Drugs of the Future 1999, 24(10): 1125-1162
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Information Update

Volume 1-23, Number 10

Estimated developmental phase for this month's updated products:

Phase I

T-82 (cognition enhancer, acetylcholinesterase inhibitor, 5-HT_3 antagonist; SSP, Arena)

Phase II

AMD-473 (antineoplastic, platinum complex; Johnson Matthey, AnorMED, AstraZeneca)
Aviptadil (treatment of erectile dysfunction; RTP Pharma)
BMS-181174 (antineoplastic; Bristol-Myers Squibb) (discontinued)
KNI-272 (anti-HIV, HIV protease inhibitor; Japan Energy)
KW-3902 (treatment of renal diseases, adenosine A_1 antagonist; Kyowa Hakko)
Ligustrazine (neuroprotectant; Chinese Univ. Hong Kong, Beijing Med. Univ.)
ML-3000 (antiinflammatory, COX/5-LO inhibitor; Merckle, EuroAlliance)
MX2 (antineoplastic; Kirin Brewery) (discontinued)
OPC-21268 (antihypertensive, treatment of heart failure, vasopressin V_{1A} antagonist; Otsuka)
Peldesine (antineoplastic, anti-HIV, antipsoriatic, PNP inhibitor; BioCryst, Torii)

Phase III

Abarelix (antineoplastic, GnRH antagonist; Praecis, Amgen, Sanofi-Synthélabo)
CP-336156 (treatment of osteoporosis, estrogen receptor modulator; Pfizer, Ligand)
Edaravone (neuroprotectant, antioxidant; Mitsubishi Chem.)
Saruplase (thrombolytic; Grünenthal) (discontinued)
Valspodar (multidrug resistance modulator; Novartis)
Vamicamide (treatment of urinary incontinence; Fujisawa) (discontinued)

Preregistered

Clinafloxacin (quinolone antibacterial; Kyorin, Warner-Lambert)
Ebselen (neuroprotectant; Daiichi Pharm.)
Lidakol® (anti-HSV; Avanir, Yamanouchi, Grelan)
Suramin sodium (antineoplastic, treatment of prostate cancer; Warner-Lambert)

Launched/Year

Alfuzosin hydrochloride (treatment of BPH, α_1-adrenoceptor antagonist; Sanofi-Synthélabo)/1988
Alteplase (thrombolytic; Roche, Genentech)/1987
Bisoprolol fumarate (antihypertensive, antianginal, treatment of heart failure; Merck KGaA)/1989
Bupropion hydrochloride (antiobesity, aid to smoking cessation, antidepressant; Glaxo Wellcome)/1989
Carvedilol (antihypertensive, antianginal, treatment of heart failure; Roche, Daiichi Pharm., SmithKline Beecham)/1991
Cefepime (cephalosporin; Dura, Bristol-Myers Squibb)/1994
Eprosartan (antihypertensive; SmithKline Beecham, Solvay, Unimed)/1997
Fexofenadine hydrochloride (treatment of allergic rhinitis, histamine H_1 antagonist; Sepracor, Hoechst Marion Roussel)/1996
Nevirapine (anti-HIV, Boehringer Ingelheim, Roxane)/1996
Rapacuronium bromide (neuromuscular blocker; Akzo Nobel, Organon)/1999
Riluzole (antiparkinsonian, treatment of ALS; Rhône-Poulenc Rorer)/1996
Rimeloxone (antiinflammatory ophthalmic; Organon, Alcon)/1995
Sirolimus (immunosuppressant, prevention of transplant rejection; Wyeth-Ayerst)/1999
Telmisartan (antihypertensive, angiotensin AT_1 antagonist; Boehringer Ingelheim, Abbott, Glaxo Wellcome)/1999
Trastuzumab (treatment of breast cancer; Genentech, Roche)/1998

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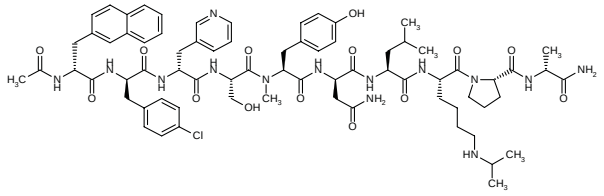
Abarelix
R-3827
PPI-149

Antineoplastic
GnRH Antagonist

EN: 251979



$C_{72}H_{95}ClN_{14}O_{14}$

Praecis; Amgen; Sanofi-Synthélabo

A study evaluating the pharmacology and pharmacokinetics of abarelix depot has shown rapid sustained suppression of testosterone levels for > 28 days in dogs administered the drug as a single s.c. or i.m. dose (1.2-3 mg/kg). Plasma abarelix levels increased on days 3-4 and exponentially declined over the next month. The same dose given at 28-day intervals for 1 year also produced sustained suppression of testosterone; recovery occurred 4-6 weeks after end of treatment with testicular histology indistinguishable from normal dogs within 3 months. A flip/flop pharmacokinetic mechanism was observed in rats administered [^{14}C]-abarelix depot with an elimination rate constant higher than the absorption rate constant; no accumulation was observed in any tissues. Elimination occurred primarily in feces (70%) and urine (30%). Reduced size and morphological regression of gonads and accessory glands were observed in both males and females. The pharmacodynamics and pharmacokinetics obtained indicate safe use of the agent in humans (1).

Results from a phase II study of abarelix depot (100 mg on days 1 and 15 and 50-100 mg every 4 weeks x 12) given to 209 patients with prostate cancer showed that the agent was well tolerated and induced castration without the initial androgen surge observed in the 33 patient cohort receiving Lupron or Zoladex. By week 1, 76% of the patients receiving abarelix were castrate as compared to 0% in the Lupron and Zoladex groups, in which 100% of the patients exhibited a testosterone surge. Similar rates of castration were observed for all groups at the end of 4, 8 and 12 weeks. Of 11 abarelix-treated patients with Stage D2 prostate cancer, 10 had objective responses by week 12 including 1 complete and 2 partial responses and 7 stable and 1 progressive disease (2-4).

The efficacy of abarelix was demonstrated in a study involving 36 patients with prostate cancer administered the agent (50 μg/kg/day s.c. for 4-12 weeks) prior to brachytherapy or radiation therapy. Treatment was well tolerated and median profound prostate gland volume (PGV) reductions of 22% and 35% were observed after 4 weeks and at the end of treatment, respectively; patients with initial PGV of 42 cc achieved 43% reductions by the end of treatment. Immediate androgen ablation was observed in all patients with 50 ng/dl testosterone levels seen in 35/36 patients within 2 weeks and all patients at the end of treatment. Out of 30 patients followed through recovery, 14, 28 and 30 recovered testosterone levels to > 100 ng/dl after 4, 8 and 12 weeks of treatment, respectively (5).

An ongoing first part of a larger phase II trial involving 35 women with endometriosis showed that abarelix depot (60, 90 or 120 mg s.c.) suppressed LH levels to 1 mIU/ml or less by the morning after injection; 5/7 women given 30 mg abarelix showed similar decreases. None of the patients receiving abarelix displayed estradiol flares. In contrast, leuprolide-treated (3.75 mg) patients displayed a rapid increase in LH (15-46 mIU/ml) and estradiol flares (up to 875 pg/ml) on day 8 postdosing. At 4 weeks postdosing, mean estradiol levels in 14/17 abarelix-treated patients were < 30 pg/ml. No adverse events were associated with abarelix (6).

Preliminary results from an ongoing phase II trial evaluating abarelix depot in women with endometriosis have been reported. The efficacy and safety of abarelix depot (30, 60, 90 or 120 mg s.c.) are being compared to those of leuprolide (3.75 mg i.m.) in 40 women with endometriosis and associated pain in this ongoing study. At time of reporting, data on 15 participants were available. Abarelix produced rapid decreases in serum LH, FSH and E_2 levels in 10/10 patients receiving the study drug and was not associated with an initial hormonal flare. Hormone suppression was maintained for up to 8 weeks in the first patient treated for that length of time. All 5 patients treated with leuprolide, in contrast, experienced rapid initial surges in serum LH, FSH and E_2 levels. No adverse events to date have been attributed to abarelix. These results, which demonstrate the safety and efficacy of abarelix in women with endometriosis, indicate that the compound has significant therapeutic potential as well as important advantages over conventional GnRH superagonists (7, 8).

Amgen has entered into a collaboration with Praecis under which the companies will codevelop and Amgen will commercialize abarelix in the U.S., Canada, Australia, Asia and several secondary markets (9).

Abarelix is in phase III European trials as a potential treatment for prostate cancer. The compound is also in clinical testing in the U.S. for the treatment of endometriosis (10, 11).

1. Molineaux, C.J. et al. *Pharmacology and pharmacokinetics of abarelix-depot, a novel, long-acting formulation of the GnRH antagonist abarelix.* Gynecol Endocrinol 1999, 13(Suppl. 1): Abst 016.

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2. Garnick, M.B. et al. *Abarelix-depot (A-D), a sustained-release (SR) formulation of a potent GnRH pure antagonist in patients (pts) with prostate cancer (PrCA): Phase II clinical results and endocrine comparison with superagonists Lupron® (L) and Zoladex® (Z).* 94th Annu Meet Am Urol Assoc (May 1-6, Dallas) 1999, Abst 1312.

3. Garnick, M. et al. *Abarelix-depot (A-D), a potent GnRH pure antagonist in patients (pts) with prostate cancer (PrCA): Initial clinical results and endocrine comparison with superagonists Lupron® (L) and Zoladex® (Z).* Gynecol Endocrinol 1999, 13(Suppl. 1): Abst 080.

4. Garnick, M.B. et al. *Abarelix-depot (A-D), a sustained-release (SR) formulation of a potent GnRH pure antagonist in patients (pts) with prostate cancer (PrCA): Phase II clinical results and endocrine comparison with superagonists Lupron® (L) and Zoladex® (Z).* Proc Amer Soc Clin Oncol 1999, 18: Abst 1233.

5. Garnick, M. et al. *Abarelix, a novel and potent GnRH antagonist, induces a rapid and profound prostate gland volume reduction (PGVR) and androgen suppression before brachytherapy (BT) or radiation therapy (XRT).* Gynecol Endocrinol 1999, 13(Suppl. 1): Abst 081.

6. Martha, P.M. et al. *The pure GnRH antagonist, abarelix-depot, rapidly and safely induces sustained suppression of the pituitary-gonadal axis in reproductive age women.* 81st Annu Meet Endocr Soc (June 12-15, San Diego) 1999, Abst P3-356.

7. Martha, P.M. et al. *Initial safety profile and hormonal dose-response characteristics of the pure GnRH antagonist, abarelix-depot, in women with endometriosis.* Gynecol Endocrinol 1999, 13(Suppl. 1): Abst 103.

8. Martha, P.M. et al. *Abarelix-depot, a potent pure GnRH antagonist, rapidly induced sustained suppression of the pituitary-gonadal axis in women with endometriosis.* Fertil Steril 1999, 71(4, Suppl. 1): Abst O-8.

9. *Amgen and Praecis to develop and commercialize abarelix.* DailyDrugNews.com (Daily Essentials) March 12, 1999.

10. *Synthelabo: Annual Report 1998.* DailyDrugNews.com (Daily Essentials) April 26, 1999.

11. *Synthelabo reports recent events in R&D.* DailyDrugNews.com (Daily Essentials) Jan 26, 1999.

Original monograph - Drugs Fut 1998, 23: 1057.

Additional References

Advis, J.P. et al. *Blockade of a synchronized preovulatory surge of LH by the novel LHRH antagonist abarelix-depot: Plasma LH and in vivo median eminence LHRH, NPY, and b-endorphin release in the ewe.* 80th Annu Meet Endocr Soc (June 24-27, New Orleans) 1998, Abst P3-657.

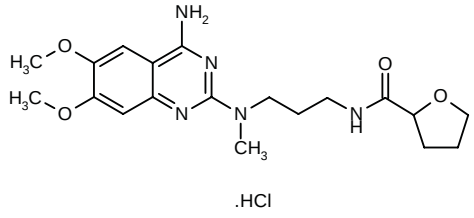
Garnick, M.B. et al. *PSA kinetics: Rates of decline are significantly more rapid following therapy with the GnRH antagonist Abarelix-Depot (A-D), compared to superagonists Lupron®) (L) and Zoladex® (Z) in prostate cancer (PrCA) patients (pts).* 94th Annu Meet Am Urol Assoc (May 1-6, Dallas) 1999, Abst 367.

Alfuzosin Hydrochloride

Treatment of BPH

α_1-Adrenoceptor Antagonist

EN: 090436



.HCl

$C_{19}H_{27}N_5O_4$.HCl

Sanofi-Synthélabo

The registration dossier for once-daily alfuzosin, already marketed in many countries as a twice-daily formulation, was filed in Europe and continues to progress in clinical trials in the U.S. This formulation provides all the advantages of alfuzosin, including its excellent safety profile, while improving compliance and providing a dependable 24-h control of the symptoms of benign prostatic hypertrophy (1).

1. *Synthelabo: Annual Report 1998.* DailyDrugNews.com (Daily Essentials) April 26, 1999.

Original monograph - Drugs Fut 1986, 11: 821.

Alteplase
Activase®

Thrombolytic

EN: 137796

Roche; Genentech

Patients treated with tissue plasminogen activator (t-PA) within 3 h after the onset of acute ischemic stroke have been shown to be 30% more likely to have minimal or no disability at 3 months than patients treated with placebo. The long-term outcomes of 624 patients randomized to t-PA or placebo were assessed using the Barthel Index, the Modified Rankin Scale and the Glasgow Outcome Scale. Treatment effect was determined using a global statistic, which favored the t-PA group at both 6 and 12 months. Nevertheless, significant differences in mortality were not noted between the t-PA and placebo groups. Furthermore, with respect to long-term response, no interaction was observed between the type of stroke identified at baseline and treatment. Recurrent stroke rates at 12 months were similar for the 2 groups. Since these 12-month results were in agreement with the findings at 3 months, it was concluded that t-PA produces a sustained benefit when administered to patients within 3 h after the onset of symptoms of stroke (1).

Alteplase (Activase®) was cleared for marketing by the Therapeutic Products Directorate of Health Canada

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for the treatment of eligible adult patients with acute ischemic stroke or brain attack within 3 h of symptom onset (2).

1. Kwiatkowski, T.G., Libman, R.B., Frankel, M. et al. *Effects of tissue plasminogen activator for acute ischemic stroke at one year.* New Engl J Med 1999, 340(20): 1781.

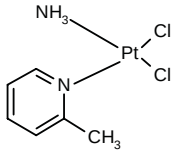
2. *Activase for acute management of stroke approved in Canada.* DailyDrugNews.com (Daily Essentials) Feb 22, 1999.

Original monograph - Drugs Fut 1985, 10: 835.

AMD-473
JM-473
ZD-0473

Antineoplastic
Platinum Complex

EN: 234240



$C_6H_7N.Cl_2Pt.H_3N$ **Johnson Matthey; AnorMED; AstraZeneca**

To date, 22 patients with advanced solid tumors have received 64 courses of therapy in a phase I trial evaluating the safety and pharmacokinetics of ZD-0473 at doses of 12-130 mg/m^2 by 1-h i.v. infusion every 3-4 weeks. At the highest dose, 3/5 patients had grade 3-4 thrombocytopenia, the dose-limiting toxicity, and 2 patients grade 3 neutropenia, whereas at 110 mg/m^2 no grade 3 or 4 hematological toxicity has been noted. ZD-0473 has not been associated with nephrotoxicity, peripheral neurotoxicity or ototoxicity in this trial. Pharmacokinetics appeared to be linear and elimination was triphasic, with half-lives of 0.26, 2.27 and 73.71 h. Plasma AUC was correlated with thrombocytopenia. Although no responses have been achieved, 7 patients have had transient disease stabilization. Further patients are being accrued at 120 mg/m^2 to determine the recommended dose for phase II trials (1).

1. Trigo, J.M., Beale, P., Judson, I.R., Raynaud, F., Ress, C., Milan, D., Wolf, L., Walker, R., Hanwell, J., Giandomenico, C. *Phase I and pharmacokinetic (PK) study of cis-amminedichloro(2-methylpyridine)platinum(II) (ZD0473), a novel sterically hindered platinum complex, in patients (pts) with advanced solid malignancies.* Proc Amer Soc Clin Oncol 1999, 18: Abst 648.

Original monograph - Drugs Fut 1998, 23: 1062.

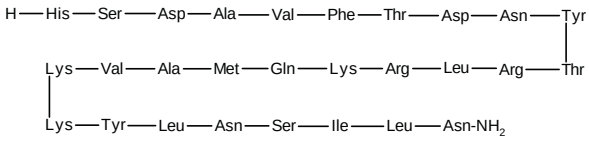
Additional Reference

Leyland-Jones, B. et al. *Genomic imbalances associated with acquired resistance to platinum analogues.* 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 563.

Aviptadil
VIP

Treatment of Erectile Dysfunction

EN: 125580



$C_{147}H_{238}N_{44}O_{42}S$ **RTP Pharma**

A dose assessment study in 304 patients with nonpsychogenic erectile dysfunction (ED) given intracavernosal VIP (25 μg) with phentolamine mesylate (1 or 2 mg) in an autoinjector showed a response rate of 83.9%; 82% of the patients from a subgroup of 183 who had withdrawn from other ED therapies also responded to treatment. In the placebo-controlled phase involving 195 patients, 75.1 and 66.5% responded to VIP with 1 and 2 mg phentolamine mesylate, respectively, as compared to 12 and 10.3% in the respective placebo groups; the median duration of erection was 54 min. Adverse effects included transient facial flushing in 33.9% and only 9 patients withdrew due to side effects. Over 85 and 95% of treated patients were satisfied with treatment and the autoinjector, respectively, and over 81 and 76% of the partners reported improved quality of life (1).

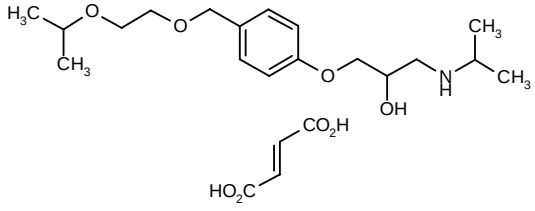
1. Sandhu, D. et al. *A double-blind, placebo controlled study of intracavernosal vasoactive intestinal polypeptide and phentolamine mesylate in a novel auto-injector for the treatment of nonpsychogenic erectile dysfunction.* Int J Impot Res 1999, 11(2): 91.

Original monograph - Drugs Fut 1987, 12: 977.

