Drugs of the Future 2001, 26(10): 999-1025

CCC: 0377-8282/2001

Information Update

Volume 1-25, Number 10

Estimated developmental phase for this month's updated products:

Preclinical

HInd(RuInd$_2$Cl$_4$) (oncolytic; German Cancer Res. Center)

Phase I

M-40403 (superoxide dismutase mimetic; MetaPhore, Pharmacia)

Phase II

AMD-473 (oncolytic; AnorMED, AstraZeneca)
CPX (treatment of cystic fibrosis; SciClone)
Elcometrine (female contraceptive, hormone replacement therapy; Population Council)
Finrozole (treatment of BPH; Orion Corp., Hormos)
GM-611 (treatment of GERD; Chugai)
GYKI-16084 (treatment of BPH; Inst. Drug Res., Ivax)
KNI-272 (anti-HIV; Japan Energy)
Peldesine (treatment of lymphoma; BioCryst, Torii)
Tonabersat (antimigraine; GlaxoSmithKline)

Phase III

Lasofoxifene tartrate (treatment of osteoporosis, treatment of breast cancer; Pfizer, Ligand)
LY-333531 mesylate hydrate (treatment of diabetic retinopathy; Lilly)
Mitiglinide calcium hydrate (antidiabetic; Kissei, Servier)
ML-3000 (antiarthritic; EuroAlliance, Forest)
Suramin sodium (oncolytic; Pfizer)
Tetrandrine (oncolytic, antihypertensive; Kaken, Chin. Acad. Med. Sci.)
Valspodar (multidrug resistance modulator; Lilly)

Preregistered

Abarelix (treatment of prostate cancer, treatment of endometriosis; Praecis, Sanofi-Synthélabo)
Ebselen (treatment of stroke, antioxidant; Aventis Pharma, Daiichi Pharm.)
Rupatadine fumarate (treatment of allergic rhinitis; Uriach)

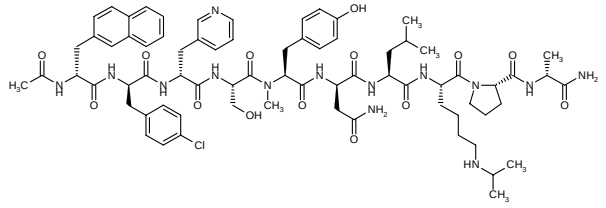
Launched/Year

Alfuzosin hydrochloride (treatment of BPH; Sanofi-Synthélabo, SkyePharma)/1988
Alteplase (thrombolytic; Roche, Genentech)/1987
Bupropion hydrochloride (antiobesity, aid to smoking cessation, antidepressant; GlaxoSmithKline)/1989
Clarithromycin (macrolide antibiotic; Abbott)/1990
Eprosartan mesilate (antihypertensive, treatment of heart failure; GlaxoSmithKline, Solvay, Unimed)/1997
Formoterol fumarate (antiasthmatic, treatment of COPD; Yamanouchi, Novartis, AstraZeneca, SkyePharma)/1986
Lidakol™ (anti-HSV; Avanir, GlaxoSmithKline)/2000
Montelukast sodium (antiallergy/antiasthmatic, treatment of allergic rhinitis; Merck & Co.)/1997
Nebivolol (antihypertensive; Janssen, Menarini, Meiji Seika, Bertek)/1997
Oxcarbazepine (antiepileptic; Novartis, Kissei)/1990
Rapacuronium bromide (neuromuscular blocker; Organon)/1999 - withdrawn 2001
Sirolimus (treatment of transplant rejection; Wyeth-Ayerst)/1999
Telmisartan (antihypertensive; Boehringer Ingelheim, Abbott, GlaxoSmithKline)/1999

Abarelix
Plenaxis®

Treatment of Prostate Cancer
Treatment of Endometriosis

EN: 251979



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

Praecis; Sanofi-Synthélabo

Researchers from the Abarelix Study Group have reported the results of a phase II open-label study comparing abarelix depot with luteinizing hormone-releasing hormone (LHRH) agonists with or without an antiandrogen, which showed that after 1 week, medical castration had been achieved in 75% of those treated with abarelix depot compared to none of those given LHRH agonists. On the other hand, none of those treated with abarelix had a testosterone surge during the first week, whereas a surge was seen in 82% of those given LHRH agonists. In this study, 209 patients with prostate cancer requiring hormone therapy were given i.m. injections of abarelix depot on days 1, 15 and 29, and then every 28 days. A prospective, nonrandomized control group consisted of 33 patients receiving LHRH agonists with or without an antiandrogen. The safety profile of abarelix depot was acceptable. Several patients reported minor and reversible dermatological complaints but no other associated allergic symptoms; safety data were not collected for the control group. No deaths were recorded in either group over the first 27 days. In addition to the rapid and consistent medical castration observed with abarelix depot in the absence of a testosterone surge, between days 4 and 13 there was a greater percentage decrease in baseline prostate-specific antigen (PSA) levels in the abarelix group compared with the control group. Further investigation is recommended to assess the long-term effects of abarelix depot (1).

A multicenter phase III study compared abarelix and leuprolide acetate in patients with early- and late-stage prostate cancer. Of the 271 participants, 180 were randomized to abarelix 100 mg and 91 received leuprolide acetate 7.5 mg. Both agents were administered i.m. every 4 weeks, with an additional dose on day 15. A surge in plasma testosterone levels was observed in 82% of the leuprolide group, in contrast to none in the abarelix group. Patients treated with leuprolide also showed surges in dihydrotestosterone, luteinizing hormone and follicle-stimulating hormone (FSH). Abarelix achieved castrate testosterone levels more rapidly than leuprolide, with 72% of abarelix-treated patients reaching castrate levels at day 8 compared to none of those receiving leuprolide. Additionally, abarelix treatment led to significantly greater decreases in PSA from baseline than leuprolide at days 15 and 29. By day 85, both agents caused a > 90% decrease in serum PSA and achieved target testosterone levels (2).

A randomized, multicenter, open-label, phase III study was carried out to compare the time to induction of castration by abarelix depot 100 mg and goserelin 3.6 mg plus bicalutamide 50 mg in 177 patients with advanced prostate cancer. Treatments were well tolerated. Nearly all patients achieved castration by day 84, and the median time to castration was 7 and 21 days in the abarelix depot and goserelin plus bicalutamide groups, respectively. Testosterone surge was seen in 96% of goserelin plus bicalutamide patients and in none of the abarelix depot patients (3).

A head-to-head, randomized, multicenter phase III trial compared abarelix depot (100 mg) to leuprolide acetate (7.5 mg) plus bicalutamide (50 mg) in 255 patients with early- and late-stage prostate cancer. Testosterone surge occurred in 86% of patients receiving leuprolide plus bicalutamide, while none of those receiving abarelix experienced such a surge. On day 8, 68% of abarelix-treated patients had achieved castration testosterone levels, as compared to none of those in the leuprolide plus bicalutamide group. At 24 weeks, all patients in both groups had achieved a 50% reduction in serum PSA (4).

Abarelix depot was the subject of a trial in 48 men with advanced symptomatic prostate cancer at risk for clinical flare phenomenon if given LHRH treatment. Patients had bone pain from skeletal metastases in 24 cases, bladder neck outlet obstruction in 13, ureteral obstruction in 7 and impending neurological compromise in 4. All received abarelix depot 100 mg i.m. on days 1, 15, 29 and then every 28 days up to 1 year. None of the patients required orchiectomy through day 85. Medical castration was achieved in 41 patients by day 8 and in 47 by day 29. Hormone levels were suppressed during treatment. An objective response was seen in 90% of patients. VAS pain scores were sharply reduced from baseline in those patients evaluated (5).

