergillosis, 8 cases of scedosporiosis, 5 cases of invasive candidiasis and 6 other fungal infections. Of these 63 patients, 60 were immunocompromised, with 27 and 14 suffering from hematological malignancies and chronic granulomatous disease (CGD), respectively. Mean duration of voriconazole treatment was 93 days. At the end of treatment, 11 and 16 patients had complete and partial responses, respectively. Thirty-six patients discontinued due to failure (25 patients), stable disease (5 patients) or intolerance (6 patients). Success rates were highest in patients with CGD (57%) and lowest in patients with hematological malignancies (25%). The incidence of serious adverse events was similar in children as in adults (1.36 *vs.* 1.15/patient). Serious treatment-related adverse events were seen in 2 patients and included ulcerated lips with rash and increased liver function tests. Other adverse events related to voriconazole treatment were skin rash (8 cases), increased liver function tests (5 cases), blurred vision (2 cases), vomiting (1 case), hypokalemia (1 case) and labile blood pressure (1 case) (23).

A multicenter, randomized trial involving a total of 837 patients with hematological malignancies (leukemia, lymphoma or myeloma) compared the efficacy of voriconazole with liposomal amphotericin B as a treatment of persistently febrile neutropenia. Mean duration of therapy with voriconazole and amphotericin B was 11 and 10 days, respectively. The overall success rates for the 2 agents were similar (26 and 31%, respectively). Significantly fewer probable and definite breakthrough fungal infections were seen in the group treated with voriconazole (1.9 *vs.* 5%). Survival rates (87 and 90%), resolution of fever during neutropenia (33 and 36%) and discontinuations due to toxicity or lack of efficacy (13 and 10%) were similar for both treatment groups. Significantly fewer cases of infusion-related reactions such as chest pain (0.2 *vs.* 4%), back pain (0 *vs.* 3%), flank pain (0.2 *vs.* 2%), dyspnea (0.2 *vs.* 7.7%) and anaphylactic reactions (0 *vs.* 1.6%) were seen with voriconazole. Although incidence of nephrotoxicity (11 *vs.* 19%) was significantly less in the voriconazole group, hepatotoxicity was similar for both groups (10 and 12%). The voriconazole-treated group had more cases of transient visual changes (24 *vs.* 1%) and hallucinations (4.3 *vs.* 0.5%) (24).

The efficacy of voriconazole was shown in an AIDS patient with multidrug resistant oral *C. glabrata* infection. The infection was resistant to ketoconazole, fluconazole, itraconazole, miconazole and nystatin and treatment with amphotericin B (i.v. 4 days/week) for 7 months regressed but did not eliminate the infection. When switched to voriconazole (200 mg b.i.d.) while also on rifabutin, lesions only slightly regressed. However, a dose of 300 mg (b.i.d.) eliminated oral candidiasis. The voriconazole dose could be reduced to 200 mg b.i.d. after stopping rifabutin (25).

A study analyzed the results from 59 patients involved in voriconazole clinical studies and compassionate-use trials to determine the efficacy of voriconazole against invasive infections caused by rare or resistant fungus (*C. neoformans*, *Fusarium solani*, *Trichosporon* spp., *Paecilomyces lilacinus*, *Histoplasma capsulatum*). Patients received voriconazole as 2 i.v. loading doses (6 mg/kg every 12 h or 400 mg b.i.d.) and maintenance dosing (4 mg/kg every 12 h or 200 or 100 mg b.i.d p.o. if over or under 40 kg, respectively); patients were switched from i.v. to oral dosing after 3 days if possible. Of the 59 patients, 8 received primary voriconazole treatment, of whom 3 had success and 5 failed, and 51 received salvage therapy, of whom 21 had success and 30 failed. Subjects were also classified according to underlying condition: of the 13 patients with AIDS/HIV, 3 had success and 10 failed; of the 13 patients with hematologic malignancy, 5 had success and 8 failed; of the 7 patients with drug- or other disease-induced immunosuppression, 4 had success and 3 failed; of the solid organ posttransplant patients, 2 had success and 3 failed; for all others, 6 had success and 4 failed. Hematological risk factors were seen in 15 of the 59 patients. Success was seen in 17 of the 44 patients who did not have hematological risk factors (26).