Bisoprolol Fumarate
Concor®

Antihypertensive
Antianginal
Treatment of Heart Failure

EN: 090488



$C_{18}H_{31}NO_4.C_4H_4O_4$ **Merck KGaA**

The Swedish Medical Products Agency has approved bisoprolol fumarate for the treatment of chronic heart failure (CHF) in addition to standard therapy. Bisoprolol is the first β_1-selective β-blocker to obtain marketing authorization for this new indication. Results of the large-scale, placebo-controlled Cardiac Insufficiency Bisoprolol

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Study (CIBIS II), specifically designed to examine all-cause mortality as the primary endpoint, have unequivocally shown that bisoprolol saves lives and reduces morbidity in CHF. All-cause mortality was reduced by 34%, sudden death by 44% and hospital admissions due to worsening heart failure by 36%. These benefits were achieved in patients already receiving standard treatment with diuretics and ACE inhibitors (1).

1. *Bisoprolol receives first European approval for chronic heart failure.* DailyDrugNews.com (Daily Essentials) June 15, 1999.

Original monograph - Drugs Fut 1986, 11: 829.

Additional References

Dargie, H.J. et al. *The Cardiac Insufficiency Bisoprolol Study II (CIBIS II).* Cardiovasc Drugs Ther 1999, 13(1): Abst 147.

Grollier, G. et al. *Intravenous and subsequent oral bisoprolol in the treatment of acute myocardial infarction.* Therapie 1991, 46(2): 147.

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

López Sendon, J. *Reduction of mortality in heart failure with beta-blockers. Direct evidence in the CIBIS-II study.* 63rd Annu Sci Meet Jpn Circ Soc (March 27-29, Tokyo) 1999.

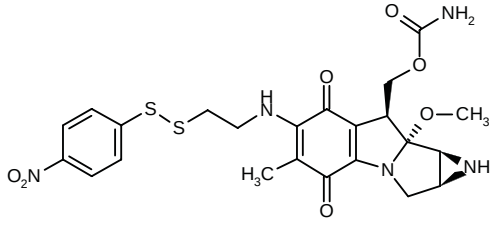
Pousset, F. et al. *Effects of bisoprolol on heart rate variability in heart failure.* Am J Cardiol 1999, 77(8): 612.

Yoshitomi, Y. et al. *Experience of immediate beta blocker bisoprolol therapy following interventional treatment in patients with acute myocardial infarction.* Jpn Pharmacol Ther 1999, 27(6): 222.

BMS-181174

Antineoplastic

EN: 102100



$C_{23}H_{25}N_5O_7S_2$ **Bristol-Myers Squibb**

A phase I study of BMS-181174 (0.8-75 mg/m^2 i.v. every 28 days) in 82 patients with tumors showed that due to toxicities such as pneumonitis and thrombophlebitis, resulting in 3 deaths, and cardiotoxicity and renal impairment, no phase II studies would be conducted with the agent (1).

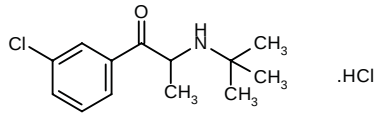
1. Macaulay, V.M. et al. *Phase I study of the mitomycin C analogue BMS-181174.* Br J Cancer 1998, 77(11): 2020.

Original monograph - Drugs Fut 1996, 21: 999.

Bupropion Hydrochloride
Zyban®

Antiobesity
Aid to Smoking Cessation
Antidepressant

EN: 119021



$C_{13}H_{18}ClNO.HCl$ **Glaxo Wellcome**

An *in vitro* study showed that functional blockade of human muscle-type nicotinic acetylcholine receptors in TE671/RD cells and ganglionic nicotinic acetylcholine receptors in SHSY5Y neuroblastoma cells with bupropion, phencyclidine and ibogaine was in the mcM range. Noncompetitive inhibition by each of these agents was demonstrated since the functional blockade was unchanged even after addition of increasing agonist concentrations. Nicotinic acetylcholine receptors, therefore, may be targets of many substances of abuse as well as for agents used in antiaddiction/antismoking therapies (1).

A total of 893 patients were enrolled in a double-blind, placebo-controlled comparison study of sustained-release bupropion hydrochloride, a nicotine patch, a combination of the two or placebo for smoking cessation therapy. Subjects were treated for 9 weeks with bupropion (150 mg/day for 3 days, then 150 mg b.i.d.) or a matching oral placebo plus an active nicotine patch or a placebo patch. The target for smoking cessation was 8 days. The 12-month abstinence rates in subjects randomized to treatment with bupropion, transdermal nicotine, bupropion + nicotine patch and placebo were 30.3%, 16.4%, 35.5% and 15.6%, respectively. Weight gain at 7 weeks was most notable in the placebo group (average of 2.1 kg), followed by the bupropion, nicotine patch and combination treatment groups (1.7, 1.6 and 1.1 kg, respectively). Withdrawals totaled 311 patients from treatment, including 79 dropouts due to adverse events. Insomnia and headache were the most frequently reported side effects. It was concluded that bupropion SR, used with or without a nicotine patch, was more effective than placebo or transdermal nicotine alone in obtaining long-term smoking cessation (2).

Bupropion SR appears to hold added potential as a weight loss treatment, according to the results of an 8-week, randomized, placebo-controlled, double-blind study in 50 obese women who were treated with bupropion SR or placebo in addition to a 1600 kcal/day diet. Drug dosing began at 100 mg/day and was escalated as tolerated to a maximum of 400 mg/day in divided doses. Women treated with bupropion SR showed significantly greater weight loss than those administered placebo (6.21% ± 3.09% *vs.* 1.56% ± 2.95% by completer analysis and 4.86% ± 3.45% *vs.* 1.26% ± 2.36% by intent-to-treat analysis). Among subjects completing the study, those on bupropion SR lost more than 5% of their

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baseline body weight as compared to placebo. A higher percentage of patients in the placebo group withdrew from the study due to dissatisfaction than in the active treatment group (32% *vs.* 4%). Bupropion SR was well tolerated, with dry mouth as the only commonly reported side effect. Patients who responded to the study drug during the 8-week treatment period have continued for up to 6 months, with signs of continued weight loss (3).

Glaxo Wellcome has launched bupropion hydrochloride (Zyban®) SR tablets as an aid to smoking cessation in Canada and has applied for approval in the E.U. (4, 5).

1. Fryer, J.D., Lukas, R.J. *Noncompetitive functional inhibition at diverse, human nicotinic acetylcholine receptor subtypes by bupropion, phencyclidine, and ibogaine.* J Pharmacol Exp Ther 1999, 288(1): 88.

2. Jorenby, D.E., Leischow, S.J., Nides, M.A., Rennard, S.I., Johnston, J.A., Hughes, A.R., Smith, S.S., Muramoto, M.L., Daughton, D.M., Doan, K., Fiori, M.C., Baker, T. *A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation.* New Engl J Med 1999, 340(9): 685.

3. Gadde, K.M. et al. *Bupropion sustained release in obesity: A randomized double-blind, placebo-controlled study.* 152nd Annu Meet Am Psychiatr Assoc (May 15-20, Washington) 1999, Abst NR634.

4. *Canadian launch announced for Zyban sustained-release tablets.* DailyDrugNews.com (Daily Essentials) Aug 21, 1998.

5. *Glaxo Wellcome seeks approval for Zyban in the E.U.* DailyDrugNews.com (Daily Essentials) March 4, 1999.

Original monograph - Drugs Fut 1978, 3: 723.

Additional References

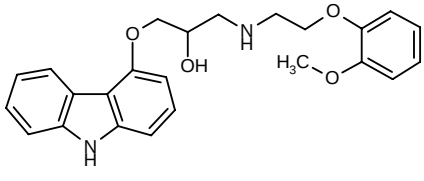
Bradley, P.S. et al. *Bupropion SR with phentermine for weight reduction.* 152nd Annu Meet Am Psychiatr Assoc (May 15-20, Washington) 1999, Abst NR587.

Hayford, K.E. et al. *Efficacy of bupropion for smoking cessation in smokers with a former history of major depression or alcoholism.* Br J Psychiatry 1999, 174: 173.

Carvedilol
Coreg®
Eucardic®

Antihypertensive
Antianginal
Treatment of Heart Failure

EN: 090701



$C_{24}H_{26}N_2O_4$

Roche; Daiichi Pharm.; SmithKline Beecham

U.K. regulatory authorities have expanded the indications of carvedilol (Eucardic®) to include the treatment of chronic heart failure. Two new lower dose strengths of carvedilol have been introduced for the heart failure indication, which specifies that the compound must be given in combination with standard therapy such as ACE inhibitors, diuretics or digitoxin (1).

Roche announced that the company has recovered marketing rights for carvedilol in most markets outside the U.S. In the U.S., Roche and SmithKline Beecham will continue to copromote carvedilol under the trade name Coreg® for the treatment of hypertension and congestive heart failure (2).

1. *CHF treatment now available in the U.K.* DailyDrugNews.com (Daily Essentials) Sept 11, 1998.

2. *Roche recovers marketing rights for β-blocker in most markets.* DailyDrugNews.com (Daily Essentials) Feb 15, 1999.

Original monograph - Drugs Fut 1983, 8: 841.

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Behn, F. et al. *Carvedilol in children with congestive heart failure - Pharmacokinetic parameters.* Naunyn-Schmied Arch Pharmacol 1999, 359(3, Suppl.): Abst 507.

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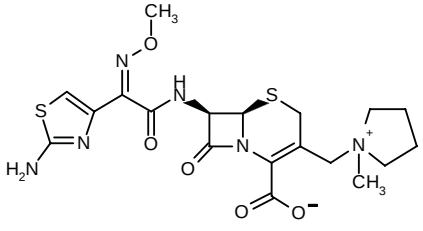
Cefepime Maxipime®

Cephalosporin

EN: 090491



$C_{19}H_{24}N_6O_5S_2$ **Dura; Bristol-Myers Squibb**

Dura and Bristol-Myers Squibb received approval from the U.S. FDA for cefepime hydrochloride (Maxipime®) for injection for use in pediatric patients aged 2 months to 16 years. The usual recommended daily dose in pediatric patients weighing up to 40 kg is 50 mg/kg administered twice daily for 7-10 days, depending on the infection treated and the severity of the infection. In clinical trials, the safety of cefepime in pediatric patients was similar to that seen in adults. The compound is contraindicated for patients who have shown hypersensitivity reactions to cefepime or the cephalosporin class of antibiotics, penicillins or other β-lactam antibiotics. The most common adverse events are local reactions, including phlebitis, pain and/or inflammation and rash. At the higher dose of 50 mg/kg every 8 h, the most common adverse events are rash, diarrhea, nausea, vomiting, pruritis, fever and headache (1).

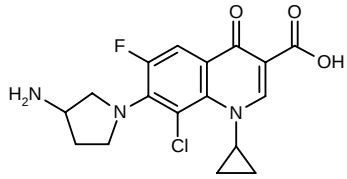
1. *Pediatric use of Maxipime approved by the FDA.* DailyDrugNews.com (Daily Essentials) Feb 3, 1999.

Original monograph - Drugs Fut 1985, 10: 805.

Clinafloxacin

Quinolone Antibacterial

EN: 127085



$C_{17}H_{17}ClFN_3O_3$ **Kyorin; Warner-Lambert**

Clinafloxacin was shown to have comparable activity against 354 Gram-negative nonfermenters, *Enterobacteriaceae*, streptococci and staphylococci as ciprofloxacin, levofloxacin, sparfloxacin, trovafloxacin, piperacillin, piperacillin/tazobactam, trimethoprim-sulfamethoxazole, ceftazidime and imipenem; 143 ciprofloxacin-susceptible (MIC = 1.0 mg/l), -intermediate (2.0 mg/l) and -resistant strains were included. Clinafloxacin showed the lowest MICs (≤ 0.5 mg/l) of all the quinolones against ciprofloxacin-susceptible, -intermediate and -resistant Gram-positive and Gram-negative strains (MIC = ≤ 16 mg/l). Synergy of clinafloxacin with the other agents against 44 Gram-negative and Gram-positive bacteria was also observed with lower MICs obtained as compared to the agent alone (1 mg/ml). Synergism was observed with ceftazidime, amikacin and imipenem against *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia, Acinetobacter* spp, *Burkholderia cepacia*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Citrobacter freundii*, *Serratia marcescens*, *Providencia stuartii* and *Morganella morganii*. Synergism was also observed with vancomycin, teicoplanin and cefotaxime against Gram-positive methicillin-resistant *Staphylococcus aureus*, *Enterococcus faecalis* and *E. faecium* and with vancomycin, penicillin G, cefotaxime and Synercid against pneumococci (1).

Although similar activities of sparfloxacin (0.5 μg), moxifloxacin (0.5 μg) and clinafloxacin (1.0 μg) were demonstrated *in vitro* against 20 strains of *Mycobacterium tuberculosis*, agent activity differed *in vivo* using a murine tuberculosis model. Whereas clinafloxacin (up to 100 mg/kg 6 times weekly) had no effect, dose-dependent bactericidal activity was observed with sparfloxacin and moxifloxacin (100 mg/kg 6 times weekly) (2).

Clinafloxacin showed sustained, potent *in vitro* antibacterial activity in a study comparing the agent with ciprofloxacin, trovafloxacin, levofloxacin, ceftazidime, cefepime, gentamicin, vancomycin, imipenem, piperacillin/tazobactam, clindamycin and metronidazole against 2000 recent clinical isolates including ciprofloxacin-resistant strains. Clinafloxacin activity was 8 times more potent than ciprofloxacin against *S. aureus* and more potent than the other quinolones against oxacillin-resistant staphylococci. Trovafloxacin and clinafloxacin activities against pneumococci were similar and 8 times greater than activities of ciprofloxacin and levofloxacin.

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Clinafloxacin and ciprofloxacin had similar activity against *P. aeruginosa*. Clinafloxacin was also active against penicillin-resistant strains; however, none of the agents were active against vancomycin-resistant enterococci. Clinafloxacin and trovafloxacin were the most active against the anaerobic strains followed by metronidazole, imipenem and piperacillin/tazobactam (3).

A study examined the *in vitro* activity of clinafloxacin and 26 other antibacterial agents against 110 clinical isolates of *S. maltophilia* using broth microdilution and agar dilution methods; results were compared with previous studies. Clinafloxacin was shown to have potent activity (MIC_{50} = 0.5 μg/ml) with 89% of the strains susceptible at ≤ 2 μg/ml. The most active treatment was trimethoprim/sulfamethoxazole with 95% of the strains susceptible. Ceftazidime and cefepime were the most potent cephalosporins with 57 and 32% of the strains, respectively, susceptible; aztreonan, aminopenicillin/β-lactamase inhibitors and carbapenems showed no activity. More than 60% of the strains were resistant to aminoglycosides and almost half were resistant to chloramphenicol. A trend toward increasing resistance to ciprofloxacin and norfloxacin was noted (4).

In a pharmacokinetic study, 12 healthy subjects received a single dose of clinafloxacin and interactions with probenecid, cimetidine, phenytoin and warfarin were examined. No adverse effects were reported and all drugs were well tolerated. Probenecid decreased total oral (24%) and renal clearance (36%) of clinafloxacin, showing that the agent was actively secreted into urine and indicating that reductions in the clinafloxacin dose may be necessary. Although cimetidine had no effect on clinafloxacin absorption, total clearance was reduced by 25% due to alterations in renal elimination; clinafloxacin dose adjustments are unnecessary in this case. Steady-state clinafloxacin clearance was increased by 50% after phenytoin administration and phenytoin clearance was reduced by 15% with steady-state clinafloxacin treatment, and therefore clinafloxacin doses should be increased in patients receiving these two agents and phenytoin plasma concentrations monitored during therapy. The *S*-enantiomer of warfarin was unaffected by steady-state clinafloxacin dosing although the *R*-enantiomer concentration was 32% higher; prothrombin times should be monitored and warfarin dose adjustments made in patients receiving these two drugs (5).

Clinafloxacin (200 mg p.o.) was shown to be potentially effective in 15 subjects undergoing bronchoscopy. At 1.27 h postdosing, mean serum, bronchial mucosa, alveolar macrophage and epithelial lining fluid concentrations were 1.54, 2.65, 15.60, and 2.71 mg/l, respectively, all exceeding the MIC_{90} for common respiratory pathogens (6).

A prospective, randomized, double-blind trial has evaluated the efficacy of clinafloxacin (200 mg every 12 h) and imipenem/cilastatin (500 mg every 6 h) in 551 patients with complicated intraabdominal infections. Of 259 patients harboring 1 or more anaerobes, 119 were infected with *Bacteroides fragilis* and 216 of these also harbored facultative or aerobic Gram-negative rods. In the clinafloxacin group, 133/162 patients were treated successfully; in the imipenem/cilastatin group, 137/170 were treated successfully. Treatment failure led to reintervention in 18 and 22 patients in the clinafloxacin and imipenem/cilastatin groups, respectively; in the case of clinafloxacin, identified organisms were primarily *B. fragilis* and other anaerobes, while in the case of the control drug the resistant organisms were enterococci and various facultatives. Photosensitive reactions and hypoglycemia were reported in 4 and 12 patients, respectively, on clinafloxacin; subjects in the control group reported 5 and 3 cases of hypoglycemia and seizures, respectively. The study has served to establish the safety and efficacy of clinafloxacin in the treatment of complicated intraabdominal infections (7).

Analysis of results from 8 multicenter, phase II/III trials in 1544 hospitalized patients with serious infections showed no significant differences in rates of mortality and treatment discontinuation between clinafloxacin-treated patients and comparator groups (ceftazidime, imipenem, ceftazidime/amikacin or pipercillin/tazobactam). Although no difference was observed in the rate of serious adverse events, significantly more clinafloxacin-treated patients reported treatment-related adverse events as compared to the comparator groups (31.9 *vs.* 24.8%); an increased incidence of confusion reactions, phototoxicity, hypoglycemia and liver-related events was seen in patients given clinafloxacin (8).

Results from a multicenter study involving a total of 2104 isolates, including nonfermenting rods, demonstrated the broad spectrum, potent antibacterial activity of clinafloxacin against several clinically important Gram-negative species (9).

A pharamacokinetic study in 16 healthy subjects showed that steady-state phenytoin (300 mg/day) did not affect the steady-state pharmacokinetics of clinafloxacin (200 or 400 mg b.i.d. p.o.). During phenytoin therapy, a slight, clinically insignificant increase (20 and 7% for 200 and 400 mg, respectively) in clinafloxacin clearance was obtained which resulted in an 18 and 10% increase in AUC values for the respective doses of clinafloxacin. It was concluded that no clinafloxacin dose adjustments are required during phenytoin treatment (10).