Two large, multicenter, randomized studies compared initial hormonal therapy for prostate cancer with abarelix depot to that with leuprolide acetate or leuprolide acetate plus Casodex. Patients in study 1 received abarelix depot 100 mg or leuprolide 7.5 mg. In study 2, patients received abarelix depot 100 mg or leuprolide plus Casodex. Testosterone surge was avoided in all abarelix depot patients and in 18% and 14% of leuprolide- and leuprolide plus Casodex-treated patients, respectively. Abarelix depot was also more rapid in inducing castration than either of the other treatments. All treatments achieved and maintained medical castration in over 90% of patients and were well tolerated (6).

In an open-label study in 242 patients with prostate cancer, abarelix depot (100 mg i.m. injection) was administered to 209 men and LHRH superagonists, with or without antiandrogens, were administered to 33 men. A surge in the serum concentration of FSH was seen on day 2 in men treated with LHRH superagonists, with and without

an antiandrogen, whereas men treated with abarelix depot experienced an immediate and sustained decrease in FSH concentration in serum. Thus, FSH appears to be an independent growth factor for prostate cancer and the decrease in FSH induced by abarelix depot could play a role in treating men with endocrine-responsive disease (7).

Amgen and Praecis have announced that they are ending their agreement to jointly develop and commercialize abarelix for injectable suspension for all indications. Although this includes ongoing programs for the treatment of hormonally responsive prostate cancer and endometriosis, Praecis stated that it remains committed to the further development and commercialization of the agent for the treatment of these two indications (8).

Praecis has met with the FDA in connection with certain issues raised by the FDA in a letter to the company regarding its application for marketing approval of abarelix depot (Plenaxis™) for the treatment of hormonally responsive prostate cancer. The FDA recommended that Praecis analyze the allergic reactions that occurred in a small subset of clinical trial patients. This analysis will be conducted utilizing existing data and samples. In addition, the FDA expressed concern that in a subset of patients testosterone suppression was not maintained beyond the 3-month pivotal study timeframe. Praecis is considering various alternatives to address this issue, which may include additional clinical trials. These trials would evaluate the use of currently available hormonal therapies in patients first treated with Plenaxis™. The company expects that these studies, if conducted, would be of relatively limited scope and duration (9).

1. Tomera, K., Gittelman, M., Gleason, D., Moseley, W., Zinner, N., Murdoch, M., Menon, M., Campion, M., Garnick, M.B. *The gonadotropin-releasing hormone antagonist abarelix depot versus luteinizing hormone releasing hormone agonists leuprolide or goserelin: Initial results of endocrinological and biochemical efficacies in patients with prostate cancer.* J Urol 2001, 165(5): 1585.

2. Zinner, N., Harris, R., Tomera, K., Mcleod, D., Gleason, D., Fotheringham, N., Campion, M., Garnick, M. *More rapid reduction in serum testosterone (T) and PSA with abarelix depot (A-D), a new GnRH antagonist, compared with leuprolide acetate.* J Urol 2001, 165(5, Suppl.): Abst 850.

3. Selvaggi, F., Khoe, G.S.S., Van Cangh, P. et al. *Comparison of abarelix depot (A-D) and goserelin (G) plus bicalutamide (B) in advanced prostate cancer: Results of a multicentre, open-label, randomised, phase III study.* Eur Urol 2001, 39(Suppl. 5): Abst 303.

4. Pessis, D., Friedel, W., Steidle, C., Trachtenberg, J., Fotheringham, N., Campion, M., Garnick, M. *Monotherapy with a new GnRH antagonist, abarelix depot (A-D), results in more rapid testosterone (T) suppression without an initial surge compared with leuprolide acetate (L) plus bicalutamide (B): Results of a multicenter phase 3 study.* J Urol 2001, 165(5, Suppl.): Abst 685.

5. Koch, M., Steidle, C., Brosman, S., Centeno, A., Friedel, W., Menchaca, D., Garnick, M. *Abarelix depot (A-D): A GnRH antagonist benefits highly symptomatic prostate cancer (PC) patients who are at risk for a clinical flare phenomenon with LHRH agonist treatment.* J Urol 2001, 165(5, Suppl.): Abst 1185.

6. McLeod, D., Trachtenberg, J. *Abarelix depot (AD) versus leuprolide (L) with and without bicalutamide (Casodex) [C] for prostate cancer: Results of two multicenter, randomized phase III studies.* Eur Urol 2001, 39(Suppl. 5): Abst 304.

7. Garnick, M.B., Campion, M. *Abarelix depot, a GnRH antagonist, v LHRH superagonists in prostate cancer: Differential effects on follicle-stimulating hormone.* Mol Urol 2000, 4(3): 275.

8. *Amgen and Praecis end their Plenaxis agreement.* DailyDrugNews.com (Daily Essentials) Sept 21, 2001.

9. *FDA requires further information for approval of Plenaxis.* DailyDrugNews.com (Daily Essentials) Sept 14, 2001.

Original monograph - Drugs Fut 1998, 23: 1057.

Additional References

Fair, W.R., Garnick, M. *Aberelix-depot (A-D) vs. leuprolide acetate ± bicalutamide (Casodex) (C), for patients with prostatic cancer: Combined results in multi-institutional, randomized, phase III studies in 526 patients.* BJU Int 2000, 86(Suppl. 3): Abst MP6.1.05.

Fisher, H. et al. *Abarelix depot (A-D) monotherapy reduces PSA levels comparable to leuprolide acetate (L) plus bicalutamide (B): Results of a multicenter trial of rising PSA, advanced (D1/D2), neoadjuvant hormonal therapy (NHT) and intermittent hormonal therapy (IHT) prostate cancer (PC) prostate cancer (PC) patients (pts).* Proc Am Soc Clin Oncol 2001, 20(Part 2): Abst 2359.

Gaylis, F. et al. *The economic value of abarelix depot therapy in highly symptomatic prostate cancer patients.* Proc Am Soc Clin Oncol 2001, 20(Part 2): Abst 2397.

Gittelman, M. et al. *Greater and more rapid decrease in prostate specific antigen (PSA) and testosterone (T) levels with abarelix depot (A-D) compared to leuprolide acetate (L): Results of a multicenter 24-week safety study.* Proc Am Soc Clin Oncol 2001, 20(Part 2): Abst 2367.

Karbon, W. et al. *Receptor binding and biological properties of abarelix, a potent GnRH receptor antagonist.* Proc Am Soc Clin Oncol 2001, 20(Part 2): Abst 2391.

Koch, M. et al. *Clinical and symptomatic response with abarelix depot (A-D), a GnRH antagonist, in highly symptomatic prostate cancer (PC) patients at risk for clinical flare with LHRH agonist treatment.* Proc Am Soc Clin Oncol 2001, 20(Part 2): Abst 2362.

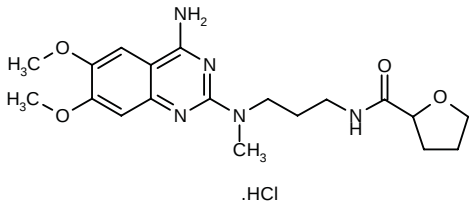
Schulman, C.C. et al. *Abarelix depot, a pure GnRH antagonist, is devoid of initial androgen and gonadotropin surge.* BJU Int 2000, 86(Suppl. 3): Abst MP6.1.04.