During the year 2001, Pfizer plans to file an NDA for voriconazole (Vfend®) for the treatment of serious fungal

infections. Vfend is designed to treat life-threatening fungal infections such as invasive aspergillosis, resistant candidiasis, as well as brain and eye infections (27).

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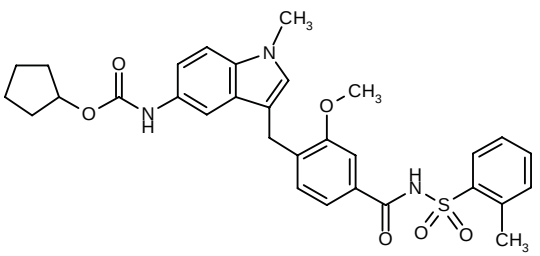

$C_{31}H_{33}N_3O_6S$ **AstraZeneca**

AstraZeneca has revised the "Precautions" and "Adverse Reactions" sections in the labeling for zafirlukast (Accolate®). Details on the principal changes are available from the FDA Web Site (1).

AstraZeneca expects approval shortly for zafirlukast in Japan. The drug is currently available in 73 countries (2).

1. *AstraZeneca posts important revisions to Accolate label.* DailyDrugNews.com (Daily Essentials) Sept 21, 2000.

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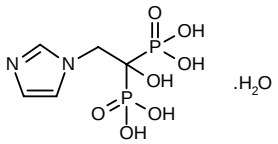

$C_5H_{10}N_2O_7P_2.H_2O$ **Novartis**

The effects of short-term zoledronate exposure (100 mM for 2, 6, 24 or 72 h) alone or in combination with tamoxifen (0.01 or 0.1 mM) or paclitaxel (2 nM) were examined in MCF7 breast cancer cells *in vitro*. Significant increases in apoptotic cells were observed following 2 and 6 h treatment with zoledronate. Treatment with zoledronate (10 mM) + paclitaxel resulted in additive effects since the number of apoptotic cells increased by 2-fold as compared to treatment with either agent alone. An even further increase in apoptotic cells (more than 2-fold) was observed following zoledronate + tamoxifen treatment, indicating synergistic effects (1).

Zoledronate has shown antiangiogenic activity in 2 preclinical models, suggesting that the agent may provide additional benefits in the treatment of cancer. Cultured human umbilical vein endothelial cell (HUVEC) proliferation induced by serum, bFGF or VEGF was dose-dependently inhibited by the agent with IC_{50} values of 4, 4 and 7 μM, respectively; pamidronate showed no significant effect in this model. Zoledronate (1-10 μM) also dose-dependently suppressed HUVEC migration and was found to induce several features of apoptosis. In addition, the agent (1-100 μg/kg/day s.c. for 5 days) dose-dependently suppressed bFGF-induced angiogenic responses as measured by blood content (IC_{50} = 4 μg/kg) and tissue weight around the implant (IC_{50} = 5 μg/kg) in a growth factor implant model; significant inhibition was observed with doses of 10 and 100 μg/kg. VEGF-induced

antiangiogenic responses were inhibited by 100 μg/kg zoledronate. Antiangiogenic activity in this model was also observed with pamidronate only at 10-fold higher doses (2).

An *in vivo* study using rabbits with carrageenan (1% x 10 articular injections over 49 days)-induced inflammatory arthritis showed the efficacy of zoledronate (3 μg/kg/day s.c. from days 1, 14 or 28 of arthritis) in preserving bone integrity. The posterior cortical wall of the distal femoral metaphysis was significantly less thick in nonarthritic normal controls and zoledronate-treated rabbits as compared to untreated arthritic animals. Cross-sectional area was similar in all groups (3).