A multicenter study using Etest strips demonstrated the potent antibacterial activity of clinafloxacin against 1947 Gram-positive bacteria including staphylococci, streptococci and enterococci responsible for serious infection in hospitalized patients. Results showed that 87, 75, 53, 78 and 99% of the isolates were susceptible to clinafloxacin (MIC = ≤ 1 mg/l), trovafloxacin (MIC = ≤ 1 mg/l), ciprofloxacin (MIC = ≤ 1 mg/l), imipenem (MIC = ≤ 4 mg/l) and vancomycin (MIC = ≤ 4 mg/l), respectively (11).

A multicenter study using Etest strips showed the potent antibacterial activity of clinafloxacin against 664 anaerobic bacteria including *B. fragilis*, *Peptostreptococcus* spp., *Clostridium perfringens* and *C. difficile* responsible for serious infection in hospitalized patients. Results

showed that 94, 84, 38, 26 and 94% of the isolates were susceptible to clinafloxacin (MIC = ≤ 1 mg/l), trovafloxacin (MIC = ≤ 1 mg/l), ciprofloxacin (MIC = ≤ 1 mg/l), ceftazidime (MIC = ≤ 8 mg/l) and imipenem (MIC = ≤ 4 mg/l), respectively; vancomycin (MIC = ≤ 4 mg/l) was active against 95% of the Gram-positive anaerobes (12).

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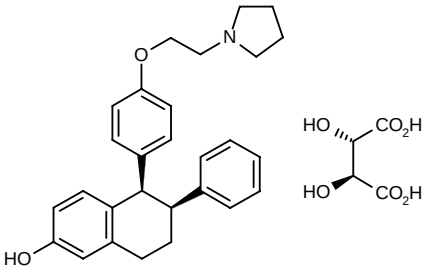
CP-336156

Treatment of Osteoporosis
Estrogen Receptor Modulator

EN: 236902



$C_{28}H_{31}NO_2.C_4H_6O_6$ **Pfizer; Ligand**

In studies in ovariectomized rats, combined treatment with CP-336156 and parathyroid hormone (PTH) restored bone mass and bone strength and added extra cancellous bone to proximal tibiae and distal femora in these animals. CP-336156 enhanced the bone restorative effects of PTH by inhibiting bone resorption more than bone formation. The beneficial effects of combining anabolic agents with SERMs for the treatment of established osteoporosis were thus confirmed (1).

CP-336156 administered at 0.1 mg/kg/day p.o. to ovariectomized rats inhibited bone resorption, prevented further bone loss and preserved bone strength in animals with established osteopenia. The compound also potentiated the bone restorative effects of PGE_2 at 1 mg/kg/day s.c (2).

The effects of CP-336156 were investigated in the adult orchidectomized rat model of male osteoporosis. CP-336156 was found to inhibit bone resorption and bone turnover, prevent bone loss, preserve bone strength and reduce serum cholesterol levels without inducing prostate hypertrophy, suggesting its utility for preventing bone loss in aging males (3).

In animals, CP-336156 exhibited a favorable pharmacokinetic profile, with rapid and extensive absorption following oral administration, moderate to high systemic plasma clearance and a large steady-state volume of distribution, as well as a long elimination half-life. Excellent pharmacokinetics were predicted in humans, with a systemic plasma clearance of about 9 ml/min/kg, a steady-state volume of distribution of 20 l/kg, an elimination half-life of over 24 h and an oral bioavailability of 50-60% (4).

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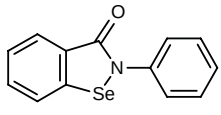
Original monograph - Drugs Fut 1998, 23: 1066.

Ebselen

Neuroprotectant

EN: 090700



$C_{13}H_9NOSe$ **Daiichi Pharm.**

Ebselen was shown to inhibit Ras-mediated transformation of NIH 3T3 fibroblasts *in vitro*. NIH 3T3 cells were transfected with the active pZIP-rasH2 expression construct or carrier DNA (salmon sperm) and incubated in the presence or absence of ebselen (25 μM) for 11-14 days. Ebselen reduced the frequency of transformation by 49.3 ± 2.9% and a 3-fold decrease in active JNK protein levels

was also observed in treated cells. Thus, ebselen may be chemopreventive via disruption of Ras signaling through inhibition of JNK activation (1).

The mechanisms of action of ebselen were investigated in an *in vivo* study with results showing that the agent may be a treatment for T-cell-mediated inflammatory disorders. Ebselen-treated mice (p.o.) were protected from canavalin A-induced liver injury, with upregulation of the antiapoptotic transcription factor NFκB, increased plasma IL-10 levels and downregulation of TNF-α observed. Ebselen-treated galactosamine-sensitive mice were also protected from staphylococcal enterotoxin B-induced liver damage and injury due to recombinant TNF treatment; increased IL-10 levels were observed in both cases. Results suggest that TNF and not CD95 receptor activation results in suppression of apoptosis-inducing proteases (2).

Results from a study in rats demonstrated the neuroprotective effects of ebselen against cerebral ischemia. Animals were treated with the agent (1 mg/ml/kg via gastric tube) 30 min prior to either 20-min occlusion of 4 arteries followed by reperfusion or 120-min occlusion alone. Ischemia-induced metabolic changes were decreased in ebselen-treated animals, including reductions in the lactate to pyruvate ratio and peak concentrations of purine catabolites. The interval of recovery for inosine and hypoxanthine levels was shortened by ebselen treatment in the group subjected to reperfusion (3).

Results from a study in rats showed that ebselen treatment reduced transient cerebral ischemia-induced lesions for at least 1 h with protection maintained for up to 5 days after reperfusion. Rats were administered ebselen (8 mg/kg p.o.) at 1.25, 7 and 19 h after occlusion of the middle cerebral artery and 2 common carotid arteries for 1 h followed by reperfusion for up to 5 days. Cortical and striatal lesions were reduced by 41 and 18% in ebselen-treated animals, respectively. Ebselen treatment also improved ischemia-induced neurological deficit even after 5 days of reperfusion which corresponded to a significant reduction (27%) in global lesions (4).

Ebselen has been shown to have significant cardioprotective effects when administered postocclusion. Ebselen (1 mg/kg i.v. bolus + 1 mg/kg i.v. 60-min infusion or 2 mg/kg i.v. bolus + 4 mg/kg 60-min infusion) or vehicle was administered 5 min before reperfusion in rabbits subjected to 30-min coronary artery occclusion and 48 h of reperfusion. Ebselen dose-dependently reduced infarct size compared to controls. The effect of the low dose was not significant compared to vehicle (infarct size = 36.6 ± 8.2% *vs.* 48.2 ± 6.8%), but high-dose ebselen did produce a significant reduction (22.0 ± 3.9%). Hemodynamic parameters were similar in all three groups. A dose-dependent increase in plasma selenium levels was also observed in the ebselen groups (5).

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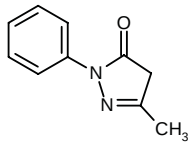
Edaravone

Neuroprotectant
Antioxidant

EN: 129588



$C_{10}H_{10}N_2O$ **Mitsubishi Chem.**

Edaravone was administered to healthy male volunteers as single (0.2, 0.5, 1.0, 1.5 or 2.0 mg/kg i.v.) and multiple (1.0 mg/kg/day x 7) doses, with 7 subjects included at each dose level to determine its safety and pharmacokinetic profile. Edaravone was well tolerated over the range of doses tested, with only isolated reports of increased serum total bilirubin and decreased serum platelet counts. Plasma drug concentrations following a single 40-min i.v. infusion of edaravone (0.2-1.5 mg/kg) peaked 40 min after initiation of the infusion and ranged from 222.53-3060.773 ng/ml. Plasma drug concentrations decreased rapidly thereafter, with $t_{1/2\alpha}$ and $t_{1/2\beta}$ values of 0.15-0.17 h and 1.45 h, respectively, at the lowest doses to 0.17 h and 0.65 h, respectively, at the highest doses. C_{max} and AUC increased in a dose-proportional fashion. When administered as a single 3-h infusion at the dose of 2.0 mg/kg, plasma concentrations of edaravone peaked (1225.96 ng/ml) at 3 h and decreased rapidly thereafter, with $t_{1/2\alpha}$, $t_{1/2\beta}$ and $t_{1/2\gamma}$ of 0.12, 0.65 and 4.38 h, respectively. Edaravone was metabolized rapidly and was excreted in the urine within 24 h after initiation of infusion, with urinary excretion rates remaining nearly constant over a range of doses and infusion times (1).

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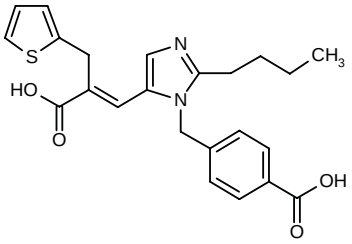
Eprosartan
Teveten®

Antihypertensive

EN: 168384



$C_{23}H_{24}N_2O_4S$ **SmithKline Beecham; Solvay; Unimed**

Unimed, a wholly owned subsidiary of Solvay, has announced that eprosartan (Teveten®) is now available in U.S. pharmacies for the treatment of hypertension of all levels of severity. Teveten® has been shown to be efficacious, well tolerated and to provide effective 24-h control of high blood pressure with once-daily dosing, regardless of age or gender. The drug is already available in Germany, Ireland, Denmark, Finland, Sweden, The Netherlands and Portugal and has been evaluated in more than 3300 patients and healthy volunteers in worldwide clinical trials. Solvay acquired the worldwide rights to market, manufacture and further develop Teveten® from SmithKline Beecham and Unimed will market and further develop the drug in the U.S. A fixed combination of the product with a diuretic is currently in late-stage development (1).

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Kovacs, S.J. et al. *Pharmacokinetics and protein binding of eprosartan in hemodialysis-dependent patients with end-stage renal disease.* Pharmacotherapy 1999, 19(5): 612.

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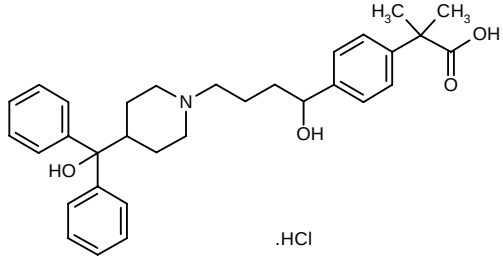
Puig, J.G. et al. *Effect of eprosartan and losartan on uric acid metabolism in patients with essential hypertension.* J Hypertens 1999, 17(7): 1033.

Tenero, D. et al. *Drug interaction studies with eprosartan, a novel angiotensin II receptor antagonist.* 2nd Int Symp Angiotensin II Antagon (Feb 15-18, London) 1999, Abst P.31.

Fexofenadine Hydrochloride
Allegra®

Treatment of Allergic Rhinitis
Histamine H_1 Antagonist

EN: 231566



$C_{32}H_{39}NO_4.HCl$ **Sepracor; Hoechst Marion Roussel**

Fexofenadine has been obtained by two new related ways (1):

1) The Grignard condensation of ethyl 2-(4-formylphenyl)-2-methylpropionate (I) with 2-(1,3-dioxolan-2-yl)ethylmagnesium bromide (II) gives the corresponding carbinol (III), which by a treatment with Amberlyst-15 yields the lactol (IV). The reductocondensation of (IV) with the piperidine derivative (V) by means of $NaBH_4$ in methanol affords the ethyl ester (VI), which is finally hydrolyzed with NaOH.

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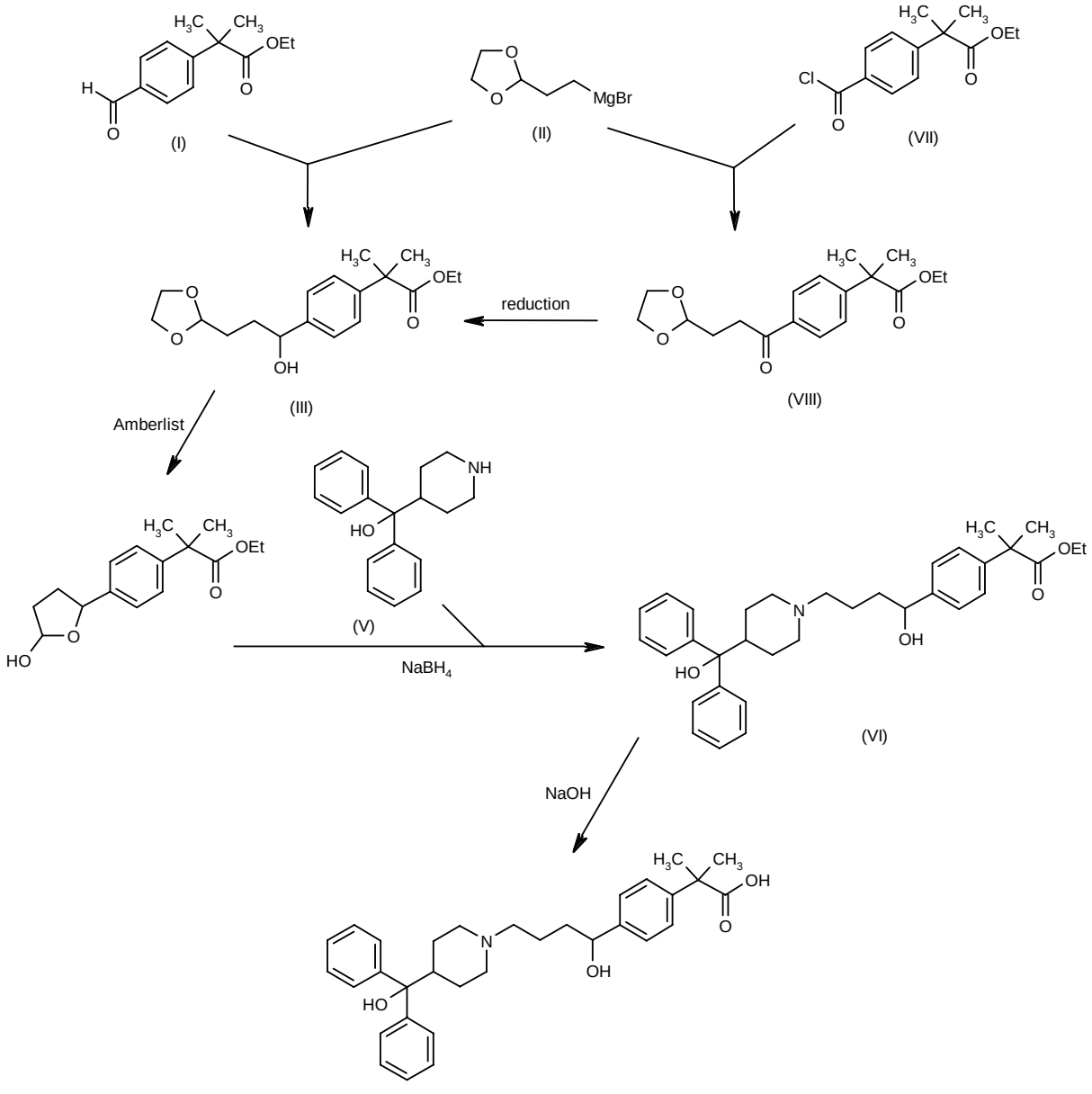
Scheme 1: Synthesis of Fexofenadine



2) The Grignard condensation of ethyl 2-[4-(chloroformyl)phenyl]-2-methylpropionate (VII) with 2-(1,3-dioxolan-2-yl)ethylmagnesium bromide (II) gives the corresponding ketone (VIII), which is reduced to carbinol (III) in the usual way.

3) The (*S*)-enantiomer of fexofenadine can be synthesized through the asymmetric reduction of the prochiral ketone (VIII) with chiral catalysts to afford the (*S*)-enantiomer of carbinol (III). Scheme 1.

The effect of once-daily fexofenadine on quality of life was evaluated in a companion study to a 2-week, double-blind trial. A total of 845 patients with seasonal allergic rhinitis received fexofenadine (120 or 180 mg). All reported significant improvement as compared to placebo. Although results from both doses were similar, the 180 mg group consistently reported better health outcomes (2).

In a multicenter clinical study, 439 patients with moderate to severe pruritus and chronic idiopathic urticaria were treated for 4 weeks with fexofenadine (20, 60, 120 or 240 mg p.o. b.i.d.) or placebo. All 4 doses of the active drug were significantly superior to placebo in terms of daily mean pruritus severity score, daily mean number of wheals and daily mean total symptom score. Patients on

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fexofenadine also reported less interference with sleep and daily activities due to wheals, resulting in improved quality of life. Efficacy in the 3 highest fexofenadine dosing groups was similar, and the incidence of adverse events was similar across all groups. The results of this study indicate that fexofenadine hydrochloride, administered twice daily at doses of 60 mg or higher, is effective and well tolerated in patients with chronic idiopathic urticaria (3, 4).

The safety and tolerability of fexofenadine (15, 30 or 60 mg b.i.d.) were evaluated in 2 double-blind, placebo-controlled studies in 875 pediatric patients with seasonal allergic rhinitis. The incidence of adverse events was not dose-dependent and was similar in all treatment groups, with headache being the most commonly reported event (6.6, 8.0, 7.2 and 9.4% in the placebo, 15, 30 and 60 mg groups, respectively). All laboratory parameters were similar in active and placebo groups (5).

The safety and efficacy of once-daily fexofenadine (60, 120, 180 or 240 mg) was assessed in a 6-week, multicenter, double-blind, placebo-controlled study in 222 patients with chronic idiopathic urticaria. The 180 mg dose was well tolerated and significantly reduced total symptom score as compared to placebo; all doses produced improvements in pruritus scores compared to placebo (6).

Results from two 4-week, placebo-controlled, multicenter trials showed that fexofenadine (60 mg b.i.d.) significantly improved health-related quality of life and work and activity impairment compared to placebo in patients with chronic idiopathic urticaria. The study assessed 169 patients for Dermatology Life Quality and 120 for work and 166 for activity impairment (7).

In a double-blind, placebo-controlled study in 861 patients with moderate to severe seasonal allergic rhinitis, treatment with once-daily fexofenadine (120 or 180 mg) resulted in significant improvement in the mean total symptom scores, with no statistical differences in reductions between the two active groups. Headache occurred in 8.9% and 7.5% of the fexofenadine and placebo groups, respectively, and was the most frequently reported adverse event (8).