Trachtenberg, J. et al. *Avoidance of FSH surge and maintained suppression of follicle-stimulating hormone (FSH) with abarelix depot (A-D) compared to leuprolide (L) ± bicalutamide in prostate cancer (PC) patients.* Proc Am Soc Clin Oncol 2001, 20(Part 2): Abst 2358.

Alfuzosin Hydrochloride
Xatral® OD

Treatment of BPH

EN: 090436



$C_{19}H_{27}N_5O_4.HCl$ **Sanofi-Synthélabo; SkyePharma**

SkyePharma and Sanofi-Synthélabo have reported that an NDA was filed with the FDA in December 2000 for Xatral® OD (alfuzosin hydrochloride 10 mg), a sustained-release once-daily formulation of Xatral®, currently available as a 2- or 3-times-a-day formulation in 80 countries for the treatment of the functional symptoms of benign prostatic hyperplasia (BPH). Xatral® OD was formulated using SkyePharma's proprietary Geomatrix® oral drug delivery technology. Xatral® OD was launched in Europe in February 2000 and is now available in six European countries and French overseas territories. Additional launches in Europe are anticipated in the near future (1).

1. *NDA filed in U.S. for once-daily Xatral.* DailyDrugNews.com (Daily Essentials) Jan 25, 2001.

Original monograph - Drugs Fut 1986, 11: 821.

Additional References

Roehrborn, C. et al. *Efficacy and safety of a once-a-day formulation of alfuzosin for lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).* Eur Urol 2001, 39(Suppl. 5): Abst 376.

Roehrborn, C.G. et al. *Prostate volume assessment is unnecessary in alpha-blocker clinical trials in symptomatic BPH patients (based on pooled results of alfuzosin OD studies).* J Urol 2001, 165(5, Suppl.): Abst 1550.

Alteplase
Activase®

Thrombolytic

EN: 137796

Roche; Genentech

Genentech has reported positive results from a large-scale phase III study of the safety of Cathflo™ Activase® (alteplase) for the treatment of occluded central venous catheters. The company reported positive results earlier this year from an efficacy study of Cathflo™ Activase®, which is currently awaiting FDA approval (1).

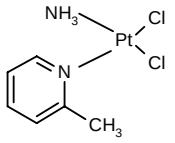
1. *Genentech highlights business and product events for Q2 2001.* DailyDrugNews.com (Daily Essentials) July 17, 2001.

Original monograph - Drugs Fut 1985, 10: 835.

AMD-473
ZD-0473

Oncolytic

EN: 234240



$C_6H_{10}Cl_2N_2Pt$ **AnorMED; AstraZeneca**

ZD-0473 has been investigated in combination with paclitaxel, gemcitabine, topotecan and vinorelbine in cisplatin-sensitive and cisplatin-resistant human ovarian carcinoma cell lines. Simultaneous exposure with paclitaxel proved to be the most synergistic of the combinations. Combination with the other three drugs in the CH1 cell line resulted in synergism, while combination with the other three drugs in the A2780 line was antagonistic. The combination of ZD-0473 and gemcitabine or topotecan was synergistic in the 15-fold acquired cisplatin-resistant A2780cisR cell line. Sequential studies revealed greater growth inhibition when ZD-0473 was administered before, as compared to after, paclitaxel in three of the four cell lines (1).

The expression of approximately 6000 gene sequences was compared in wild-type SKOV-3 ovarian carcinoma cells treated with cisplatin and in SKOV-3 cells with acquired platinum resistance using cDNA array technology. In the resistant cell line, 31 sequences were increased by at least 3-fold. RNA levels of IL-6 were increased in wild-type cells after cisplatin administration. Treatment with ZD-0473, a non-cross-resistant platinum compound, resulted in different gene expression patterns, suggesting it may have clinical value in malignancies resistant or unresponsive to cisplatin (2).

To understand the major mechanisms of resistance to oxaliplatin, two colon and two ovarian carcinoma human cell lines were made oxaliplatin-resistant and treated with ZD-0473. The experiments revealed non-cross-resistance between ZD-0473 and oxaliplatin in the four resistant cell-lines. Exposure to increasing concentrations of oxaliplatin rendered the lines resistant, moreso in the colon than in the ovarian models. ZD-0473, however, circumvented resistance in all cell lines. Non-cross-resistance to cisplatin and the trinuclear platinum drug BBR-3464 was also seen in the colon lines. Glutathione levels were comparable within the HCT116, HT29 and CH1 cell-line pairs (3).

A phase I trial of ZD-0473 combined with paclitaxel was carried out in patients with advanced solid

malignancies to determine the maximum tolerated doses of the drugs used in combination and to assess toxicity. A 3-h infusion of paclitaxel was followed 30 min later by a 1-h infusion of ZD-0473 on day 1 of each 21-day cycle. A total of 10 patients have completed treatment with paclitaxel at a constant dose of 135 mg/m^2 together with ZD-0473 at 60, 90 or 120 mg/m^2. Short-lived and non-dose-limiting grade 3/4 neutropenia and/or thrombocytopenia were observed. Mild nausea, diarrhea and metallic taste were also noted. There have been 4 cases of disease stabilization but no responses. Maximum tolerated dose for phase II trials had not been determined at the time of reporting (4).

In a phase I trial, ZD-0473 was administered in combination with gemcitabine to 13 patients with advanced solid malignancies. ZD-0473 (60-120 mg/m^2) was given as a 1-h infusion on day 1 and gemcitabine (750 mg/m^2) as a 30 min infusion on days 1 and 8 with the cycle repeated every 21 days. Toxicities during cycle 1 included thrombocytopenia, neutropenia and mild nausea. Up to the time of reporting, myelosuppression was more pronounced in pretreated patients and no nephrotoxicity or neurotoxicity was observed. At the time of reporting there was 1 partial response, 2 minor responses and 3 stable disease. Overall, the combination appeared to be well tolerated with promising antitumor activity (5).

AnorMED has announced that AstraZeneca will review the design and timetable for the phase III clinical trial program for ZD-0473 in ovarian cancer. ZD-0473 is a new-generation platinum-based anticancer agent which AnorMED has licensed to AstraZeneca. This decision was based on a review of recently available data that questioned the response rate previously seen in platinum-resistant ovarian cancer patients. The response rate in second-line platinum-sensitive ovarian patients has been maintained and remains encouraging. In addition, emerging data from ongoing phase I and phase II clinical studies in a variety of indications continue to support the conclusion that ZD-0473 is an active drug with a manageable toxicity profile. Further, ZD-0473 has not been associated with clinically relevant nerve, kidney or hearing toxicities in clinical studies. AstraZeneca will reappraise the ZD-0473 development program, including ovarian cancer studies. Meanwhile, all ongoing trials continue to recruit patients in a broad range of tumor types (6).

1. Rogers, P.M., Boxall, F., Allot, C.P., Stephens, T., Kelland, L.R. *In vitro combination studies with the sterically hindered platinum drug, ZD0473, in cisplatin-sensitive and -resistant human ovarian carcinoma cell lines.* Clin Cancer Res 2000, 6(Suppl.): Abst 352.