A study in calcitriol (0.251 μg/day/mouse for 3 days)-induced hypercalcemic C3H/HeJ mice showed that zoledronate pretreatment (10 μg/kg on day −1) significantly reduced hypercalcemia. At 24 and 48 h after the final dose of calcitriol, serum calcium levels were significantly reduced in zoledronate-treated animals to 14.7 ± 0.9 and 13.4 ± 0.9 mg/dl, respectively, as compared to 17.2 ± 1.1 and 16.5 ± 1.1 mg/dl, respectively, in controls. Animals treated with the agent also exhibited decreased dehydration, piloerection and cachexia (4).

A study using BALB/c-nu/nu mice implanted with human MDA-231 breast cancer cells showed that zoledronate (0.2, 1 and 5 μg/mouse s.c. on days 23-32 post-transplantation) markedly inhibited tumor-induced osteolysis. The agent significantly reduced lesion area by more than 80% as compared to ibandronate (1 μg/mouse s.c. on days 23-32) or aldendronate (10 μg/mouse s.c. days 23-32) which showed no significant effect. Treatment with zoledronate (1 and 5 μg) and ibandronate (1 μg) significantly reduced osteoclast number/mm^2 in cancellous bone to almost 90%. In addition, zoledronate (0.3 μg/day) decreased bone metastases in a murine model inoculated with 4T1 murine mammary cancer cells (into the mammary foot pad); marked decreases in metastases observed on day 28 were produced with a zoledronate dose of 5 μg/mouse (i.v. for 7 days postinoculation). It was concluded that zoledronate may slow osteolysis and suppress tumor growth (5).

A study using DBA-1 mice showed that treatment with zoledronate (10 μg/kg s.c. once/week for 4 weeks) or SDZ-PTS-893 (50 μg/kg s.c. 5 times/week) starting 6 weeks after ovariectomy restored trabecular architecture. Tibial, femoral and lumbar vertebral bone volume fractions were significantly increased with both agents and treatment also resulted in changes in Tb.N, Tb.Th, Tb.Sp and BS/BV. The effects of SDZ-PTS-893 were partially lost during a 4-week recovery period after treatment, suggesting that the drug's effects were reversible and continuous treatment is required (6).

A study using dogs with uncemented titanium femoral prosthesis and a cemented acetabular cup as a model of aseptic loosening of hip implants, showed that zoledronate (2 or 10 μg/kg s.c. once/week) treatment significantly increased the mechanical properties of bone (*i.e.*, elastic modulus and bending stress of longitudinal femur strips) and increased periosteal new bone formation. More pronounced effects were observed with the higher dose (7).

The population pharmacokinetics of zoledronic acid as a single 5-min (2, 4 or 8 mg) or 15-min (2, 8 or 16 mg) i.v. infusion were examined in 2 studies involving a total of 32 cancer patients with bone metastases. Plasma concentrations of the agent were dose proportional. The intersubject variability of total body clearance, clearance and volume of distribution for the central compartment V1 were 61.4 and 33.8% for the two studies, respectively. The population $t_{1/2\alpha}$, $t_{1/2\beta}$ and $t_{1/2\gamma}$ were 0.23, 1.75 and 167 h, respectively. The long $t_{1/2\gamma}$ and high K_{inB}/K_{outB} ratio indicated fast uptake and slow release of the agent from bone. The clearance of the agent was positively correlated to creatinine clearance but not to body weight, body mass index, gender, age or race. Renal clearance for the agent was 82 ± 35% of creatinine clearance (8).

Zoledronic acid entered phase II clinical trials for the treatment of postmenopausal osteoporosis last year (9).