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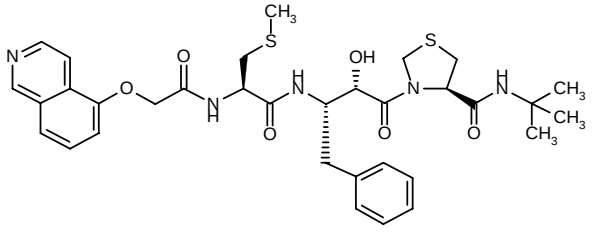
KNI-272

Anti-HIV
HIV Protease Inhibitor

EN: 188524



$C_{33}H_{41}N_5O_6S_2$ **Japan Energy**

A phase I trial has examined the pharmacokinetics, toxicity and activity of oral KNI-272 in patients with AIDS or symptomatic HIV infection. In the preliminary pharmacokinetic phase of the study, patients received 2 or 4 mg/kg i.v. on day 1, a single oral dose of 2 or 4 mg/kg on day 2 in the fasting state, and a single oral dose with food on day 3. In the second phase, patients who successfully completed the first stage without toxicity were

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administered an i.v. dose on day 1, single oral doses on days 2 and 3 to assess pharmacokinetics, and then oral doses every 6 h (8, 16 and 26.4 mg/day) for 12 weeks. The oral bioavailability of KNI-272 capsules ranged from 22-55%, with no significant differences between fasting and fed patients. Elevations in hepatic transaminases were dose-limiting at the 26.4-mg dose, although this could be reduced by escalating the dose over 4 weeks. The maximum tolerated dose with 4-week dose escalation was 40 mg/kg/day. At doses of 26.4 mg and 40 mg, evidence of antiviral activity was noted, with median decreases in plasma HIV RNA of 0.2-0.3 $\log_{10}$ copies/ml which were maintained for up to 8 weeks of treatment. CD4 cell counts showed a tendency to increase only with the highest dose. Overall, these preliminary clinical results demonstrated good oral absorption and plasma levels exceeding the IC_{50} at doses that were generally well tolerated. However, KNI-272 has a narrow therapeutic index and only modest anti-HIV activity (1).

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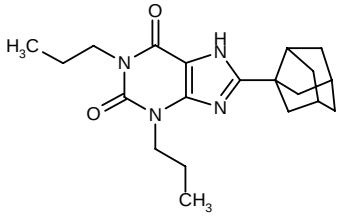
KW-3902

Treatment of Renal Diseases
Adenosine A_1 Antagonist

EN: 170942



$C_{20}H_{28}N_4O_2$ **Kyowa Hakko**

A study in dogs indicated that pretreatment with KW-3902 is effective in preventing ischemia-reperfusion injury to the liver. Two-week survival in dogs administered KW-3902 (1 fg/kg/min by continuous intraportal infusion over 60 min) prior to ischemia was 83.3%, whereas in untreated control dogs it was 25%. Postreperfusion hepatic tissue blood flow improved significantly in the KW-3902-treated group as compared to controls. Furthermore, treatment attenuated liver enzyme release and alterations in adenine nucleotides. cAMP concentrations remained higher during ischemia and reperfusion in the treated group than in controls, and histopathologic examination showed that hepatic architecture was better preserved. Thus, KW-3902 appears to have potential application in the prevention of ischemia-reperfusion injury after liver transplant surgery and during associated surgical procedures (1).

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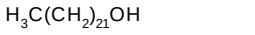
Lidakol®

Anti-HSV

EN: 183153



$C_{22}H_{46}O$ **Avanir; Yamanouchi; Grelan**

The mechanism of action of Lidakol® resulting in cell resistance to herpes simplex viral (HSV) infection was investigated in an *in vitro* study. Results showed that treatment significantly inhibited fusion-dependent dequenching of octadecyl rhodamine B chloride (a fluorescent probe inserted into the HSV envelope), indicating that treatment decreases fusion between the plasma membrane and HSV envelope. Cellular resistance was found to decrease with a $t_{1/2}$ of approximately 3 h following drug removal. Lidakol® treatment of cells resulted in a 70% reduction in expression of a reporter gene inserted into the viral genome, indicating reduction in viral gene expression with treatment. Cells transfected with lacZ gene exhibited a 75% decrease in β-galactosidase production with Lidakol® treatment, suggesting that the agent decreases release of virion-associated proteins (1).

The safety and efficacy of Lidakol® cream were assessed in a randomized, double-blind, placebo-controlled, multicenter trial in which 737 otherwise healthy subjects with oral-facial herpes simplex were given topical therapy with either placebo or Lidakol® 5 times/day until healing or for a maximum of 10 days. Drug-treated individuals had significantly lower median time to healing (4.1 days), 18 h shorter than the placebo group. Drug treatment also significantly reduced the following as compared to placebo: time from treatment initiation to complete cessation of herpes associated pain and/or burning, itching or tingling; time from treatment initiation to complete healing of lesions which progressed to vesicular or later stages; time from the first experience of pain to first reduction in pain; and time from treatment initiation to cessation of the soft-ulcer crust stage. Aborted episodes were experienced in 40% and 34% of the Lidakol® and placebo-treated patients, respectively. Adverse effects were mild and similar in both groups (2).

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Avanir signed a manufacturing agreement with Bausch & Lomb to produce Lidakol® 10% cream for recurrent oral-facial herpes infections (3).

The FDA has requested additional clinical data for Avanir's application for approval of Lidakol® cream for the treatment of oral-facial herpes. The company is awaiting a letter from the FDA outlining the basis for their request before addressing the matter (4-8).

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6. *FDA requests additional data to support n-docosanol NDA.* DailyDrugNews.com (Daily Essentials) July 27, 1999.

7. *Avanir submits info on topical herpes treatment for final review.* DailyDrugNews.com (Daily Essentials) Aug 10, 1999.

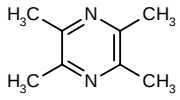
8. *FDA requests additional clinical data for Avanir's docosanol cream.* DailyDrugNews.com (Daily Essentials) Sept 24, 1999.

Original monograph - Drugs Fut 1992, 17: 879.

Ligustrazine

Neuroprotectant

EN: 149375



$C_8H_{12}N_2$

Chinese Univ. Hong Kong; Beijing Med. Univ.

An *in vitro* study using rat cerebral cortex cells showed that ligustrazine treatment suppressed the hypoxia-induced increase in LPO levels suggesting that the agent like SOD may protect cells from hypoxia-induced lipid peroxidation (1).

Ligustrazine at moderate or high doses was shown to significantly inhibit collagen synthesis and proliferation in cultured cardiac fibroblasts while low doses of the agent antagonized norepinephrine-stimulated collagen synthesis and proliferation (2).

Ligustrazine was shown to suppress fast and slow action potential duration, amplitude and force of contraction as well as the maximal upstroke velocity of slow action potentials in guinea pig ventricular papillary muscle and pig coronary artery. The compound also stimulated slow action potentials and contraction but was ineffective in preparations in which β-adrenoceptors were blocked. In pig coronary artery, increasing extracellular Ca^{2+} resulted in increased action potential amplitude and decreased contractile response to high KCl (3).

Injections of ligustrazine have been shown to effectively clear the hydroxy-free radical OH with a maximum clearance rate of 38.7% (4).

A study showed that a 30-min pretreatment of cultured cerebrovascular endothelial cells with ligustrazine inhibited the TNF-α and LPS upregulated ICAM-1 expression observed at 24 h (5).

Ligustrazine may protect myocardial cells against injury due to hypoxia and glucose deficiency since treatment of cells with the compound was shown to improve the incorporation ratios of [^{3}H]-Leu and [^{3}H]-uridine, enhance protein synthesis and RNA levels and induce nitric oxide synthase expression (6).

Ligustrazine was shown to inhibit oxygen free radical formation, enhance SOD and GSH-Px activity and promote fetal growth, suggesting that it may be effective as a treatment for intrauterine growth retardation (7, 8).

In mice with immune-mediated aplastic anemia, ligustazine was shown to promote proliferation of bone marrow stem and progenitor cells by increasing CD34 antigen expression (9).

In a study in hypoxic-ischemic neonatal rats, treatment with ligustrazine was shown to lower plasma and cerebral cortex MDA and SOD levels and reduce neuronal degeneration in gray matter, hippocampus and cerebellum, as compared to untreated animals. Results suggest that oxygen free radical formation is one of the pathogenic factors involved in perinatal hypoxic-ischemic brain damage and TMP may provide protection against injury via indirect antioxidation (10).

A study in rabbits has shown that plasma MDA increased and SOD and GSH-Px decreased following hemorrhagic shock and reperfusion with normal solutions resulted in even higher MDA and lower SOD and GSH-Px values. However, reperfusion with ligustrazine reduced MDA and increased SOD and GSH-Px levels, suggesting that the agent can alleviate lipid peroxidation and may effectively protect against cellular damage during hemorrhagic shock (11).

Ligustrazine was shown to selectively increase plasma nitric oxide content in CSF and plasma of patients with cerebral infarction (12).

Ligustrazine was shown to correct imbalances in TxA_2 and PGI_2 observed during cardiopulmonary bypass in patients with congenital heart disease and pulmonary hypertension. A total of 15 patients were treated with 3 mg/kg (i.v.) ligustrazine after anesthesia induction followed by 1 mg/kg infused into the oxygenator following bypass. Results were obtained from blood samples taken after anesthesia induction, 15 min after beginning bypass, 5 min after release of aortic cross-clamp and 20 min, 6 h and 24 h after bypass (13).

A study in which 100 patients with cerebral infarction were treated with either ligustrazine (120 mg/day i.v.) or

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xantinol nicotinate (300-900 mg/day i.v.) for 10 days with a second course administered 2-3 days later, showed that xantinol-treated patients had higher response (88%) and efficacy (72%) rates as compared to the ligustrazine group (70% and 32%, respectively) (14).

The effects of defibrase and ligustrazine as a treatment for acute ischemic cerebrovascular disease were examined in 63 patients. The efficacy rates were 97% for defibrase and 88% for ligustrazine. Whereas platelet aggregation rates and blood viscosity were decreased with both compounds, coagulation factor 1 (fibrinogen) and lipids were reduced only in the defibrase-treated group (15).

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14. Chang, L.-J., Zhang, S.-R., Chang, W.-P., Zhang, H.-J., Qin, S.-L. *Xantinol nicotinate vs. ligustrazine in treating cerebral infarction.* New Drugs Clin Rem 1997, 16(1): 15.

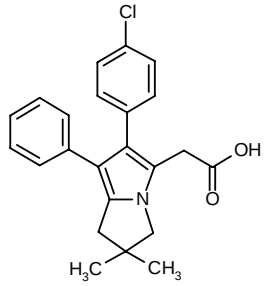
15. Guo, Z.-F., Jiang, H.-D., Li, X.-J., Sun, Z.-L., Dong, Z.-C. *Defibrase vs. ligustrazine in treating acute ischemic cerebrovascular disease.* Chin J New Drugs Clin Rem 1998, 17(5): 295.

Original monograph - Drugs Fut 1991, 16: 904.

ML-3000

Antiinflammatory
COX/5-LO Inhibitor

EN: 210861



$C_{23}H_{22}ClNO_2$ **Merckle; EuroAlliance**

An alternative route to improve the yield of a previous reported synthesis of ML-3000 [Cossy, J and Belotti, D., J Org Chem, 1997, 62 (23), 7900] has been reported: The reduction of the oxoacetic ester intermediate (I) can also be performed stepwise by treatment of (I) with tosylhydrazine (II), isolation of the corresponding tosylhydrazone (III) and reduction with sodium cyanoborohydride in ethanol to yield the expected acetate (IV). Finally, this compound is hydrolyzed with NaOH as already described (1). Scheme 2.

ML-3000 demonstrated outstanding gastroduodenal tolerability in a 4-week clinical study in 120 healthy volunteers (males and females aged 30-77 years). The volunteers were divided into four groups: ML-3000 at 200 mg b.i.d., ML-3000 at 400 mg t.i.d., naproxen at 500 mg t.i.d. or placebo. Endoscopic evaluations of the gastric and duodenal mucosa were performed before and after the 4-week treatment period. Subjects treated with both doses of ML-3000 had results similar to those observed in the placebo group, whereas subjects in the naproxen group developed substantial, frequent lesions of the gastric and duodenal mucosa (2).

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2. *Novel antiinflammatory agent ML-3000 shows excellent gastroduodenal tolerability.* DailyDrugNews.com (Daily Essentials) July 1, 1999.

Original monograph - Drugs Fut 1995, 20: 1007.

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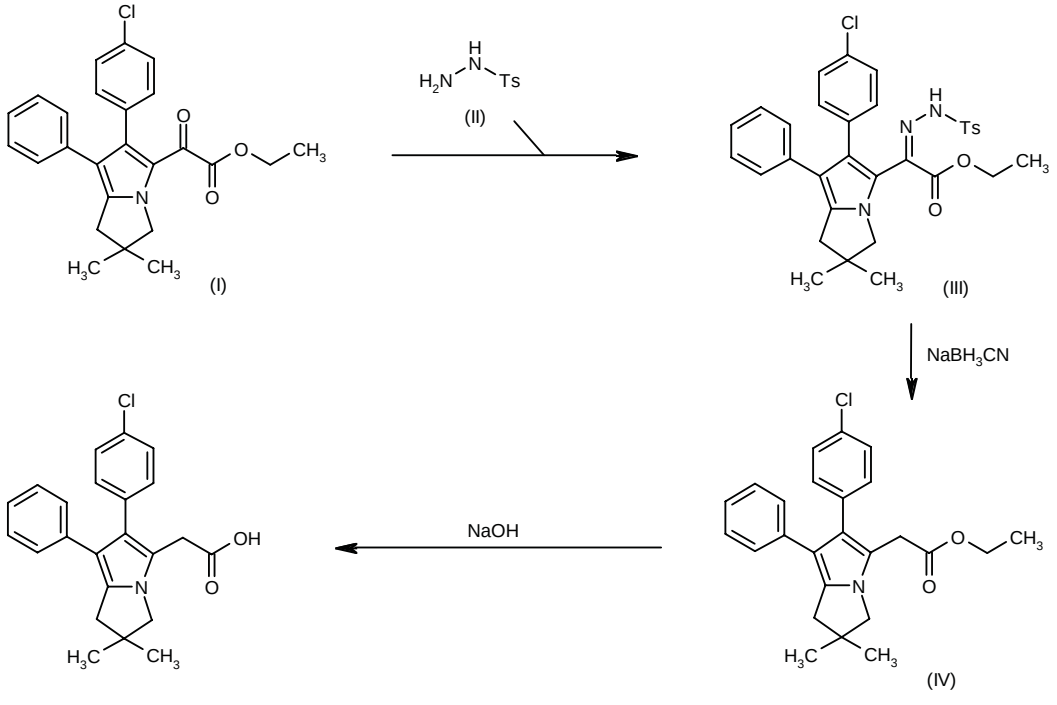
Scheme 2: Synthesis of ML-3000



Additional Reference

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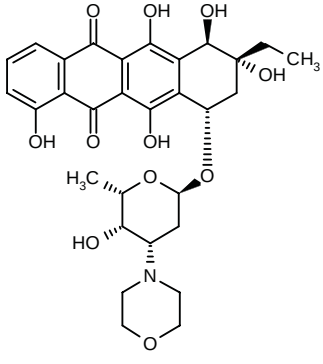
MX2
KRN-8602

Antineoplastic

EN: 127759



$C_{30}H_{35}NO_{11}$ **Kirin Brewery**

A phase II study of KRN-8602 (15 mg/m^2/day i.v. on days 1-3 at 3-4 week intervals) in 37 patients with refractory metastatic breast cancer showed that the agent had only modest activity accompanied by severe toxicity. Six patients had a partial response and no complete responses were observed after at least 2 treatment cycles. Adverse events included moderate to severe myelosuppression, grade 3 or 4 leukopenia (65%) and severe nausea and vomiting (44%) (1).

A multicenter phase II study showed the efficacy of KRN-8602 combination therapy to overcome drug resistance in 74 patients with drug-resistant acute myeloid (AML) or acute lymphoblastic leukemia (ALL). Patients with AML were given a bolus of KRN-8602 (15 mg/m^2 i.v. for 5 days) and cytarabine (100 mg/m^2 24 h continuous infusion for 7 days) and ALL patients were treated with KRN-8602, vincristine (1.4 mg/m^2 i.v. bolus once/week) and prednisolone (40 mg/m^2 3 h infusion for 5 days). The complete remission rates in AML and ALL patients were 36.4% (16/44) and 24.1% (7/29), respectively, and the overall response rates were 52.3% (23/44) and 51.7% (15/29), respectively. There were 29 relapsed AML cases in which a higher complete remission rate was obtained (51.7%). The most frequent side effects were nausea/vomiting and anorexia; several cases of CNS disorders and peripheral neuropathy were observed although incidence of severe neurotoxicities was low (2).

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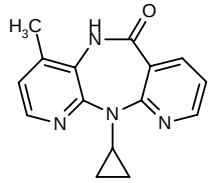
Nevirapine
Viramune®

Anti-HIV
Reverse Transcriptase Inhibitor

EN: 170581



$C_{15}H_{14}N_4O$ **Boehringer Ingelheim; Roxane**

Roxane Laboratories has received approval from the FDA to market a pediatric formulation of nevirapine (Viramune®) to treat infants and children infected with HIV. Nevirapine is only the seventh pediatric AIDS drug to be approved by the FDA, whereas 14 such compounds are approved for use in adults, and is the first NNRTI approved for use in children (1).

Boehringer Ingelheim has received approval from the European Commission to market Viramune® to treat infants and children infected with HIV. The recommended pediatric dosing is 4 mg/kg once daily for 2 weeks, followed by 7 mg/kg twice daily for children between 2 months and 8 years of age, and 4 mg/kg twice daily for children 8 years and older (2).

A joint Uganda-U.S. study has demonstrated that a single oral dose of nevirapine given to an HIV-infected woman in labor and another to her baby within 3 days of birth reduces the transmission rate by half compared to a similar short course of zidovudine (AZT). This safe, highly effective drug regimen is approximately 200 times cheaper than the long-course AZT regimen used in the U.S. and nearly 70 times cheaper than a short course of AZT given to the mother during the last month of pregnancy. Interim analysis of data from 310 individuals in the nevirapine group and 308 in the AZT group showed that nevirapine was markedly more effective. At 14-16 weeks of age, 13.1% of infants who received nevirapine were infected with HIV, as compared to 25.1% of those in the AZT group. Both drugs appeared to be safe and well tolerated, but nevirapine resulted in a 47% reduction in mother-to-infant transmission compared to a short course of AZT (3).

1. *New treatment option for pediatric HIV/AIDS now available in U.S.* DailyDrugNews.com (Daily Essentials) Nov 27, 1998.

2. *Pediatric formulation of Viramune now available in the E.U.* DailyDrugNews.com (Daily Essentials) July 9, 1999.