2. Dizon, D.S., Yan, X.-J., Spriggs, D. *A comparison of gene expression analyses in SKOV-3 wild-type and resistant ovarian carcinoma cells following treatment with cisplatin and a non-cross-resistant platinum analogue, ZD-0473.* Proc Amer Assoc Cancer Res 2001, 42: Abst 2276.

3. Sharp, S.Y., O'Neill, C.F., Boxall, F., Rogers, P., Stephens, T., Keland, L.R. *Non-cross resistance between oxaliplatin and ZD0473 in acquired oxaliplatin-resistant colon ovarian carcinoma cell lines.* Clin Cancer Res 2000, 6(Suppl.): Abst 354.

4. Anthoney, D.A., Gatzemeier, U., Groth, G., Kaye, S.B., Cosaert, J. *ZD0473 combined with paclitaxel in refractory solid malignancies: A phase I dose-escalating study.* Clin Cancer Res 2000, 6(Suppl.): Abst 355.

5. Stevenson, J.P., Redlinger, M., Sun, W., Giantonio, B., Raskay, B., Koehler, M., O'Dwyer, P.J. *Phase I trial of the novel platinum analog ZD0473 administered in combination with gemcitabine to patients with advanced cancers.* Clin Cancer Res 2000, 6(Suppl.): Abst 540.

6. *AstraZeneca reassesses ZD-0473 phase III clinical program in ovarian cancer.* DailyDrugNews.com (Daily Essentials) Sept 4, 2001.

Original monograph - Drugs Fut 1998, 23: 1062.

Additional References

Akiyama, Y. et al. *Overcoming of cisplatin-resistance by ZD-0473 in human lung cancer cells.* Jpn J Cancer Res 2001, 92(Suppl.): Abst 644.

Bonomi, P. et al. *Phase II trial to assess the activity of ZD0473 in patients with small-cell lung cancer who have failed one prior platinum-based chemotherapy regimen.* Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 1284.

Gatzemeier, U. et al. *A phase I dose-escalation study of ZD0473 combined with paclitaxel in refractory solid malignancies.* Proc Am Soc Clin Oncol 2001, 20(Part 2): Abst 2775.

Giaccone, G. et al. *Phase II trial of ZD0473 in patients with mesothelioma relapsing after one prior chemotherapy regimen.* Proc Am Soc Clin Oncol 2001, 20(Part 2): Abst 2781.

Gore, M. et al. *ZD0473 phase II monotherapy trial in second-line ovarian cancer.* Proc Am Soc Clin Oncol 2001, 20(Part 2): Abst 2501.

Hausher, P.F. et al. *The growth inhibitory effect of ZD0473 a novel platinum compound is not influenced by mismatch repair proficiency.* Proc Amer Assoc Cancer Res 2001, 42: Abst 4362.

Hoctin-Boes, G. et al. *Safety profile of ZD0473 in phase II trial of patients with advanced cancers.* Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 1372.

Koizumi, F. et al. *Effect of ZD0473 on specific gene transcript in a human lung cancer cell line and its cisplatin resistant subline.* Jpn J Cancer Res 2001, 92(Suppl.): Abst 625.

Medina, L. et al. *ZD0473 exhibits marked in vitro anticancer activity in human tumor specimens.* Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 1751.

O'Dwyer, P.J. et al. *Phase I trial of the novel platinum analogue ZD0473 in combination with gemcitabine (GEM) for patients with advanced cancers.* Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 1354.

Oe, T. et al. *Quantitation of the 2-methyl pyridine-containing platinum drug ZD0473 in human plasma ultrafiltrate.* Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 352.

Quoix, E. et al. *ZD0473 phase II monotherapy trial in first-line non-small cell lung cancer.* Proc Am Soc Clin Oncol 2001, 20(Part 2): Abst 2774.

Stevenson, J.P. et al. *Pharmacokinetic (PK) pharmacodynamic (PD) trial of the novel platinum compound ZD0473 administered*

as an IV infusion every 21 days. Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 450.

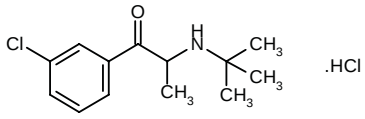
Treat, J. et al. *Phase II monotherapy trial of ZD0473 as second-line therapy in non-small cell lung cancer.* Proc Am Soc Clin Oncol 2001, 20(Part 2): Abst 2808.

Warren, M. et al. *Comparison of ZD0473- and cisplatin-DNA adducts with respect to damage recognition, translesion synthesis, and mismatch repair.* Proc Amer Assoc Cancer Res 2001, 42: Abst 3063.

Bupropion Hydrochloride
Zyban®

Antiobesity
Aid to Smoking Cessation
Antidepressant

EN: 119021



$C_{13}H_{18}ClNO.HCl$ **GlaxoSmithKline**

A 26-week multicenter, randomized, double-blind, placebo-controlled study evaluated the efficacy of bupropion SR in conjunction with a low-calorie diet in obese subjects with mild to moderate depressive symptoms without major depression. Researchers found that patients who received the antidepressant medication lost more weight (4.6% weight loss) compared to those taking placebo (1.8% weight loss) (1).

Findings were presented from a randomized, double-blind, placebo-controlled, crossover study comparing the efficacy of sustained-release bupropion (150-300 mg/day) with placebo in improving neuropathic pain in 41 nondepressed patients. Participants spent 6 weeks in random order in the placebo and active treatment phases. A comparison of the mean average pain score at baseline with that at the end of week 6 showed a reduction of 1.7 points with bupropion SR, but no change with placebo. A significant reduction in the degree to which pain interfered with quality of life was also observed with bupropion SR compared with both baseline and placebo. Side effects of bupropion SR were generally mild. These results indicate that bupropion SR is an effective and well-tolerated treatment for neuropathic pain (2).

1. *Research on promising antiobesity agents presented at NAASO meeting.* DailyDrugNews.com (Daily Essentials) Oct 9, 2001.

2. Semenchuk, M.R., Sherman, S.J., Davis, B.E. *Double-blind randomized trial of bupropion SR for the treatment of neuropathic pain.* Neurology 2001, 56(8, Suppl. 3): Abst P03.116.

Original monograph - Drugs Fut 1978, 3: 723.

Additional References

Anderson, J.W. et al. *Bupropion SR significantly enhances weight loss when used with a moderate-intensity lifestyle intervention.* Diabetes 2001, 50(Suppl. 2): Abst 85-OR.

Anderson, J.W. et al. *Clinical trial using bupropion SR with a moderate-intensity lifestyle intervention.* Obes Res 2000, 8(Suppl. 1): Abst PB81.

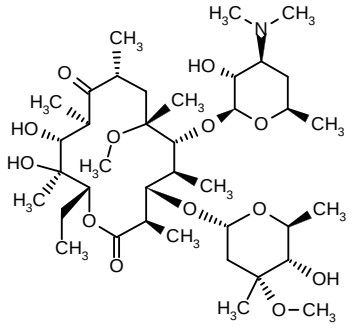
Gadde, K.M. et al. *Bupropion for weight loss: An investigation of efficacy and tolerability in overweight and obese women.* Obes Res 2001, 9(9): 544.

Semenchuk, M. et al. *Double-blind randomized trial of bupropion SR for the treatment of neuropathic pain.* 17th World Congr Neurol (June 17-22, London) 2001, Abst LB005.