Novartis has received a positive opinion from the Committee for Proprietary Medicinal Products (CPMP) for zoledronic acid (Zometa®) for the treatment of tumor-induced hypercalcemia (TIH). The regulatory application was based on international clinical trials in which the agent was compared to pamidronate, the standard treatment for TIH, and was equally well tolerated. Ongoing trials are evaluating the efficacy of zoledronic acid in treating bone metastases in breast, prostate, lung and other solid tumors and in multiple myeloma. To date, zoledronic acid has been approved in several countries, including Canada, Switzerland, Brazil, Peru, Venezuela, the Dominican Republic, Thailand, Mexico, Latvia and Chile. The FDA granted Novartis an approvable letter and an application seeking approval for the drug in Australia is currently under review (10).

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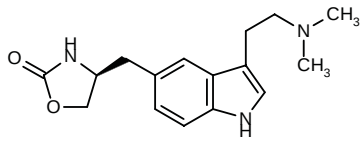

$C_{16}H_{21}N_3O_2$ **AstraZeneca**

A clinical study was performed to compare the peripheral vascular effects of sumatriptan and the second-generation drugs zolmitriptan and rizatriptan in patients with migraine headaches. This trial was a double-blind, placebo-controlled, 4-way crossover study in 16 patients with migraine given equipotent doses of sumatriptan (50 mg), rizatriptan (10 mg), zolmitriptan (2.5 mg) and placebo and evaluated using ultrasonography and applanation tonometry at 1.5 h. The results showed a small increase in mean arterial pressure on all active treatments. Significant decreases in brachial and carotid artery diameter were seen on all active treatments and sumatriptan, rizatriptan and zolmitriptan, particularly the latter, also decreased isobaric compliance of the brachial artery (11, 11 and 23%, respectively). Only zolmitriptan produced a significant decrease in temporal artery diameter (12%), and temporal artery resistance increased following sumatriptan (26%) and zolmitriptan (40%). Flow-induced vasodilatation, a measure of endothelial function, was not affected by the triptans. Overall, these results suggest that selective 5-HT$_{1B/1D}$ receptor agonists produce vasoconstriction and reduce the compliance of conduit arteries, particularly in muscular arteries, whereas the triptans exhibit cranioselectivity for resistance arteries over conduit arteries. It is suggested that both sumatriptan and second-generation triptans should be used with caution in patients at risk for cardiovascular events (1).

Oral doses of 5 and 10 mg zolmitriptan have shown efficacy over placebo in the treatment of cluster headache in a trial involving 124 patients in 3 countries. In this randomized, double-blind, crossover outpatient study, a 5-point scale (none, mild, moderate, severe, very severe) was used to rate the intensity of either episodic or chronic cluster headaches. Only moderate to very severe headaches were treated. In patients with episodic cluster headache, zolmitriptan 10 mg resulted in a 2-point or greater improvement on the pain scale in 47% of patients, whereas the same results were seen in 29% of those on placebo. At 30 min, mild or no pain was reported by 60, 57 and 42% of patients treated with zolmitriptan 10 mg, zolmitriptan 5 mg and placebo, respectively. Both doses

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were well tolerated. In patients with chronic cluster headache, in contrast, neither dose of zolmitriptan was statistically significantly superior to placebo. The researchers concluded that zolmitriptan 5 mg offers an effective treatment of episodic cluster headaches with the advantage of oral administration. They also suggested that a nasal spray formulation, which would provide potentially improved efficacy with lower drug exposure and have a faster onset of action, may be even more effective (2).

AstraZeneca has submitted an NDA to the Japanese authorities for zolmitriptan (Zomig®) for the acute treatment of migraine with or without aura. In a large placebo-controlled dose-response study completed in Japan, zolmitriptan was shown to significantly reduce the severity of migraine headache, with complete resolution of headache in some patients. There was also a reduction in other migraine-associated symptoms such as nausea, vomiting, phonophobia and photophobia. The pharmacokinetics, clinical efficacy and tolerability were very similar to the results obtained in similar Western studies which have already been used to attain approval in over 60 countries (3).

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