3. *Short-course nevirapine effective in reducing mother-to-infant transmission of HIV.* DailyDrugNews.com (Daily Essentials) July 20, 1999.

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Guay, L.A. et al. *Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial.* Lancet 1999, 354(9181): 795.

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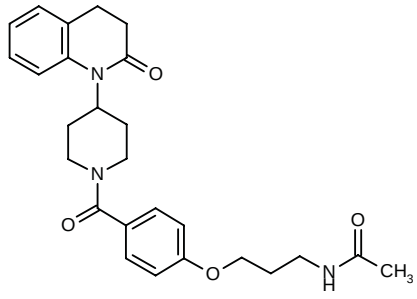
OPC-21268

Antihypertensive
Treatment of Heart Failure
EN: 176607 *Vasopressin V_{1A} Antagonist*



$C_{26}H_{31}N_3O_4$ **Otsuka**

OPC-21268 was shown to relieve ethanol-induced congestive hyperemia and injury in gastric mucosa in rats in a study in which animals were treated with saline, ethanol or title compound 2 h prior to ethanol. OPC-21268-treated rats had dose-dependently improved ulcer scores and histologically confirmed reductions in gastric injury. Saline and OPC-21268-treated animals had significantly higher values for gastric mucosal blood flow and erythrocyte velocity and lower erythrocyte volumes as compared to animals treated with ethanol alone. Ethanol administration did not alter plasma vasopressin levels, although significant 3-fold increases in gastric tissue vasopressin content was observed 15, 30 and 60 min after administration, suggesting that vasopressin was generated locally following ethanol administration (1).

1. Sugimoto, I., Narimiya, N., Odagiri, M., Ohnishi, A., Tanaka, T. *Protective effect of a vasopressin-1 selective antagonist, OPC-21268, against ethanol-induced damage of the rat gastric wall.* Dig Dis Sci 1999, 44(3): 503.

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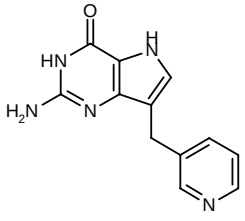
Peldesine

Antineoplastic
Anti-HIV
Antipsoriatic
PNP Inhibitor

EN: 193376



$C_{12}H_{11}N_5O$ **BioCryst; Torii**

An improved synthesis of [^{14}C]-peldesine has been reported: The reaction of *S*-methyl-[^{14}C]-isothiourea (I) with methyl chloroformate (II) by means of tetrabutylammonium bromide in dichloromethane gives *N*,*N*'-bis(methoxycarbonyl)-*S*-methyl-[^{14}C]-isothiourea (III). This compound is condensed with 3-amino-4-(3-pyridylmethyl)-1*H*-pyrrole-2-carboxylic acid methyl ester (IV) by means of acetic acid in methanol, yielding the labeled guanidine (V). The cyclization of (V) by means of sodium methoxide in methanol affords the carbamate precursor (VI), which is finally deprotected with NaOH in hot water (1). Scheme 3.

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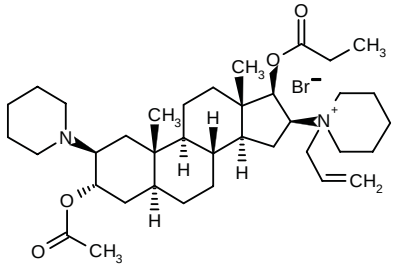
Rapacuronium Bromide *Neuromuscular Blocker*
Raplon®

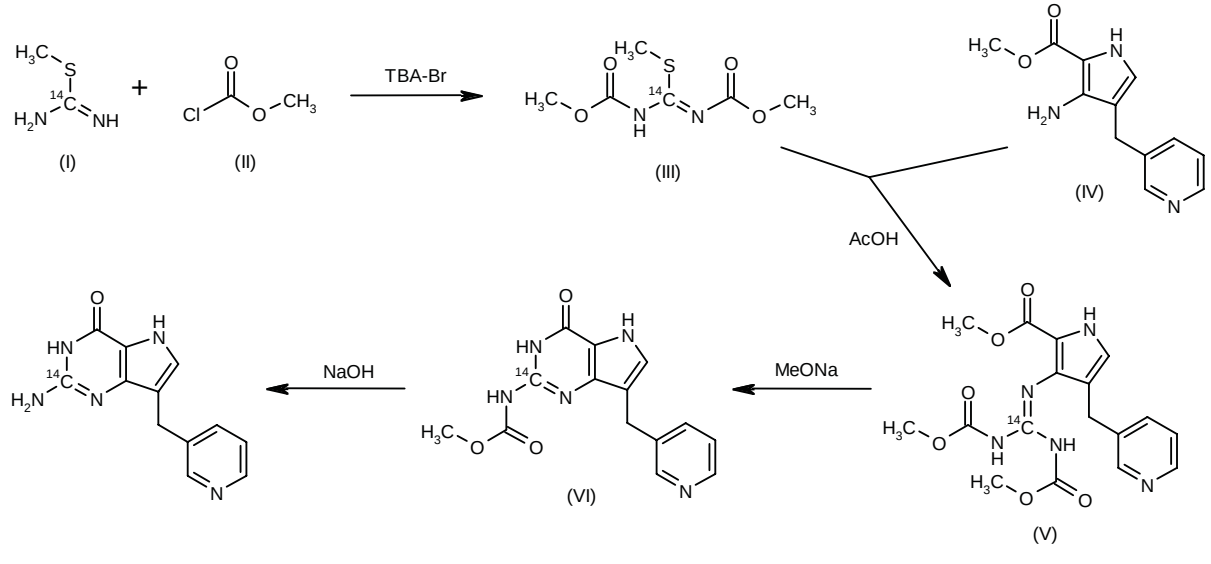
EN: 203872



$C_{37}H_{61}BrN_2O_4$ **Akzo Nobel; Organon**

A pharmacokinetic study involving 24 patients scheduled for elective surgery showed that the lower clearance of the 3-desacetyl metabolite of rapacuronium is responsible for prolonging the time course of muscle relaxant effects during rapacuronium maintenance treatment. Patients pretreated with midazolam (7.5-15 mg p.o.) and undergoing thiopental (4-6 mg/kg i.v.) and fentanyl (1-3 μg/kg i.v.) anesthesia received either a short-term

Scheme 3: Synthesis of [^{14}C]-Labeled Peldesine



infusion of rapacuronium or its metabolite until single-twitch stimulation height was decreased by 70% to achieve a maximal block of 90%. The median clearance of rapacuronium was 7.28 ml/kg/min with 6.25% excreted in urine. Clearance of the metabolite was 1.06 and 1.28 ml/kg/min for short infusion and bolus regimens, respectively, with 53.5% and 51.9%, respectively, excreted in urine. The rate constant of transport between plasma and the biophase was larger for rapacuronium (0.449 *vs.* 0.105/min min) and higher EC_{50} values (4.70 *vs.* 1.83 μg/ml) for neuromuscular block were observed as compared to the metabolite. Results are consistent with rapacuronium's rapid onset and short to intermediate duration of action (1).

Renal failure was shown not to significantly affect the neuromuscular action of a single dose of rapacuronium bromide (1.5 mg/kg) in a study in which adductor pollicis twitch tensions were measured in 10 healthy volunteers and 10 patients with renal failure. At 1 min, twitch tension was less in patients than in volunteers (92% *vs.* 99%) although the time to 90% and peak twitch depression were similar for both groups. Clearance of the agent was 32% less in patients than volunteers and was found to decrease by 0.909% per year of age; steady-state distribution was 14% less in women than men and 16% less in patients as compared to healthy individuals (2).

The population pharmacokinetics of rapacuronium (1.5 mg/kg i.v. bolus + maintenance infusion) were determined in 37 patients undergoing surgery with desflurane, sevoflurane, isoflurane or propofol anesthesia. Rapacuronium had a high elimination clearance and a 3-compartment model described the drug's pharmacokinetics. While V2, V3 and CL1 increased with increasing lean body mass, age, anesthesia and hematocrit were not significant covariates (3).

The quick onset and offset of action of rapacuronium bromide was shown to be due to rapid equilibration between plasma and effect sites. The twitch tensions of the adductor pollicis and laryngeal adductors were measured in 10 volunteers anesthetized with the agent (1.5 mg/kg). Rate constants of 0.405 and 0.630/min were obtained for equilibration between plasma and adductor pollicis and laryngeal adductors, respectively; no differences were noted in the steady-state plasma concentration that suppressed twitch by 50% and the Hill factor for the two muscles (4).

A randomized multicenter study in 234 normal weight and 101 obese subjects showed that clinically acceptable intubating conditions were more frequent after succinylcholine (97.4%) as compared to rapacuronium (89.4%). Anesthetics used included fentanyl with thiopental or alfentanil with propofol and did not influence intubation; subject group also did not influence intubation. Significant differences were observed in the maximum increase in heart rate achieved after intubation with rapacuronium (23.1%) and succinylcholine (9.4%) and in the incidence of pulmonary side effects, including bronchospasm and increased airway pressure (10.7 *vs.* 4.1%) (5).

An open-label, randomized study examined the cardiovascular effects of rapacuronium during isoflurane anesthesia in 45 patients undergoing elective surgery. Patients given 1, 2 or 3 mg/kg of the drug had increases in heart rate of 110, 115 and 118%, respectively. Only 3 mg/kg significantly decreased systolic/diastolic blood pressure by 91/82% with values returning to baseline after 15 min. A transient increase in airway pressure was observed in 6 patients after rapacuronium administration with 2/6 showing decreased oxygen saturation without audible wheezing. No other adverse effects were observed (6).

Rapacuronium bromide (Raplon®) has been launched for the first time in the U.S., where it is indicated for use in inpatients and outpatients, as an adjunct to general anesthesia to facilitate tracheal intubation and to provide skeletal muscle relaxation during short surgical procedures. Raplon® is supplied as a sterile, nonpyrogenic lyophilized cake in 5- and 10-ml vials containing 100 and 200 mg, respectively, of rapacuronium bromide base. Following reconstitution with sterile water for injection or bacteriostatic water for injection, an isotonic preparation for i.v. injection at a concentration of 20 mg/ml is obtained (7, 8).

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McCourt, K.C. et al. *Spontaneous or neostigmine-induced recov-*

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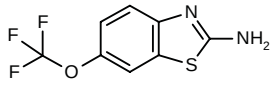
Sato, K. et al. *The effect of different non-depolarizing muscle relaxants on [^{3}H]noradrenaline release from isolated human atrium appendage.* Fundam Clin Pharmacol 1999, 13(Suppl. 1): Abst PM174.

Riluzole
Rilutek®

Antiparkinsonian
Treatment of ALS

EN: 111447



$C_8H_5F_3N_2OS$ **Rhône-Poulenc Rorer**

The initiation of a phase III clinical trial evaluating the potential utility of riluzole tablets in the treatment of patients with recent, untreated symptoms of PD was announced by Rhône-Poulenc Rorer. The study will enroll more than 1000 patients at 120 locations worldwide and is designed to determine the ability of riluzole to slow progression of PD (1).

An open-label pilot trial of riluzole was conducted in 6 patients with advanced Parkinson's disease and dyskinesias associated with long-term levodopa. Treatment with riluzole was begun following a 2-week drug-free period, at a dose of 25 mg once daily, which was increased over 8 days to 50 mg b.i.d. for 4 weeks. A 24% decrease in the mean number of waking hours of dyskinesias/day and a 30% decrease in the mean number of waking hours of severe dyskinesias/day were reported (by patients and/or caregivers) on riluzole compared to baseline, whereas parkinsonian signs and symptoms did not worsen. No side effects were observed. Thus, riluzole may be useful for suppressing levodopa-induced dyskinesias in PD and may also allow the use of higher doses of levodopa for improving mobility and quality of life without an increase in involuntary movements (2).

The results from a pilot trial of riluzole in patients with early, previously untreated PD have been reported. This double-blind, placebo-controlled trial enrolled 20 patients with PD who were randomized to receive riluzole (50 mg b.i.d.) or placebo for 6 months, followed by a 6-week washout period. Nineteen patients completed the study and preliminary analysis showed no significant effect for riluzole on motor function. Diarrhea and transient gastrointestinal cramps were reported by 1 patient each but did not require discontinuation of treatment. No evidence of efficacy was obtained in this small, short-term study (3).

In a 6-week, open-label trial, 8 subjects with Huntington's disease were administered riluzole (50 mg b.i.d.). Treatment was well tolerated with a significant improvement (35%) in chorea rating scores observed; there were no effects on dystonia or total functional capacity scores. A trend toward reductions in lactate/creatine ratios in basal ganglia but not occipital cortex spectra was also noted (4).

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4. Rosas, D. et al. *Riluzole therapy in Huntington's disease (HD).* Mov Disord 1999, 14(2): 326.

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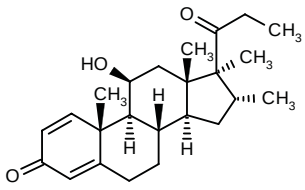
Ziv, I. et al. *Riluzole: A novel potential therapeutic approach for levodopa-induced dyskinesias.* Parkinsonism Relat Disord 1999, 5(Suppl.): Abst P-TU-152.

Rimexolone
Vexol®

Antiinflammatory Ophthalmic

EN: 136805



$C_{24}H_{34}O_3$ **Organon; Alcon**

A new synthesis of rimexolone from prednisolone has been described: The reaction of prednisolone (I) with tosyl chloride in pyridine gives the 21-tosylate (II), which is treated with sodium iodide in acetone to yield the 21-iodo derivative (III). The deiodination of (III) with refluxing acetic acid affords 21-deoxyprednisolone (IV), which is dehydrated with semicarbazide in water at 80-5 °C, yielding the trienone (V). The silylation of (V) with TMS-Cl and pyridine gives the protected compound (VI), which is methylated with methyl iodide and lithium bis(trimethylsilyl)amide to afford the 21-methyl derivative (VII). A new methylation of (VII) with $Me_2Cu(CN)Li_2$ followed by silylation with TMS-Cl affords the silylated dimethyl enol ether (VIII), which is submitted to a third methylation with methyl iodide and benzyltrimethylammonium fluoride in THF, giving the silylated 16,17,21-trimethyl derivative (IX). Finally, this compound is desilylated to rimexolone with 6M HCl in methanol (1). Scheme 4.

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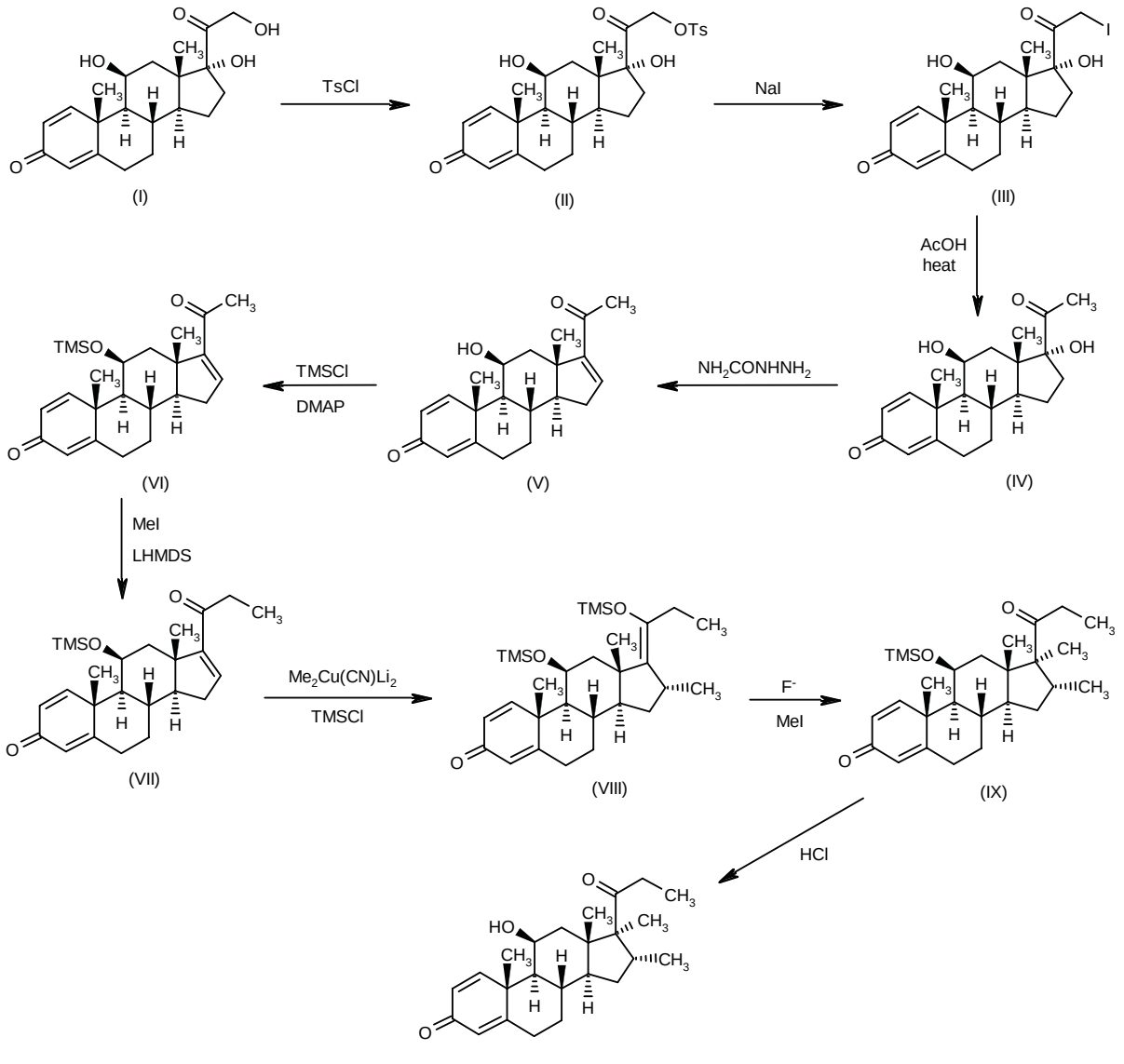
Scheme 4: Synthesis of Rimexolone



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Saruplase
Rescupase®

Thrombolytic

EN: 122882

Grünenthal

Following review of Grünenthal's marketing application for saruplase (Rescupase®) for the acute treatment of myocardial infarction, the European Committee for Proprietary Medicinal Products (CPMP) has voted not to recommend granting marketing authorization. More than 3700 patients were treated with saruplase in the company's clinical trials program, in which the total mortality rate for patients treated with the agent was reduced to 6.26%. The risk of hemorrhagic stroke associated with the drug was 0.83%, similar to that for other thrombolytics. Nonetheless, the CPMP decreed that a larger sample size was needed in order to confirm the favorable risk/benefit ratio for saruplase. Grünenthal has

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announced that it will now concentrate its development efforts on projects in the areas of pain and infection (1).