Clarithromycin
Biaxin® XL

Macrolide Antibiotic

EN: 121880



$C_{38}H_{69}NO_{13}$ **Abbott**

Abbott Laboratories has received FDA approval of a new 7-day indication for clarithromycin extended release tablets (Biaxin® XL) for the treatment of mild to moderate community-acquired pneumonia in adults. The study used in the approval demonstrated that the clinical cure rate achieved with Biaxin® XL is comparable to that achieved with Levaquin®, a leading quinolone antibiotic (1).

1. *FDA approves new seven-day treatment for community-acquired pneumonia.* DailyDrugNews.com (Daily Essentials) Aug 7, 2001.

Original monograph - Drugs Fut 1987, 12: 952.

Additional References

Adler, J.L. et al. *Phase III, randomized, double-blind study of clarithromycin extended-release and immediate-release formulations in the treatment of patients with acute exacerbation of chronic bronchitis.* Clin Ther 2000, 22(12): 1410.

Banerjee, D. et al. *The effect of 3 months oral clarithromycin on sputum bacterial colonisation in stable moderate to severe chronic obstructive pulmonary disease (COPD).* Eur Respir J 2001, 18(Suppl. 33): Abst 1044.

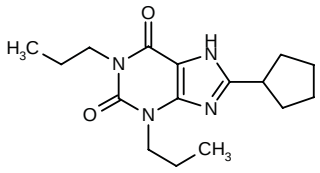
Banerjee, D. et al. *The effects of oral clarithromycin on airway inflammation in moderate to severe chronic obstructive pulmonary disease (COPD) - A double blind randomised controlled trial.* Eur Respir J 2001, 18(Suppl. 33): Abst P2239.

  CCC: 0377-8282/2001

CPX
DPCPX

Treatment of Cystic Fibrosis

EN: 164501



$C_{16}H_{24}N_4O_2$ **SciClone**

SciClone announced that it has successfully reformulated CPX, a protein repair therapy for cystic fibrosis (CF), as an oral suspension and now intends to initiate expanded U.S. phase II studies. An initial phase II study aimed at replicating in patients the protein repair results demonstrated in preclinical studies was completed earlier this year. This trial demonstrated that CPX was safe and well tolerated. However, the absorption characteristics of CPX in CF patients precluded attainment of the sustained CPX plasma concentrations that are necessary to evaluate efficacy. The new formulation takes advantage of the solubility characteristics of CPX and has shown promising absorption characteristics and much higher blood levels than achieved previously in multiple animal model systems, and it will soon be tested in healthy volunteers and CF patients (1).

The E.U. has granted orphan drug status for CPX for the treatment of cystic fibrosis. CPX is currently in phase II trials in the U.S., where the drug has already been assigned orphan drug status by the FDA (2).

1. *SciClone reformulates CPX for CF.* DailyDrugNews.com (Daily Essentials) Nov 14, 2000.

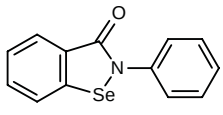
2. *SciClone's CPX for cystic fibrosis assigned orphan drug status in E.U.* DailyDrugNews.com (Daily Essentials) May 23, 2001.

Original monograph - Drugs Fut 2000, 25: 1011.

Ebselen
Harmokisane®

Treatment of Stroke
Antioxidant

EN: 090700



$C_{13}H_9NOSe$ **Aventis Pharma; Daiichi Pharm.**

The neuroprotective action of ebselen has been found to be due in part to the agent's ability to modulate the NMDA receptor redox site and inhibit calcium influx through the receptor during ischemia. Ebselen 3-30 μM was found to reverse the potentiation of NMDA-activated whole cell currents induced by 4 mM DTT in cultured cortical neurons. Membrane conductance was not affected by ebselen alone, and ebselen did not act as a direct NMDA receptor antagonist. Ebselen oxidized NR_1/NR_{2B} receptors expressed in CHO cells and acted as an oxidant at recombinant nicotinic acetylcholine receptors expressed in COS-7 cells, restoring carbachol-induced whole cell currents after DTT treatment (1).

Decreases in oxidative stress induced by ebselen may allow the drug to prevent early alcohol-induced liver injury, according to a study in rats. Intragastric ebselen (50 mg/kg b.i.d.) or vehicle were administered to rats fed high-fat liquid diets with or without ethanol for up to 4 weeks. At 4 weeks, ebselen was found to significantly blunt increases in serum ALT levels which were 4-fold those in the ethanol-treated group compared to controls. Ebselen also significantly blunted ethanol-related fatty accumulation, mild inflammation and liver necrosis. Neither ethanol nor ebselen administration influenced glutathione peroxidase activity in serum or liver tissue. Ebselen, however, significantly blocked ethanol-induced increases in serum nitrate/nitrite, NF-κB activity, number of infiltrating neutrophils and accumulation of 4-hydroxynonenal (2).

A study has found that ebselen may have protective effects against hydrophobic bile-acid induced liver injury. Ebselen (30 mg/kg/day for 10 days) was administered to rats with or without deoxycholic acid (DCA; 1% of diet for 10 days). Ebselen administered simultaneously with DCA was found to significantly reduce the decreases in protein levels of CYP1A1 and 3A2 (86 and 65% of control, respectively) and to significantly diminish the DCA-induced increases in serum alkaline phosphatase and alanine aminotransferase activity (1.3- and 2.8-fold of control, respectively) (3).

1. Herin, G.A., Aizenman, E. *Ebselen oxidizes the NMDA receptor redox modulatory site: A novel mechanism for neuroprotection.* Soc Neurosci Abst 2000, 26(Part 1): Abst 183.13.

2. Kono, H., Arteel, G.E., Rusyn, I., Sies, H., Thurman, R.G. *Ebselen prevents early alcohol-induced liver injury in rats.* Free Radical Biol Med 2001, 30(4): 403.

3. Tanaka, M., Takezawa, N., Kumai, T., Watanabe, M., Matsumoto, N., Kibayashi, S. *Effects of ebselen on hepatic drug-metabolizing enzymes in rats with deoxycholic acid (DCA)-induced liver injury.* Jpn J Pharmacol 2001, 85(Suppl. I): Abst P-496.

Original monograph - Drugs Fut 1984, 9: 741.

Additional References

Araki, T. et al. *The mechanism of reaction of ebselen with superoxide in aprotic solvents as examined by cyclic voltammetry and ESR.* Chem Pharm Bull 2001, 49(5): 541.

Kim, H.R. et al. *The effects of thiol compounds and ebselen on nitric oxide activity in rat aortic vascular responses.* J Auton Pharmacol 2001, 21(1): 23.

Kobayashi, T. et al. *Preventive effect of ebselen on acute gastric mucosal lesion development in rats treated with compound 48/80.* Eur J Pharmacol 2001, 414(2-3): 271.

Namura, S. et al. *Ebselen reduces cytochrome c release from mitochondria and subsequent DNA fragmentation after transient focal cerebral ischemia in mice.* J Cereb Blood Flow Metab 2001, 21(Suppl. 1): Abst 481.

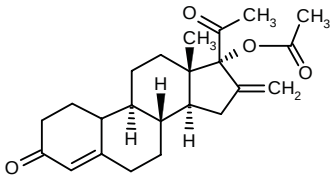
Noiri, H. et al. *Effects of ebselen on acute ischemic renal failure in rats.* Jpn J Nephrol 2001, 43(3): Abst P-335.

Sies, H., Parnham, M. *Ebselen: Prospective therapy for cerebral ischaemia.* Expert Opin Invest Drugs 2000, 9(3): 607.

Elcometrine
Nestorone®

Female Contraceptive
Hormone Replacement Therapy

EN: 277410



$C_{23}H_{30}O_4$ **Population Council**

A pharmacological study has compared elcometrine to levonorgestrel and 3-keto-desogestrel. In steroid receptor binding studies, 3-keto-desogestrel showed the highest binding affinity to progesterone receptors, followed by elcometrine, levonorgestrel and progesterone. Levonorgestrel and 3-keto-desogestrel, but not elcometrine, showed significant binding to androgen receptors. None of the agents bound to estrogen receptors. In tests of the McPhail index in immature rabbits and in pregnancy maintenance and ovulation inhibition tests in rats, elcometrine was the most potent of the progestins. In rabbits, subcutaneously administered elcometrine was over 100-fold more potent than oral elcometrine. Elcometrine demonstrated no androgenic or anabolic activity. Levonorgestrel and 3-keto-desogestrel, but not elcometrine, showed significant binding to sex hormone binding globulin. In immature ovariectomized rats, levonorgestrel and 3-keto-desogestrel, but not elcometrine, showed uterotropic activity. Elcometrine showed significant binding to glucocorticoid receptors but no glucocorticoid activity *in vivo* (1).

According to Orion Pharma, the research program for the development of a gel preparation containing elcometrine has been discontinued, mainly for commercial reasons (2).

1. Kumar, N., Koide, S.S., Tsong, Y.Y., Sundaran, K. *Nestorone(R): A progestin with a unique pharmacological profile.* Steroids 2000, 65(10-11): 629.

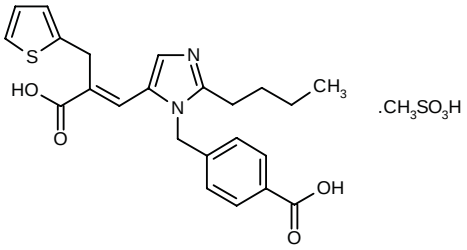
2. *Orion drops development of gel formulation of progestin.* DailyDrugNews.com (Daily Essentials) Sept 19, 2001.

Original monograph - Drugs Fut 1979, 4: 743.

Eprosartan Mesilate
Teveten®

Antihypertensive
Treatment of Heart Failure

EN: 168384



$C_{23}H_{24}N_2O_4S.CH_4O_3S$ **GlaxoSmithKline; Solvay; Unimed**

Eprosartan mesilate (Teveten®) was launched in January 2001 in Canada for the treatment of mild to moderate hypertension. Solvay has reported that the drug is now available as a 600-mg tablet, thus facilitating patient dosing – one tablet once daily. Teveten® is also available in the U.S., Germany, Denmark, Finland, Sweden, The Netherlands and Portugal. Solvay acquired the worldwide rights to market, manufacture and further develop Teveten® from GlaxoSmithKline. Unimed, a subsidiary of Solvay, markets the drug in the U.S. (1, 2).

A new study, the TOP CAT (Teveten Optimal Blood Pressure Community Assessment Trial) Hypertension Trial, has begun in Canada to evaluate the efficacy of eprosartan mesilate in conjunction with home blood pressure monitoring. The TOP CAT trial will study 200 patients at 35 primary care centers across the country. Study subjects will be patients between the ages of 60 and 84 years with mild to moderate essential hypertension. Patients will be randomized to treatment with eprosartan mesilate alone or in conjunction with the use of home blood pressure monitoring. All patients will receive 10 weeks of treatment with eprosartan mesilate 600 mg once daily, with safety and efficacy assessment conducted at regular intervals. Complete results of the trial will be published next year (3).

1. *Solvay launches Teveten in Canada for hypertension.* DailyDrugNews.com (Daily Essentials) Jan 10, 2001.

2. *New dose of Teveten now available in Canada.* DailyDrugNews.com (Daily Essentials) May 31, 2001.

3. *Solvay commences Canadian study of Teveten in combination with home blood pressure monitoring.* DailyDrugNews.com (Daily Essentials) June 19, 2001.

Original monograph - Drugs Fut 1997, 22: 1079.

  CCC: 0377-8282/2001

Additional References

Gremmler, B. et al. *Therapy with ACE-inhibitors combined either with eprosartan or telmisartan increases cardiac output in severe chronic heart failure.* Eur J Heart Fail 2001, 3(Suppl. 1): S19.

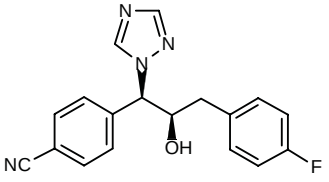
Murdoch, D.R. et al. *ADEPT: Addition of the AT_1 receptor antagonist eprosartan to ACE inhibitor therapy in chronic heart failure trial: Hemodynamic and neurohormonal effects.* Am Heart J 2001, 141(5): 800.

Suzuki, G. et al. *Eprosartan, a selective AT_1-receptor antagonist, improves left ventricular ejection fraction and prevents chamber dilation in dogs with heart failure.* Circulation 2000, 102(18, Suppl.): Abst 2606.

Finrozole
MPV-2213ad

Treatment of BPH

EN: 213033



$C_{18}H_{15}FN_4O$ **Orion Corp.; Hormos**

Finrozole is a steroid metabolism inhibitor in phase II for male obstructive urinary dysfunction (1).

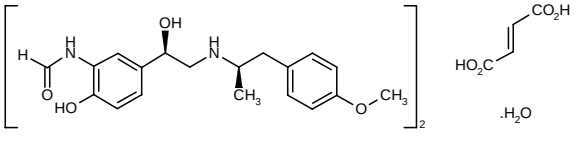
1. *Company profile: Hormos Medical.* DailyDrugNews.com (Daily Essentials) May 16, 2001.

Original monograph - Drugs Fut 1998, 23: 1071.

Formoterol Fumarate
Foradil®
Oxeze®
Oxis®

Antiasthmatic
Treatment of COPD

EN: 125563



$C_{38}H_{48}N_4O_8.C_8H_8O_8.H_2O$ **Yamanouchi; Novartis; AstraZeneca; SkyePharma**

In December 2000, the SkyeHaler formulation of formoterol fumarate (Foradil®) entered phase III European trials and U.S. phase III trials have also commenced. Launches in the U.S. and Europe are anticipated to take place in 2003 (1).

Health Canada has approved Oxeze® Turbuhaler®, containing formoterol, on an as-needed basis for the control and relief of asthma symptoms. The as-needed indication is expected to simplify treatment because the drug's rapid onset of action will allow many patients to reduce the number of inhalers they use, as they may no longer need to use a short-acting β-agonist due to formoterol's dual action. The Oxeze® Turbuhaler® was originally approved in Canada in February 1998 for twice-daily, long-term management of asthma. Since then, clinical trial data have revealed that the rapid onset of action of the product provides quick relief during asthma attacks. The product offers an advantage over the much shorter acting conventional bronchodilators currently recommended for the treatment or prevention of exercise-induced bronchoconstriction. This product is known as the Oxis® Turbuhaler® in other countries (2).