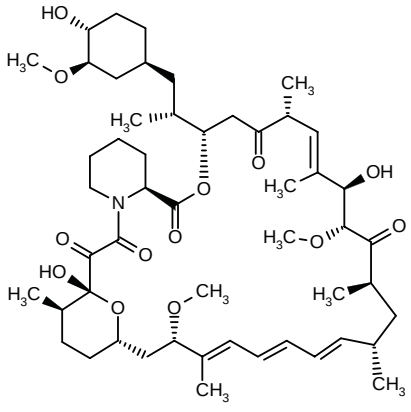
1. *CPMP declines to recommend approval of saruplase marketing application.* DailyDrugNews.com (Daily Essentials) Aug 18, 1999.

Original monograph - Drugs Fut 1986, 11: 851.

Sirolimus
Rapamune®

Immunosuppressant
Prevention of Transplant Rejection

EN: 175652



$C_{51}H_{79}NO_{13}$ **Wyeth-Ayerst**

The kinetics of rapamycin action were observed in a study using human rhabdomyosarcoma cell lines (Rh1, Rh30) treated with the agent for 1 h or 6 days. Short and continuous rapamycin treatment induced growth arrest and apoptosis in both cell lines; apoptosis occurred at 24 and 144 h and may have been p53-independent since both cell lines carry p53 mutants. Rh1 and Rh30 clones expressing a mutant mammalian target of rapamycin (mTOR) were shown to be > 3000-fold resistant to rapamycin suggesting that rapamycin-induced growth arrest and apoptosis is mediated via mTOR inhibition. In the presence of IGF-I known to protect both cell lines from apoptosis, rapamycin-treated Rh1 cells continued to proliferate while Rh30 cells were arrested although viable in the G_1 phase. Further analysis of IGF-I-stimulated p70(S6K) activity after 1 h of rapamycin treatment showed that rapamycin dissociated slowly from FKBP-12 ($t_{1/2}$ = 17.5 h) in the presence of a competitor (FK-506) with no recovery of p70(S6K) activity in the absence of competitor. The $t_{1/2}$ of rapamycin is normally 9.9 h and thus is relatively unstable in cell culture conditions (1).

An *in vitro* study showed that rapamycin (1-100 nM) did not stimulate endothelin-1 secretion by cultured human umbilical vein endothelial cells in contrast to ciclosporin (10 μM) and IL-1β, which dose-dependently increased secretion. Rapamycin significantly inhibited serum-stimulated endothelial cell growth, indicating bioactivity of the agent. The results may explain the protective effects observed with rapamycin as compared to ciclosporin in animal models of transplant vasculopathy and chronic rejection (2).

Sirolimus in contrast to ciclosporin was shown to arrest and reverse the progression of graft vascular disease in cynomolgus monkeys with aortic allografts in which treatment was initiated on day 45 posttransplant (3).

A study comparing 4 rodent models of chronic graft vascular disease (CGVD) showed that rapamycin (3 mg/kg/day i.p.) reversed CGVD in PVG grafts as compared to ciclosporin, which had no effect; ACI isografts did not show CGVD at day 90. Rapamycin significantly inhibited the increased levels of anti-donor antibody at day 90 (4).

The effects of rapamycin on mitogen-stimulated bovine airways smooth muscle cell proliferation were recently investigated. Pretreatment with rapamycin at noncytotoxic concentrations (0.5-1.0 nM) inhibited DNA synthesis by 100% and cell division by 53% in β-hexosaminidase A-stimulated cells, and DNA synthesis by 30% and cell division by 15% in insulin-stimulated cells. These results suggest that rapamycin may be a useful therapeutic agent for the airways remodeling observed in asthma (5).

A novel model has been described in which permanent tolerance was induced in C57BL10 mice with B10.A skin grafts through administration of polyclonal ALS (0.5 ml rabbit anti-mouse on days -1, 2 and 5 with respect to grafting), donor bone marrow (150 million cells on day 7) and sirolimus (24 mg/kg on day 6). At 200 days postgrafting, graft survival was 100%. Tolerant mice rejected grafts from BALB/c donors but retained second B10.A grafts transplanted between days 14 and 120. Administration of IL-2 (5000 units given multiple times between days 14-120) did not disrupt tolerance. Multilineage chimerism (*i.e.*, 10% of recipient splenocytes and peripheral blood leukocytes were of donor origin by day 30) remained stable for the duration of the study (> 200 days). This persistent multilineage chimerism was shown to be due to peripheral clonal deletion (detectable at 20 days) and immunoredirection (6).

The safety and efficacy of sirolimus were assessed in a prospective, randomized, double-blind, double-dummy, multicenter phase III trial. In addition to ciclosporin (150-350 ng/ml) and corticosteroids, 719 renal allograft recipients were given either sirolimus (2 or 5 mg/day) or azathioprine (2-3 mg/kg/day) within 24-48 h of transplantation. Initial results from 450 patients show overall patient and graft survival of 98% and 97%, respectively (7).

Similar efficacy but different toxicities were reported for sirolimus and ciclosporin in an open, randomized, multicenter trial in which 83 renal allograft recipients received sirolimus or ciclosporin in addition to azathioprine (2 mg/kg) and steroids. The incidence of acute rejection was 41.5% and 38.1% in the sirolimus and ciclosporin groups, respectively, at 1 year. Patient survival was 100% in both groups and graft survival was 98% and 93% for sirolimus- and ciclosporin-treated patients,

respectively. Hypolipidemia and thrombocytopenia were reported for some patients but improved after 3 months when dose and trough levels of sirolimus were reduced. Higher incidence of tremor, hypertrichosis and hypertension were observed in the ciclosporin group. Mean serum creatinine levels were normal in the sirolimus group while levels were consistently lower in the ciclosporin group at 3, 6 and 12 months (8).

The safety and efficacy of sirolimus were assessed in a prospective, randomized, double-blind, multicenter, 3-year trial in which, in addition to ciclosporin and prednisone, 576 renal allograft recipients were given either sirolimus (2 or 5 mg/day) or placebo. Initial results from 420 patients show overall patients and graft survival of 96% and 95%, respectively (9).

In a randomized, multicenter trial, 41 renal allograft recipients were administered a triple-therapy regimen with azathioprine, steroids and ciclosporin or sirolimus (24 mg/m^2) given within 24 h of transplantation followed by subsequent dosing (starting at 12 mg/m^2) individualized from day 7 to achieve 30 ng/ml target trough levels and 15 ng/ml 2 years later. Target concentrations were obtained and laboratory abnormalities such as hypertriglyceridemia and reduced platelet counts were improved when sirolimus target trough levels were lowered to 15 ng/ml (10).

A study confirmed that ciclosporin pharmacokinetics are not altered by sirolimus (2 mg/day 4 h after ciclosporin) coadministration for 2 weeks in stable renal transplant patients on long-term ciclosporin therapy. However, sirolimus did appear to alter C_{max} at 2 weeks (from 558 ng/ml pretreatment to 583 and 706 ng/ml at 1 and 2 weeks, respectively) with increases in AUC values (from 2535 to 2660 and 2773, respectively). The t_{max} of 120 min was unchanged (11).

A randomized trial has shown that rapamycin (5 mg/day) was as effective as ciclosporin as a base therapy in 19 renal transplant recipients switched to rapamycin (14-204 months or within 2 weeks posttransplant) because of ciclosporin or Tac nephrotoxicity, chronic rejection + ciclosporin nephrotoxicity, lymphoma and Hodgkin's disease or diabetes onset. Significant decreases in serum creatinine were observed at 2-3 months after the switch in the 12 patients with ciclosporin nephrotoxicity. Blood pressure was stable after the switch and 2 patients were able to reduce antihypertensive therapy. Facial dysmorphism improved in 1 patient and diabetes resolved in another at 6 months postswitch. Pneumonia was observed in 6 patients with 5 requiring hospitalization, although all recovered. One reversible acute rejection was observed in a patient on rapamycin and mycophenolate mofetil (MMF) at 3 months. No loss of grafts occurred (12).

A pharmacokinetic, pharmacodynamic study in 120 renal transplant patients treated for at least 2 years with rapamycin and ciclosporin reported that 7 patients had acute and 17 chronic rejection, where the incidence of chronic rejection was inversely proportional to rapamycin dose and was related to lower rapamycin absorption according to AUC values. Chronic rejection also correlated with the percent coefficient of variation of dose-corrected average ciclosporin concentration. Pharmacokinetics were similar in cohorts treated with liquid or solid tablet formulations, although the dose-corrected average ciclosporin concentration was significantly higher in patients switched from one formulation to another (13).

The oral bioavailability of sirolimus (5 mg p.o.) was shown to increase with ketoconazole treatment (200 mg p.o. for 10 days) given at steady state in a study with 23 healthy volunteers. With ketoconazole, sirolimus $AUC_{0\text{-}144h}$ increased 11-fold (297 ± 93 *vs.* 3319 ± 1048 ng/h/ml) and CL/F (250 ± 68 *vs.* 24.9 ± 17.7 ml/h/kg) and V_{ss}/F (19.3 ± 6.3 *vs.* 2.3 ± 1.3 l/kg) decreased. C_{max} increased 4.4-fold and t_{max} and MRT 1.4-fold; no change in $t_{1/2}$ was observed. Identical CL/F and V_{ss}/F ratios show that the changes in sirolimus were due to an effect of ketoconazole on bioavailability of sirolimus and not on elimination (14).

Results from 2 randomized, double-blind, placebo-controlled studies involving 1295 kidney transplant recipients given sirolimus (2 or 5 mg/day), azathioprine or placebo with ciclosporin and corticosteroids showed that sirolimus-treated patients had reduced acute rejection rates and were less likely to require rescue treatment, dialysis or renal biopsy as compared to placebo and azathioprine groups (15).

The therapeutic efficacy and safety of sirolimus were evaluated in an open, randomized, multicenter European study in 78 human renal allograft recipients. Patients in the study were randomized prior to transplantation to treatment with either sirolimus or ciclosporin in combination with MMF and tapering doses of steroids. Sirolimus and ciclosporin doses were calculated based on whole blood trough levels, while MMF was administered at a fixed dose of 2 g/day. Graft survival and patient survival, determined at 12 months, were similar in the sirolimus group (92.5% and 97.5%, respectively) and the ciclosporin group (89.5% and 95%, respectively). The number of moderate or severe biopsy-confirmed graft rejections was also similar in the 2 groups (6/40 for sirolimus *vs.* 4/38 for ciclosporin), but the overall incidence of biopsy-confirmed rejections was significantly lower on ciclosporin (18.4% *vs.* 40% for sirolimus). The most frequent side effects associated with sirolimus treatment were diarrhea, thrombocytopenia, hypercholesterolemia and hyperlipidemia, while tremor, hypertrichosis, hyperuricemia, increased creatinine levels and CMV infection were more frequent with ciclosporin (16).

Data from 2 open, randomized, multicenter European studies were pooled in order to determine the differences in renal function of transplant recipients receiving immunosuppressive drug therapy with sirolimus or ciclosporin. Records were analyzed for 81 and 80 patients treated with sirolimus and ciclosporin, respectively, in combination with azathioprine or MMF and steroids. Nankivell GFR values were significantly higher from weeks 10-24 in sirolimus-treated patients. Levels of serum uric acid were significantly lower and those of

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magnesium were significantly higher for patients on sirolimus, both remaining more frequently in the normal range. A tendency toward mild hypokalemia was observed in the sirolimus group. Based on its excellent renal safety profile, sirolimus appears to represent an important alternative to drugs such as ciclosporin, which act via the calcineurin pathway (17).

A double-blind, randomized, multicenter placebo-controlled trial in 576 recipients of mismatched first kidney grafts showed that rapamycin (2 or 5 mg p.o.) added to ciclosporin and steroid therapy significantly reduced the incidence and severity of rejection. Composite endpoints (including graft survival, patients survival and rejection rate) were 25%, 11% and 29% for groups receiving 2 and 5 mg rapamycin or placebo, respectively, at 6 months with significant differences observed at 1 year. Adverse effects were similar in all treatment groups (18).

Rapamycin was shown to lower the required dose of ciclosporin to achieve target trough levels (275-350 μg/ml) as compared to MMF in a study in 32 renal transplant recipients followed for an average of 7.7 months. Higher incidence (7/18) of ciclosporin nephrotoxicity was observed in the group receiving rapamycin and ciclosporin (2 mg/day p.o.) as compared to those given MMF and ciclosporin (2/14). The rapamycin group also exhibited elevated serum creatinine as compared to the other group (19).

A randomized, double-blind study comparing sirolimus (2 or 5 mg/day) with azathioprine added to ciclosporin and corticosteroids in 719 renal transplant patients showed that HRQOL scores from the Kidney Transplant Questionnaire, SF-36, Health Thermometer and Mental Health Index, were similar in all 3 treatment groups at 6 months posttransplant. Acute rejection negatively affected the physical functioning and well-being domains of the HRQOL scores (20).

A randomized, multicenter trial in which 576 recipients of primary mismatched kidneys were given rapamycin (2 or 5 mg/day) or placebo combined with daily ciclosporin and prednisone therapy showed that after 1 year of treatment, addition of rapamycin to therapy significantly reduced the frequency (19 and 11% *vs.* 29% in placebo) and severity of rejection and tended to improve graft and patient survival. Adverse events were not increased (21).

A randomized, double-blind, placebo-controlled phase III study in 576 renal transplant recipients receiving sirolimus (2 or 5 mg/day) or placebo with ciclosporin and prednisone therapy showed that there were no significant differences in treatment effects between African Americans and non-African Americans. Both groups experienced improved treatment with sirolimus with no differences in adverse effects or graft or patient survival (22).

No significant differences in the pharmacokinetics of sirolimus (2 or 5 mg/day) were observed between Black and non-Black renal transplant patients in a phase II study at 6 months posttransplant. The study compared sirolimus with azathioprine (2-3 mg) added to ciclosporin therapy. Significant treatment benefit was observed with sirolimus as compared to azathioprine in all races. Black patients required significantly higher ciclosporin doses to achieve sufficient whole blood trough levels. However, all patients on sirolimus, regardless of race, required lower doses of cilcosporin as compared to the azathioprine group to reach trough ciclosporin levels (23).

A study in 6 lung transplant recipients who when given calcineurin inhibitors (CI)-, ciclosporin- or tacrolimus-based immunosuppression therapy developed hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura and/or renal insufficiency showed that sirolimus + reduced-dose CI + prednisone can be used in these patients. Patients with life-threatening toxicity discontinued CI and were given sirolimus + MMF or azathioprine + prednisone. Two patients receiving sirolimus + dose-reduced CI discontinued due to side effects. Those patients remaining on sirolimus showed stable lung function after 1-6 months. Thrombocytopenia observed in 2 patients was resolved with dose reductions, and hyperlipidemia seen in 2 patients was controlled with dose reductions and HMG-CoA reductase inhibitor therapy (24).

Combination treatment with low-dose oral tacrolimus (0.03 mg/kg b.i.d. adjusted to achieve 3-8 ng/ml trough levels) and sirolimus (5 mg/kg/day p.o.) was shown to be well tolerated and effective in a study involving 16 liver or kidney-pancreas transplant recipients administered the agents 4 h apart immediately after surgery; patients also received prednisone (20 mg/day). No rejections were observed although 2 liver patients died due to a CVA at 6 weeks or abdominal bleeding on day 26. Kidney function remained normal or returned to normal in nonuremic and uremic patients, respectively. Minimal adverse effects and toxicities were observed with the combination treatment (25).

A multicenter, randomized, double-blind study comparing sirolimus (2 or 5 mg/day) with azathioprine (2-3 mg/kg/day) added to ciclosporin and corticosteroids in 719 renal transplant patients showed that sirolimus reduced the incidence of biopsy-proven acute rejection without decreasing graft or patient survival or increasing the risk of infection or malignancy. Incidence of adverse effects was similar in all groups, although increases in cholesterol and triglyceride levels were more common with sirolimus treatment and thrombocytopenia was observed more often in the group receiving 5 mg sirolimus as compared to 2 mg sirolimus or azathioprine (26).

A European multicenter, randomized, open-label, concentration-controlled trial in 83 first cadaveric renal allograft recipients on corticosteroids and azathioprine showed that at 12 months, graft survival (89% and 90%), patient survival (100% and 98%) and incidence of acute rejection (41% and 38%) were similar for sirolimus- and ciclosporin-treated patients, respectively. At 3 and 4 months, serum uric acid and magnesium were normal and serum creatinine was significantly lower in the group

receiving sirolimus. Significantly higher incidence of hypertriglyceridemia (51 *vs.* 12%), hypercholesterolemia (44 *vs.* 14%), thrombocytopenia (37 *vs.* 0%), leukopenia (39 *vs.* 14%), increases in liver enzymes and hypokalemia were observed in the sirolimus group, with all symptoms improving at 2 months posttransplant. Cytomegalovirus, herpes simplex and pneumonia were also higher in sirolimus-treated patients. In the sirolimus group, gingival hyperplasia was not reported, tremor was uncommon and less hypertension was observed (17 *vs.* 33%). No malignancies were detected in the sirolimus group as compared to 2 in the ciclosporin-treated cohort (27).

Therapy with sirolimus (target levels: 20-25 μg/l) and reduced-dose Neoral (target: 150-200 μg/l) and prednisone was shown to be safe and effective in 8 liver transplant recipients with preexisting malignancy. Azathioprine was substituted for sirolimus and Neoral and steroid doses were decreased after 2-3 rejection-free months. All patients were alive at 2-24 months posttransplant with 1 patient discontinuing sirolimus due to rash; 4 patients continue on sirolimus monotherapy, 1 is on tapered steroid, 1 on tapered Neoral and 1 is < 2 months posttransplant. One and 3 patients had acute rejection prior to initiation of and during sirolimus treatment, respectively. No tumor recurrence was observed. Observed infectious complications requiring treatment were 1 case each of CMV viremia, pseudomembranous colitis, cutaneous fungal infection and penile HSV II. Hyperlipidemia warranting diet change and treatment with lipid-lowering agents was observed in 3 patients. Leukopenia/thrombocytopenia was observed in 1 patient and was reversed with dose decreases (28).

The incidence of hyperlipidemia in renal transplant recipients given sirolimus with ciclosporin and prednisone was higher as compared to pretransplant. Hyperlipidemia onset occurred at 1 month, peaked at 3 months and stabilized with lipid-lowering therapy. Female gender and presence of hypercholesterolemia were the pretransplant factors predisposing subjects to hypercholesterolemia. Treatment with β-blockers or presence of concomitant bephrotic syndrome increased severity of hyperlipidemia. Eight of the 83 patients had serum triglyceride levels > 1000 mg/dl and high (> 500 mg/dl) elevations in cholesterol were observed in 3 patients. Two patients had myocardial infarctions and 1 suffered a cerebrovascular accident (29).

The Rapamune Global Study Group has conducted a trial involving 576 primary mismatched renal allograft recipients who were randomized to treatment with sirolimus (2 or 5 mg/day) or placebo in addition to ciclosporin and corticosteroids. The primary endpoint was efficacy failure, defined as either biopsy-confirmed acute rejection, graft loss or death within 6 months after transplant. During the 6-month study period there were no significant intergroup differences in graft or patient survival (88-93% and 95-98%, respectively). However, the overall primary composite endpoint rate was 25% and 19% for the 2 and 5 mg/day sirolimus groups compared to a rate of 37% in the placebo group. This reflected a much higher incidence of biopsy-confirmed acute rejection in the placebo group (29%) than in the low- and high-dose sirolimus groups (19% and 11%, respectively). The overall severity of acute rejection was significantly and detectably lower with high-dose and low-dose sirolimus, respectively, as compared to placebo. The need for antibody therapy to treat the first rejection episode was significantly lower on low-dose sirolimus than placebo (2.2% *vs.* 7.7%). The incidences of side effects and infections were similar in all three groups, although hyperlipidemia was more frequent with sirolimus (30).

Sirolimus (Rapamune®) has been approved in the U.S. and is marketed by Wyeth-Ayerst for the prevention of organ rejection in patients receiving renal transplants. The company has also filed for European approval of the compound. The use of sirolimus in combination with ciclosporin and corticosteroids is recommended. Sirolimus is supplied as an oral solution at a concentration of 1 mg/ml in glass bottles containing 60 and 150 ml and in unit-of-use pouches containing 1, 2 and 5 ml (31-36).

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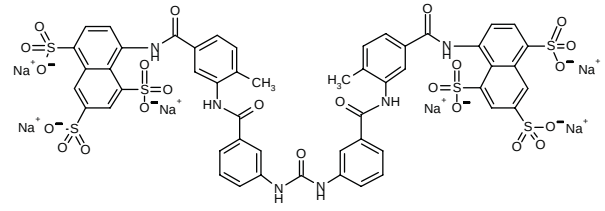

$C_{51}H_{34}N_6Na_6O_{23}S_6$ **Warner-Lambert**

Studies on the mechanism of action of suramin (150 mM) showed that 24 h treatment of prostate cancer cells caused a 7-to 15-fold increase in formation of topoisomerase cleavable complexes; similar results were seen with suramin-treated isolated nuclei but to a lesser extent. However, treatment of cells with suramin and topoisomerase-active agents did not increase the cleavable complexes. These results suggest that suramin does not alter cellular topoisomerase I or II, form cleavable complexes alone or increase stability of group-topoisomerase-DNA intermediates. Suramin treatment also did not change cellular resistance to etoposide, camptothecin or cisplatin (1).

Suramin was shown to alter ATP degradation and/or suppress purinergic neurotransmission in a study examining the effects of the agent on apyrase activity in hippocampal synaptosomes of adult rats and on retention of inhibitory avoidance learning in rats. Suramin significantly and noncompetitively inhibited apyrase-stimulated ATP and ADP hydrolysis in synaptosomes (K_i = 72.8 and 1.09 μM, respectively). The response latency of rats during step-down avoidance training was significantly and dose-dependently reduced when animals were intrahippocampally infused with the agent (0.01, 0.1, 1 and 10 μg) post-training and 24 h before testing. Amnesic effects of suramin were suggested to be via antagonism of hippocampal P_2-purinoceptors and NMDA receptors (2).

Suramin (210-260 mg/kg i.p. once per week) was shown to slow growth of human prostate carcinoma cell line (DU145) xenografts on nude mice with a 43% and 55% inhibition observed on days 29 and 57, respectively. Growth of suramin-resistant DU145 xenografts was slightly enhanced by all doses of suramin with 100-342% enhancement observed on day 29. Nadir plasma suramin levels were maintained near target with these doses (3).

Suramin was shown to inhibit angiogenesis *in vitro* and *in vivo*. In rat aortic rings *in vitro*, suramin dose-dependently decreased vascular cell growth with maximum effects at a concentration of 400 μg/ml. Microvessel sprouting in fibrin was also inhibited by treatment with 50 μg/ml with the sprouting index significantly reduced from 0.35 ± 0.04 to 0.14 ± 0.02 mm^2/gray level. *In vivo* studies using the rat model of corneal neovascularization following chemical injury or medium from cells secreting

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angiogenic fibroblast growth factor 3, showed that suramin (1.6 mg/eye/day) decreased blood vessel length and the ratio between the area of blood vessels and the total area of the cornea. Suramin given i.p. (30 mg/kg/day) also markedly decreased neovascularization in rat mesentery following chemical injury (4).

Suramin (1 mM) was shown to dose-dependently inhibit VEGF and b-FGF-stimulated bovine choroidal endothelial cell migration, proliferation and tube formation *in vitro*. The agent may be a potential adjunct in the treatment of choroidal neovascularization (5).

Suramin given in a typical prostate cancer dosing regimen to 12 patients with recurrent high grade astrocytomas with or without prior nitrosourea therapy was shown to be well tolerated although responses to the agent may be delayed for months. Toxicities were mild and reversible with grade 3-4 neutropenia, constipation, diarrhea or nausea observed in only 3 patients. No complete or partial responses were observed at 12 weeks and the median times to progression and survival were 55 and 191 days, respectively. Since 1 patient, removed from the study for progressive disease at 10 weeks, had a partial response at 7 months, it is possible that evaluation of the effect of the agent should be performed at delayed time points. Another patient had stabilization and lived for 2.2 years without further therapy. Pharmacokinetics from 11 patients showed that target serum concentrations of the agent were attained (100-300 mcg/ml) (6).

A phase II, 12-week trial of fixed dose suramin (i.v. 1-h infusions of 1000, 400, 300, 250 and 200 mg/m^2 on days 1-5 and 275 mg/m^2 on days 11, 15, 19 and 22 then weekly for 9 doses) in 14 patients with advanced, progressive renal cell carcinoma showed no activity of the agent. Treatment was well tolerated with no treatment-related deaths observed. Four patients showed grade 3 toxicities (neutropenia, dyspnea, diarrhea and anemia) and 2 had grade 4 (hyperglycemia and neutropenia). No responses were observed out of the 13 evaluable patients and the majority developed progressive disease with only 3 completing the 12-week course. From these results, it was concluded that no further trials are warranted (7).

Suramin was shown to prolong plasma IGF-I levels indicating a possible role for this growth factor in the pathogenesis of bone pain in hormone-refractory prostate cancer in a randomized, double-blind, placebo-controlled, phase II trial in 197 patients. Suramin + hydrocortisone given for 78 days resulted in improved pain response and time-to-disease progression as compared to patients treated with placebo + hydrocortisone. The mean percent change in plasma IGF-I concentrations for suramin + hydrocortisone and placebo + hydrocortisone, respectively, were –18 and +34, –22 and +69, +21 and +44 and +66 and +60 for treatment days 8 and 78 and at follow-up at 3 and 6 months, respectively (8).

A randomized, double-blind, placebo-controlled study of suramin + hydrocortisone in 458 patients with hormone-refractory prostate cancer showed an association between PSA (50% decrease for at least 28 day) response and increased objective responses and overall survival. A PSA response was achieved in 73% of patients treated with suramin + hydrocortisone as compared to 16% in the placebo + hydrocortisone group. After employing the landmark method, 112 patients in both groups withdrew on or before day 43. PSA response in patients treated with suramin + hydrocortisone was associated with median increases of 88 days for objective progression-free survival and 303 days in overall survival (9).

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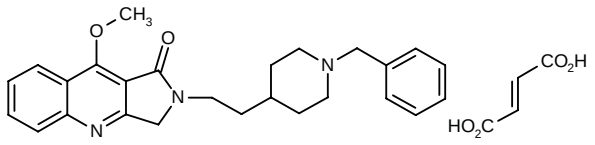

$C_{26}H_{29}N_3O_2.C_4H_4O_4$

SSP; Arena

T-82 was shown to possess potent antiamnestic effects in a variety of animal models and may have potential as an agent in treating Alzheimer's disease. Scopolamine- and cycloheximide-induced amnesia were improved by T-82. In addition, T-82 (0.03-0.3 mg/kg p.o.) significantly improved scopolamine-induced deficits in spatial memory tasks (1).

T-82 may improve the impairment of reference and working memory through its effect on neurotransmitters. T-82 (3, 10 and 30 mg/kg i.p.) dose-dependently increased acetylcholine content in the rat hippcampus. E-2020 and THA similarly increased acetylcholine content, although the effects of THA were weak. To a lesser degree than that found with ACh, T-82 (10 and 30 mg/kg i.p.) raised the content of 5-HT in the hippocampus. E-2020 demonstrated a similar effect on 5-HT whereas THA did not (2).

SS Pharm. is codeveloping T-82, currently in phase I testing in the U.S., with Arena Pharmaceuticals, who will conduct clinical trials through phase II, at which point it will out-license the product. SS Pharm. will retain the rights to conduct further development of the compound in Japan (3).

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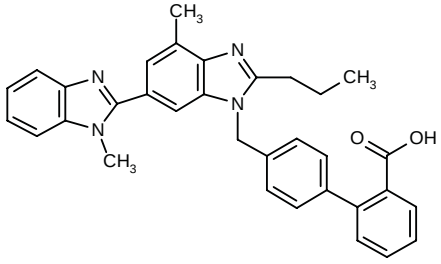

$C_{33}H_{30}N_4O_2$

Boehringer Ingelheim; Abbott; Glaxo Wellcome

Glucuronidation of telmisartan was observed in microsomes of rat liver, kidney and small intestine but not in lung microsomes; glucuronidation was almost absent from microsomes of liver from the Gunn rat. Glucuronidation occurred in microsomes of human liver, kidney, duodenum, ileum and jejunum. Glucuronidation rate was pH-dependent and UGT1A1 catalyzed the reaction (K_m = 27-30 μM) while UGT1A4 and UGT1A6 were ineffective, suggesting that enzymes of the UGT1 family may be involved in glucuronidation of telmisartan. Glucuronidation of telmisartan by microsomes of human liver, kidney or small intestine did not follow simple Michaelis-Menten kinetics and differences in the kinetics were noted between kidney and liver microsomes (1).

While < 2.3% of telmisartan was detected in rat bile, 96% of its major 1-*O*-acylglucuronide was found. The metabolite was cleaved by glucuronidase, a reaction inhibited by saccharo-1,4 lactone. The metabolite had a $[M + H]^+$ ion, m/z 515, and a second fragment ion of lower intensity (m/z 497). The structure of 1-*O*-acylglucuronide was established after the aromatic protons in the 1H NMR spectrum of the metabolite were assigned by 2D NMR spectroscopy. Primary human hepatic 1-*O*-acylglucuronide was found to be identical to the metabolite from rat bile (2).

Telmisartan 1-*O*-acylglucuronide was shown to be extremely stable with a degradation half-life of 26.2 h as compared to 0.5 h for diclofenac 1-*O*-acylglucuronide. The two 1-*O*-acylglucuronides both showed the formation of respective aglycons and the formation of different isomeric acylglucuronides. The isomeric acylglucuronides of telmisartan were 2-*O*-, 3-*O*- and 4-*O*-acylglucuronides (α,β-anomers). Due to its high stability, telmisartan 1-*O*-acylglucuronide would be expected to have low covalent binding to proteins, therefore reducing the risk for adverse reactions involving autoimmune responses (3).

The pharmacokinetics of telmisartan were examined following ^{14}C-telmisartan administration to rats (1, 10 and 30 mg/kg i.v., i.p.v. or i.d.). The gut was determined to be

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the major biotransformation pathway of this agent with rapid absorption of telmisartan observed after i.d. administration; maximal glucuronide levels after i.d. administration were 0.658 (5 min), 1.54 (15 min) and 2.52 (15 min) μg/ml for 1, 10 and 30 mg/kg doses, respectively. The rat liver was also found to dose-dependently biotransform and sequester telmisartan (4).

The biological activity of the telmisartan metabolite 1-*O*-acylglucuronide was characterized and pharmacokinetics examined after i.v. injection (1.34 and 4.02 mg/kg) into rats. No significant reduction in diastolic blood pressure after 1-*O*-acylglucuronide administration was seen as compared to the rapid decrease observed after telmisartan (1 mg/kg i.v.). While telmisartan significantly inhibited angiotensin II pressor responses, 1-*O*-acylglucuronide had no effect. Plasma clearance of 1-*O*-acylglucuronide was rapid with a terminal half-life of 0.17 h and clearance was higher than that of telmisartan (103 *vs.* 15.6 ml/min/kg). 1-*O*-Acylglucuronide was not observed to be hydrolytically cleaved to the parent compound (5).

Telmisartan was shown to lower blood pressure, decrease cardiac hypertrophy and attenuate renal excretion of protein and albumin in hypertensive diabetic rats. SHR (9-10 weeks old) injected with streptozocin (45 mg/kg i.v. bolus) to induce diabetes were given telmisartan (3 and 10 mg/kg/day by oral gavage) or vehicle 7 days later and treated for 8 months; nondiabetic SHR served as controls. Blood pressure in diabetic SHR was significantly and dose-dependently reduced by telmisartan treatment. Untreated diabetic SHR developed proteinuria and albuminuria as compared to nondiabetic SHR. Telmisartan treatment significantly and dose-dependently attenuated proteinuria and albuminuria in diabetic SHR. After 8 months of treatment cardiac hypertrophy was also significantly reduced in diabetic SHR (6).

A multicenter, randomized, double-blind, parallel-group trial involving 89 hypertensive patients given either telmisartan (80 mg), lisinopril (20 mg) or placebo once daily for up to 8 weeks, showed that incidence of cough was significantly higher (60%) in lisinopril-treated patients as compared to the telmisartan (16%) and placebo (10%) groups. Incidence of respiratory infection in both treated groups was similar although significantly higher than in the placebo group. No differences in adverse events were observed between groups and both telmisartan and lisinopril reduced blood pressure in a similarly effective manner (7).

In a multicenter, randomized, double-blind, double-dummy, placebo-controlled trial, once daily telmisartan (40, 80, 120 or 160 mg) for 12 weeks was compared to enalapril (20 mg) in 433 patients with hypertension. All doses of telmisartan produced greater reductions in supine blood pressure than enalapril and both drugs were significantly more effective than the placebo. Incidence and type of side effects were similar in both groups except cough which was more prevalent in the enalapril group; 1 case of angioedema was reported in the enalapril group (8).

Telmisartan (20, 40, 80, 120 or 160 mg once daily) was effective in reducing blood pressure in a randomized, placebo-controlled trial involving 277 patients with mild to moderate hypertension. After 4 weeks of treatment, all doses of telmisartan significantly lowered trough blood pressure as compared to the placebo. A significant linear dose-response curve was observed for systolic but not diastolic pressure with reductions of 6.5-14.9 mmHg and 6.5-10.1 mmHg, respectively, maintained for 1 week. Plasma telmisartan levels were similar at 1 h and at day 7 and 28 with a mean half-life of 24 h. Incidence and type of adverse effects were not dose-dependent and were similar in all groups (9).

In a multicenter, randomized, placebo-controlled, double-dummy, double-blind, titration-to-response trial, telmisartan (40-80 and 80-120 mg) was as effective as atenolol (50-100 mg) in the treatment of 229 patients with mild to moderate hypertension. Diastolic and systolic supine blood pressure values were significantly different from placebo in both treatment groups. Control of diastolic blood pressure was observed in a similar number of patients receiving 80-120 mg telmisartan (46%) and atenolol (51%) while only 32% of patients receiving 40-80 mg telmisartan showed a response. Incidence and type of side effects were similar in both groups with headache and dizziness the most common; side effects were mild to moderate (10).

In a multicenter, randomized, double-dummy, double-blind, titration-to-response trial, long-term telmisartan (40-80 and 80-120 mg) for 26 weeks was as effective as atenolol (50-100 mg) in the treatment of 533 patients with mild to moderate hypertension. Control of diastolic and systolic blood pressure was observed in 84% and 80%, respectively, of the telmisartan-treated patients compared to 78% and 68%, respectively, of atenolol-treated patients. Final systolic/diastolic blood pressure reductions of 20.9/14.4 mmHg and 16.7/13.3 mmHg were observed in the telmisartan and atenolol groups, respectively. Slightly less incidence of male impotence (0.69% *vs.* 2.29%) and fatigue (0.89% *vs.* 3.49%) was reported in patients on telmisartan compared to those on atenolol (11).

In an 8-week multicenter, randomized, open-label, dose-titration trial, telmisartan (80-160 mg once daily) was compared to enalapril (20-40 mg) in 85 patients with severe hypertension; hydrochlorothiazide (25 mg) and amlodipine (5 mg) were added to regimens if supine diastolic blood pressure was $\geq$ 90 mmHg. After 8 weeks, diastolic blood pressure was < 90 mmHg in 55% of the patients receiving telmisartan compared to only 35% in the enalapril group. Reductions in systolic/diastolic blood pressure with telmisartan and enalapril monotherapy were 14.6/13.2 mmHg and 13.0/12.9 mmHg, respectively. A slightly higher incidence of diuretic addition occurred in the group receiving telmisartan and addition of amlodipine further reduced blood pressure in both groups. Incidence and type of side effects (transient and mild to moderate) were similar in both groups; 1 case of angioedema was observed in the enalapril group (12).

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In a multicenter, randomized, double-dummy, double-blind, titration-to-response trial, telmisartan (40-80 and 80-160 mg) was as effective as lisinopril (10-20 and 20-40 mg) in the treatment of 578 patients with mild to moderate hypertension. Diastolic blood pressure was significantly controlled in 82.8% of the telmisartan-treated patients with a reduction of 19.9/16.0 mmHg in systolic/diastolic blood pressure and in 87% of the lisinopril-treated patients with a reduction of 18.0/14.7 mmHg. Incidence of cough was significantly lower in the telmisartan group (3% *vs.* 7%) and fewer withdrawals due to side effects were observed in this group (11% *vs.* 16%); 2 cases of angioedema were reported in the lisinopril group (13).