Novartis has launched Foradil® Aerolizer™ in the U.S. following its approval by the FDA in February 2001 for the maintenance treatment of asthma. Foradil® Aerolizer™, currently available in 85 countries, provides quick symptomatic relief within 5 min while allowing patients to obtain 12 h of long-acting bronchodilatation on a recommended dose of 12 mcg twice daily. The Aerolizer™ is an easy-to-use, low-resistance, dry powder inhaler system that provides minimal dose-to-dose variability and enables patients to check if they have inhaled the entire dose of medication. Clinical results published recently showed Foradil® Aerolizer™ to be more effective in improving lung function in patients with asthma compared with albuterol/salbutamol administered via a metered-dose inhaler. Clinical trials involving over 1600 chronic obstructive pulmonary disease (COPD) patients have also demonstrated excellent clinical efficacy for Foradil® compared to current standard therapy with ipratropium bromide and theophylline (3).

The FDA has cleared Foradil® Aerolizer™ for long-term administration in the maintenance treatment of bronchoconstriction in patients with COPD, including chronic bronchitis and emphysema (4).

1. *SkyePharma summarizes major achievements over past year.* DailyDrugNews.com (Daily Essentials) April 30, 2001.

2. *Oxeze Turbuhaler approved in Canada for control and relief of asthma symptoms.* DailyDrugNews.com (Daily Essentials) March 30, 2001.

3. *Novartis launches Foradil Aerolizer in the U.S.* DailyDrugNews.com (Daily Essentials) May 30, 2001.

4. *Foradil now cleared for use in COPD in the U.S.* DailyDrugNews.com (Daily Essentials) Oct 17, 2001.

Original monograph - Drugs Fut 1977, 2: 639.

Additional References

Benhamou, D. et al. *Onset of action of formoterol and salbutamol in patients with chronic obstructive pulmonary disease (COPD).* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A281.

Benhamou, D. et al. *Rapid onset bronchodilation with formoterol or salbutamol in patients with chronic obstructive pulmonary disease (COPD).* Eur Respir J 2001, 18(Suppl. 33): Abst 3470.

Cazzola, M. et al. *Effects of pretreatment with a single conventional dose of formoterol Turbuhaler (F) on the dose-response curves to F in patients with partially reversible COPD.* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A278.

Cazzola, M. et al. *Formoterol via turbuhaler (F) versus salbutamol via pressurized metered-dose inhaler (SB) in acute exacerbations of COPD.* Eur Respir J 2001, 18(Suppl. 33): Abst P2870.

Dahl, R. et al. *Formoterol (Foradil®) improves lung function and quality of life (QOL) parameters in patients with reversible or poorly reversible COPD.* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A280.

Dahl, R. et al. *Inhaled formoterol dry powder versus ipratropium bromide in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med 2001, 164(5): 778.

Della Cioppa, G. et al. *Formoterol demonstrates bronchodilator efficacy in patients with reversible or poorly reversible chronic obstructive pulmonary disease (COPD).* Eur Respir J 2001, 18(Suppl. 33): Abst 1258.

Di Marco, F. et al. *Acute effect of formoterol, salmeterol, albuterol, oxitropium bromide and placebo on FEV_1, inspiratory capacity and dyspnea in COPD.* Eur Respir J 2001, 18(Suppl. 33): Abst P2604.

D'Urzo, A.D. et al. *In patients with COPD, treatment with a combination of formoterol and ipratropium is more effective than a combination of salbutamol and ipratropium - A 3-week, randomized, double-blind, within-patient, multicenter study.* Chest 2001, 119(5): 1347.

Kottakis, I. et al. *Effects of formoterol and salmeterol on inspiratory capacity: Results from a single-dose, 5-period cross-over study in stable, poorly reversible, stage II and III COPD patients.* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A278.

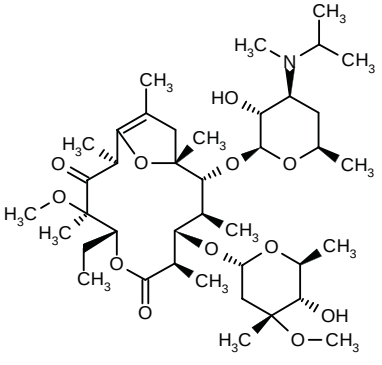
Kristufek, P. et al. *Bronchodilatory effects of formoterol in patients with chronic obstructive pulmonary disease (COPD) are not influenced by concomitant corticosteroid use.* Eur Respir J 2001, 18(Suppl. 33): Abst 3473.

Kristufek, P. et al. *Inhaled formoterol (Foradil(R)) improves lung function in patients with both reversible and poorly reversible COPD.* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A280.

GM-611

Treatment of GERD

EN: 205573



$C_{40}H_{69}NO_{12}$ **Chugai**

GM-611 has been compared to placebo for its effects on delayed gastric emptying in a double-blind, randomized trial in 104 patients with symptomatic gastroparesis conducted in the U.S. Patients received placebo or GM-611 at doses of 10 mg b.i.d., 20 mg b.i.d., 20 mg t.i.d. or 30 mg b.i.d. for 28 days. All doses of GM-611 produced significant improvement in gastric emptying compared to placebo, with 30 mg b.i.d. and 10 mg b.i.d. having the greatest gastric emptying-accelerating effect. It is suggested that further evaluation of GM-611 in the treatment of symptomatic gastroparesis is warranted (1).

Chugai has announced that the U.S. phase II trials of GM-611 have been placed on clinical hold by the FDA pending final review of the results of rodent carcinogenicity studies. The preliminary results of a 2-year rat carcinogenicity study to the FDA reported an increased incidence of lymphomas in animals receiving the highest dose, a dose approximately 1600-fold higher than the highest daily dose administered in the clinical trials. There was no increase in the incidence of tumors in a 6-month mouse carcinogenicity study in which the highest daily dose was about 6400-fold higher than the highest daily dose administered in clinical trials. In an ongoing assessment of these studies, additional analyses are being conducted and the results will be discussed with the FDA (2).

1. Fang, J., McCallun, R., Kipnes, M.K. et al. *GM-611, a motilin-receptor agonist, accelerates gastric emptying in patients with symptomatic gastroparesis (GP).* Dig Dis Week (May 20-23, Atlanta) 2001, Abst 2375.

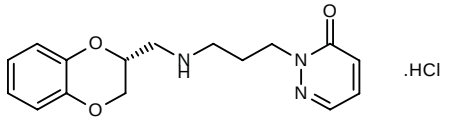
2. *Clinical hold placed on GM-611 pending analysis of animal toxicity studies.* DailyDrugNews.com (Daily Essentials) June 20, 2001.

Original monograph - Drugs Fut 1994, 19: 910.

GYKI-16084
IDR-16084

Treatment of BPH

EN: 241391



$C_{16}H_{19}N_3O_3.HCl$ **Inst. Drug Res. (HU); Ivax**

Ivax's Hungarian subsidiary, the Ivax Institute for Drug Research, has received clearance to conduct a multicenter, placebo-controlled phase II study of GYKI-16084 in men with benign prostatic hypertrophy (BPH). It is anticipated that 200 patients will be enrolled in the study. Phase I studies demonstrated the compound to be more uroselective, with a greatly reduced incidence of side effects such as dizziness, fainting and sexual dysfunction typical of the currently used drugs (1).

  CCC: 0377-8282/2001

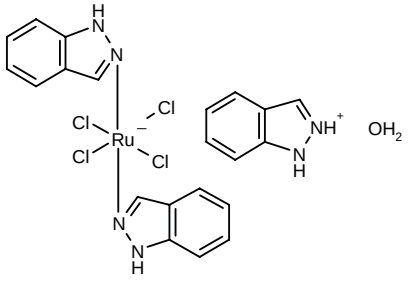
1. *Ivax set to begin phase II study of GYKI-16084 for BPH.* DailyDrugNews.com (Daily Essentials) June 14, 2001.