A pharmacokinetic study of telmisartan in healthy and hypertensive patients given single and multiple doses (i.v. and oral) reported that 98% of the unchanged compound was eliminated in feces with a terminal half-life of 24 h. Greater proportional increases in C_{max} and AUC were observed with oral administration and steady state was reached within 7 days; no accumulation was observed after multiple dosing. High volume of distribution (500 l) and rapid total clearance (> 800 ml/min) were observed following administration of 160 mg (i.v.) and plasma concentrations and AUC values increased dose-proportionally. Absolute bioavailability was input rate-dependent with rates of 42% and 57% observed for 40 and 160 mg (p.o.), respectively. Telmisartan bound tightly (> 99.5%) to plasma proteins (mainly albumin) and binding was permissive (14).

Telmisartan has been launched in the U.S., Germany and Spain and has been approved by the Committee for Proprietary Medicinal Products. Supplied as tablets containing 40 and 80 mg, it is marketed under the trade name Micardis® for the treatment of hypertension (15-19).

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An *in vitro* study examined the effects of protease inhibitors on HER2 shedding in breast cancer cell lines overexpressing HER2 (BT-474, SK-BR-3), demonstrating that shedding is metalloprotease-dependent. Although serine, cysteine and aspartic protease inhibitors did not inhibit shedding, HER2 cleavage was dose-dependently suppressed by 70-80% by EDTA (10 mM), batimastat (5 μM) and TIMP-1 (5 μg/ml); TIMP-2 had no effect. Pervanadate-induced shedding was effectively inhibited by pretreatment with batimastat and pretreatment of cells with trastuzumab (30 nM) decreased HER2 shedding by 73% (1).

The antitumor activities of trastuzumab, SPI-077 and cisplatin alone or in combination were demonstrated in a study in which tumor bearing nude mice were treated 6 days after inoculation. Each agent alone had significant antitumor activity with tumor growth rates of 13.51, 4.74 and 9.24 obtained for cisplatin (4 mg/kg/week), SPI-077 (4 mg/kg/week) and trastuzumab (0.5 mg/kg twice/week), respectively, compared to 29.89 for controls. Combination treatment with trastuzumab and SPI-077 (0.5 mg/kg twice/week + 6 mg/kg/week) was the most effective treatment, showing a significantly reduced tumor growth rate of 1.08 (2).

Results from a phase I trial of trastuzumab (i.v. every 2 weeks prior to pulses of IL-2) + low dose IL-2 (1.25 MIU/m^2/day with pulses of 15 MIU/m^2/day x 3 every 2 weeks) in 25 patients with HER2 overexpressing solid tumors (breast, head and neck, ovarian) have shown that the regimen was well tolerated and effective. No trastuzumab-related dose-limiting toxicities (DLT) were observed in 18 patients receiving doses of 1, 8 or 4 mg/kg, although 12 patients had IL-12-related DLT including platelet (4), constitutional (5), rash (1), diarrhea (1) and neutrophil (1) toxicities. When the IL-2 dose was reduced (1 MIU/m^2/day with 12 MIU/m^2 pulses) in 7 patients, no DLT were seen. One patient given 4 mg/kg trastuzumab developed severe neck pain and dyspnea during infusion. One complete and 2 partial responses were seen in breast cancer patients receiving 4 mg/kg trastuzumab and no responses were observed with 1 and 2 mg/kg (3).

A multicenter, randomized controlled trial in 469 female patients with HER2 positive metastatic breast cancer evaluated treatment with trastuzumab alone or given simultaneously with doxorubicin + cyclophosphamide (AC) or paclitaxel chemotherapy. At a mean follow-up of 25 months, chemotherapy + trastuzumab was superior to chemotherapy alone in terms of mean overall survival (25.4 *vs.* 20.9 months) with a relative risk of death of 0.77. Trastuzumab was well tolerated except for a higher incidence of class III/IV cardiac dysfunction in the AC + trastuzumab group (19%) as compared to the paclitaxel + trastuzumab (4%) group. Overall survival was also superior in chemotherapy + trastuzumab groups over groups receiving trastuzumab alone (4).

Trastuzumab (4 mg/kg loading then 2 mg/kg/week i.v.) was shown to improve Global Quality of Life (GQL) and social function in an open-label, single-agent study in 222 women with metastatic breast cancer who had progression following 1-2 prior chemotherapy regimens. Median duration of response was 9.1 months and adverse effects were mild to moderate with the exception of cardiac dysfunction in 2%. Significant improvements in GQL and social function scores were observed as assessed by patient-administered EORTC-QLQ-C30 at baseline and every 12 weeks. Patients with complete or partial responses had improvement in HRQL scores ranging from 7-20 points (5).

A phase II study demonstrated the safety and efficacy of trastuzumab + 1-h taxol in 42 patients with $HER2^+$ or $HER2^-$ metastatic breast cancer. Following pretreatment with dexamethasone (10 mg), diphenhydramine (50 mg) and cimetidine (300 mg), patients were given taxol (90 mg/m^2 i.v. over 1 h) followed by trastuzumab (2 mg kg i.v. over 30 min with a 4 mg/kg dose over 90 min in week 1). A mean of 16 infusions/patient were given with a mean dose intensity of 82 mg/m^2/week. Dose-limiting toxicity was grade 3/4 neutropenia (10%) with 2 febrile neutropenia events observed. Other grade 3/4 toxicities were diarrhea (7%) and onycholysis with infection (7%). No significant decreases in left ventricular ejection fraction were observed at week 8 and 16. One patient given a cumulative dose of 615 mg/m^2 4 weeks before taxol + trastuzumab had transient chronic heart failure. Of the 26 evaluable patients, 23 responded which included 3 complete responses; 20/28 $HER2^+$ patients and 3/8 $HER2^-$ patients responded (6).

A therapy optimizing study showed that normalization of erbB-2 serum levels in patients with metastatic breast cancer may be an important tool for determining the optimal schedule for monoclonal antibody treatment with agents such as trastuzumab. The study correlated the clinical course of stage IV breast cancer (according to WHO criteria) with the shed of erbB-2 fragment and CA27.29 tumor marker serum levels from samples taken from 32 patients given paclitaxel (90 mg/m^2/week x 6 every 9 weeks). Of the 28 evaluable patients, 9 were erbB-2^+ (> 15 U/ml) with a mean protein expression at baseline of 65 U/ml. The overall response rate was 36% with a rate of 62% obtained in erbB-2^+ patients. In responders, serum erbB-2 was reduced to below detection levels. However, patients with stable and progressive disease also showed normalized erbB-2 serum levels. ErbB-2 levels correlated with serum CA27.29 (7).

Trastuzumab (Herceptin®) has been launched by Roche in Switzerland and is indicated for the treatment of those patients with metastatic breast cancer who have tumors that overexpress the protein HER2 and as a single agent for the treatment of those who have received one or more chemotherapy regimens for their metastatic disease. It is also indicated in combination with paclitaxel for treating patients who have not received chemotherapy for their metastatic disease. Trastuzumab has also been approved in Canada (8, 9).

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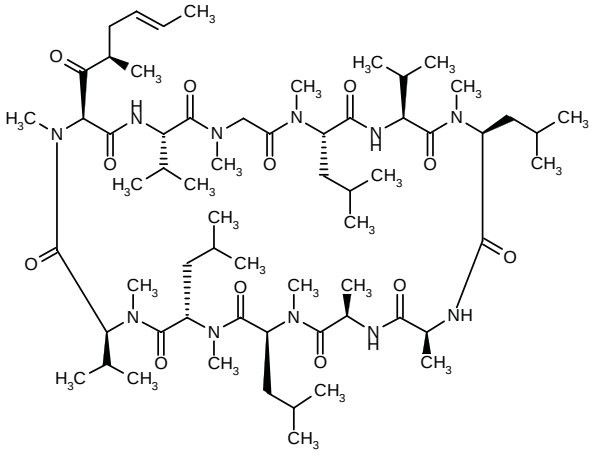

$C_{63}H_{111}N_{11}O_{12}$ **Novartis**

SDZ-PSC-833, was shown to activate ceramide synthesis in human MDR epidermoid carcinoma cells (KB-V-1) using [^{3}H]palmitic acid as a tracer. A 40% increase and > 3-fold increase in ceramide production as compared to control cells was observed at 15 min and 3 h after SDZ-PSC-833 (5 μM) treatment, respectively; dose-dependence was demonstrated at 24 h with ceramide levels 2.5- and 13.6-fold higher after treatment with 1 and 10 μM SDZ-PSC-833, respectively. SDZ-PSC-833-induced increases in ceramide were inhibited by the

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ceramide synthetase inhibitor, fumonisin B-1. Ceramide mass analysis by TLC lipid charring further showed that the agent enhanced ceramide synthesis in both KB-V-1 cell and wild-type KB-3-1 cells. Progressive decreases in cell survival correlated to ceramide increases, suggesting possible cytotoxic effects of ceramide, and SDZ-PSC-833-treated cells also showed olgionucleosomal DNA fragmentation typical of apoptosis. Cell survival was reduced 20% by vinblastine or SDZ-PSC-833 (1 μM) alone as compared to 0% with coadministration indicating reversal of MDR with SDZ-PSC-833; synergistic ceramide production was also observed with coadministration and vinblastine toxicity was enhanced by the agent in wild-type cells (1).

Results from an *in vitro* study suggest that combination therapy with PSC-833 and idarubicin may be effective in reversing MDR in leukemia cells. Although PSC-833 did not affect cytotoxicity or intracellular accumulation/retention of idarubicin or its metabolite, idarubicinol, in parent K562 cells, accumulation of idarubicin and idarubicinol was restored to 104% and 116%, respectively, in P-glycoprotein-overexpressing MDR K562/D1-9 cells after 60 min incubation with the agent (0.4 μM). Retention was also restored and the resistance indices of idarubicin and idarubicinol decreased from 20- to 4-fold and 104- to 1.5-fold, respectively, following PSC-833 treatment (2).

Ritonavir was shown to inhibit P-glycoprotein more potently than SDZ-PSC-833 indicating that the agent may improve brain uptake of HIV protease inhibitors important in the treatment of AIDS dementia complex. The effect of P-glycoprotein inhibition on saquinavir uptake into porcine primary brain capillary endothelial cells *in vitro* was examined; saquinavir uptake occurs through a combination of diffusional uptake and an opposing saturable extrusion process. Saquinavir uptake into cells was significantly and dose-dependently enhanced up to 2-fold by SDZ-PSC-833 (IC_{50} = 1.13 μM) and ritonavir inhibited P-glycoprotein mediated extrusion of saquinavir (IC_{50} = 0.2 μM) (3).

SDZ-PSC-833 was shown to inhibit both doxorubicin and vinblastine cellular transport via human P-glycoprotein (P-gp) in an *in vitro* study using monolayers of LLC-GA5-COL150 cells which overexpress P-gp. P-gp-mediated transport of doxorubicin and vinblastine was dose-dependently inhibited by both SDZ-PSC-833 (IC_{50} = 0.29 and 3.66 μM, respectively) and ciclosporin (IC_{50} = 1.06 and 5.10 μM, respectively); intracellular accumulation of doxorubicin and vinblastine increased with treatments. SDZ-PSC-833 may be more effective than ciclosporin since the former agent was not transported by P-gp and was more lipophilic (4).

While PSC-833 at a dose of 0.1 mg/kg significantly reduced biliary excretion clearance of digoxin (from 3 to 0.5 ml/min/kg) in rats, 3 mg/kg was needed to significantly reduce clearance of vincristine (from 36 to 9 ml/min/kg); 3 mg/ml reduced renal clearance of vincristine by 30% but did not affect that of digoxin. The tissue-to-plasma digoxin but not vincristine (1.07 *vs.* 1.37 at 2 h) ratio in brain was significantly increased (0.34 *vs.* 1.64) 6 h after PSC-833 administration (5).

A study has shown that liposomal formulations of doxorubicin reduced the inhibitory effects of the MDR modulator, valspodar, on doxorubicin clearance. When free doxorubicin and valspodar were administered to rats implanted with jugular vein and bile duct catheters for constant sampling, significant decreases in renal and biliary clearances and increases in plasma AUC were observed. However, when doxorubicin was given in liposomal formulation (EPC/Chol or PEG-DSPE/DSPC/Chol), the valspodar-induced decreases in clearance were markedly reduced; no significant differences were observed in clearance when PEG-DSPE/DSPC/Chol doxorubicin was given alone or with valspodar (6).

PSC-833 was evaluated in preclinical trials in combination with vincristine and vinblastine. The effects of the study drug, a P-glycoprotein pump inhibitor, on the intracellular uptake of [^{3}H]-vincristine and [^{3}H]-vinblastine by HCT-15 and COLO-205 cells were studied *in vitro*. Whereas valspodar increased the uptake of both alkaloids in HCT-15 cells –a cell line with extensive expression of P-gp–, it did not have the same effect in COLO-205 cells, which have only minimal expression of P-gp. *In vivo* in solid tumor-inoculated mice, infusion of PSC-833 (10 μg/h) increased the HCT-15 tumor disposition of [^{3}H-]-labeled vincristine and vinblastine to levels similar to those observed *in vitro* (7).

PSC-833 has been evaluated in a dose-ranging phase I trial enrolling older (> 55 years) patients with newly diagnosed AML. PSC-833 was administered as a loading dose of 2 mg/kg by 2-hour infusion plus a concurrent administration of 10 mg/kg/day by continuous infusion over 120 h. Chemotherapy consisted in mitoxantrone (4 mg/m^2 x 5) plus etoposide (40 mg/m^2 x 5) starting at 40% of the standard dose and escalated in cohorts of eight patients each. PSC-833 was generally well tolerated; a 25% dose reduction was required in only one patient suffering ataxia, and only limited grade IV/V non-hematological toxicities have been reported. Early results indicate that addition of the P-glycoprotein pump inhibitor PSC-833 to a chemotherapy regimen incorporating mitoxantrone and etoposide is effective in the treatment of older, chemotherapy-naive patients with AML; further investigation is being pursued (8).

The results of a phase II study have been published, providing further evidence of the efficacy of valspodar in combination with chemotherapy in patients with acute myelogenous leukemia (AML). The multicenter study enrolled 39 patients with refractory or relapsed AML, who received a combination of mitoxantrone, etoposide and cytarabine (MEC) plus the P-glycoprotein (P-pg) inhibitor valspodar; 37 patients could be evaluated for response. Based on evidence of pharmacokinetic interactions of etoposide and mitoxantrone with valspodar at a higher dose in the first cohort of subjects, the doses of the chemotherapeutic agents were reduced substantially. In a second cohort of patients, treatment for 5 days with mitoxantrone (4 mg/m^2) plus etoposide (40 mg/m^2) plus

cytarabine (1 g/m^2) plus valspodar (pretreatment loading dose of 2 mg/kg over 4 h, then at 10 mg/kg/day for 5 days) was well tolerated. Complete or partial remissions were obtained in 43% of patients receiving MEC plus valspodar (12 CR and 4 PR); no response was seen in the remaining 21 patients receiving the valspodar-containing regimen. P-glycoprotein function and its inhibition by valspodar were assessed using rhodamine-123 efflux in 19 patients, and the results showed that the median percentage of blasts expressing P-gp was higher in leukemic cells with valspodar-inhibitable rhodamine efflux as compared to those without valspodar-inhibitable rhodamine efflux (49% *vs.* 17%). The latter finding is in line with other reports providing evidence of several mechanisms contributing to multidrug resistance in human malignancies, and supports the use of multifunctional MDR modulators or the combined use of blockers of various resistance mechanisms in order to more effectively circumvent MDR in hematologic malignancies. Based on the findings of the current study, the Eastern Cooperative Oncology Group has initiated a phase III trial in the U.S. evaluating valspodar in a similar group of patients (9).

A study examining 45 chronic lymphocyte leukemia patients for MDR showed that those individuals who developed resistance to VAD (i.v. vincristine, doxorubicin and oral dexamethasone) chemotherapy more frequently express P-glycoprotein (P-gp)170. The study used *ex vivo* assays including a functional assay using doxorubicin retention, a cytotoxicity assay (MTT) and 4 monoclonal antibodies. P-gp170 was most frequently detected with MRK-16 (48%) antibody, by functional modulation of doxorubicin retention by PSC-833 (40.6%) and by functional modulation of the MTT assay with vincristine (0.29) and doxorubicin (0.39) with PSC-833 (1 μg/ml). Three patients who developed resistance to VAD chemotherapy expressed P-gp170. Expression of P-gp170 was also shown to increase with advancing disease stage and prior treatment but not with prior alkylating agent therapy (10).

The efficacy and safety of PSC-833 (5 mg/kg/day p.o. 28 doses total; for 6 days/21-day cycle) in combination with vinblastine (0.6 or 0.75 mg/m^2/days 120 h continuous infusion between the 6th and 7th dose of PSC-833) were evaluated in a phase I/II open-label study involving 23 patients with pretreated advanced renal cell cancer. The maximum tolerated dose of vinblastine was 0.6 mg/m^2/day; hyponatremia, the dose limiting toxicity, occurred in both patients receiving 0.75 mg/m^2/day. No complete or partial responses were observed and frequent adverse effects of grade 3 or 4 included bilirubinemia (61%), hypertension (43%), ataxia (30%), malaise (22%), hypertension (17%) and nausea (17%). It was concluded that PSC-833 modulation of the P-gp efflux pump could not overcome vinblastine resistance in these patients (11, 12).

The efficacy and safety of PSC-833 (4 mg/kg p.o. q.i.d. x 24 doses for 7 days) combined with VAD (vincristine 0.2 mg/day i.v.; doxorubicin 7.0 mg/m^2/day i.v.; dexamethasone 40 mg/day p.o. days 2-5 and 16-19) was demonstrated in 41 patients with VAD-refractory multiple myeloma. Out of the 41 patients who completed 138 cycles, 36 were evaluated showing that myelosuppression was moderate with treatment and objective responses were seen in 10% of the patients. Grade 3/4 granulocytopenia (36%) and grade 3/4 thrombocytopenia (11%) were reported and toxicities included reversible ataxia (36%) and hyperbilirubinemia (19%). Trough PSC-833 concentrations (> 1000 ng/ml) shown to reverse multidrug resistance *in vitro* were achieved in 12/13 patients (13).

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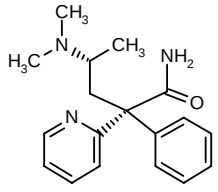

$C_{18}H_{23}N_3O$ **Fujisawa**

Fujisawa has withdrawn the NDA for vamicamide from the Japanese regulatory authority. Fujisawa conducted additional clinical trials with vamicamide to support the NDA data, comparing its efficacy and safety with an approved drug. After careful analysis of the trial results, however, it was concluded that the results failed to show that vamicamide was significantly superior to the active control in overall improvement of disease condition and equal to the active control in terms of usefulness (1).

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