Original monograph - Drugs Fut 1999, 24: 1072.

HInd(RuInd$_2$Cl$_4$)

Oncolytic

EN: 163968



$C_7H_7N_2.2C_7H_6N_2.Cl_4Ru.H_2O$ **German Cancer Res. Ctr.**

To better understand the mode of action of ruthenium(III) complexes, the interaction of HIm *trans*-[RuCl$_4$(im)$_2$] and HInd *trans*-[RuCl$_4$(ind)$_2$] with four nucleoside monophosphates was investigated using capillary electrophoresis. The experiments revealed a preference for GMP- and AMP-coordination and a decrease in pH, which significantly increased the amount of bound nucleotide (1).

1. Kung, A., Pieper, T., Keppler, B.K. *Investigations into the interaction between tumor-inhibiting ruthenium(III) complexes and nucleotides by capillary electrophoresis.* J Chromatogr B - Biomed Sci Appl 2001, 759(1): 81.

Original monograph - Drugs Fut 1990, 15: 992.

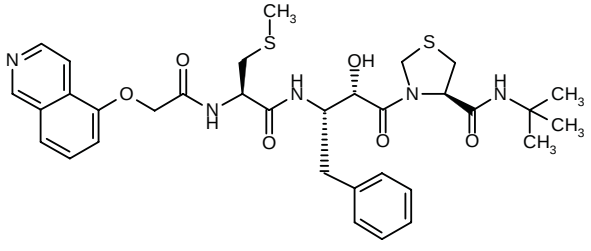
Additional Reference

Kung, A. et al. *Hydrolysis of the tumor-inhibiting ruthenium(III) complexes HIm trans-[RuCl$_4$(im)$_2$] and HInd trans-[RuCl$_4$(ind)$_2$] investigated by means of HPCE and HPLC-MS.* J Biol Inorg Chem 2001, 6(3): 292.

KNI-272

Anti-HIV

EN: 188524



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

The binding affinity of KNI-272 to the wild-type mutant V82F/I84V has been determined by thermodynamic analysis. KNI-272 binds to the protease with a favorable binding enthalpy, the origin of which lies in the coupling of the binding reaction to the burial of 6 water molecules. Atomic packing is optimized at the inhibitor/protein interface by the bound water molecules, enhancing favorable interactions which offset unfavorable enthalpy. The association constant to the mutant is 100-500 times weaker, a decrease in binding affinity corresponding to an increase in Gibbs energy of binding of 3-3.5 kcal/mol originating from less favorable enthalpy and entropy changes. Calorimetric binding experiments demonstrated that the binding of the inhibitor is linked to the protonation/deprotonation of two groups which have been identified as one of the aspartates in the catalytic aspartyl dyad in the protease and the isoquinoline nitrogen in the inhibitor molecule. These groups have pH values of 6.0 and 4.8 in the uncomplexed form and 6.6 and 2.9 in the complex form. The binding affinity is maximal between pH 5-6 when it is nearly 6 x 10^{10} M^{-1}. A buffer- and pH-independent binding enthalpy of -6.3 kcal/mol was calculated (1).

A study has found at least two inhibition targets for KNI-272 in the HIV-1 life cycle. In cells infected acutely with HIV-1 and cultured in the presence of KNI-272, proviral DNA was detected but reduced by the agent in a concentration-dependent manner. No expression of HIV-1 Gag proteins or production of virus particles were found. KNI-272 was not seen to directly inhibit reverse transcription. Morphological examination of HIV-1 particles from infected cells cultured with KNI-272 revealed that KNI-272 blocked maturation of viral particles (2).

Preliminary studies with KNI-272 in HIV-infected patients showed some evidence of antiretroviral activity and generally good tolerance, significant elevations in hepatic transaminases being seen in some patients at higher doses. Another phase I/II trial has been conducted with a novel microsphere formulation of KNI-272 at higher doses. Eighteen patients with symptomatic HIV disease were administered escalating doses up to 60 mg/kg/day. No consistent virological or immunological effects were seen and the only serious adverse event considered to be drug-related was one case of reversible elevation in hepatic transaminases. KNI-272 was rapidly absorbed but had a very short half-life (0.25-1.1 h), which was attributed to rapid metabolism of the drug. It is suggested that the pharmacokinetics of KNI-272 may be improved by concomitant administration of drugs inhibiting cytochrome P450-mediated metabolism such as ritonavir, indinavir, nelfinavir or delavirdine, which have been shown to increase exposure to the drug in animal studies. Further studies will be necessary to determine if this also occurs in humans and if increased exposure to the drug is associated with increased antiretroviral efficacy and/or toxicity (3).

1. Velazquez Campoy, A., Luque, I., Tood, M.J., Milutinovich, M., Kiso, Y., Freire, E. *Thermodynamic dissection of the binding energetics of KNI-272, a potent HIV-1 protease inhibitor.* Protein Sci 2000, 9(9): 1801.

2. Goto, T., Nakano, T., Kohno, T., Morimatsu, S., Morita, C., Hong, W., Kiso, Y., Nakai, M., Sano, K. *Targets of a protease inhibitor, KNI-272, in HIV-1-infected cells.* J Med Virol 2001, 63(3): 203.

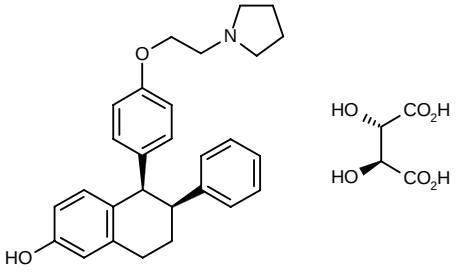
3. Churchill, D.R., Slade, P.M., Youle, M., Gazzard, B.G., Weber, J.N. *A phase I/II study of the safety and activity of microsphere formulation of KNI-272 in patients with HIV-1 infection.* J Antimicrob Chemother 2001, 47(3): 353.

Original monograph - Drugs Fut 1996, 21: 1022.

Lasofoxifene Tartrate
CP-336156

Treatment of Osteoporosis
Treatment of Breast Cancer

EN: 236902



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

Long-term (6 months) treatment of male rats with lasofoxifene preserved bone mass and strength by inhibiting age-related increases in bone resorption and bone turnover. The drug also reduced total serum cholesterol without affecting prostate weight, further supporting the use of selective estrogen receptor modulators for protecting elderly men from age-related changes in bone and serum cholesterol (1).

The effects of lasofoxifene on bone loss were evaluated in a study of ovariectomized cynomolgus monkeys. Monkeys were placed into 1 of 5 groups: ovariectomized, sham operated, ovariectomized plus premarin 0.021 mg/kg p.o., ovariectomized plus lasofoxifene 1 mg/kg p.o. and ovariectomized plus lasofoxifene 5 mg/kg p.o. Once-daily treatment with lasofoxifene was shown to prevent bone loss due to ovariectomy in the lumbar vertebrae during the first 7 months of the study. Reduced bone biomarker and histomorphometric data indicated that the drug suppresses bone turnover and may be useful for the treatment of postmenopausal osteoporosis (2).

The effects of lasofoxifene tartrate on bone and the uterus were examined in ovariectomized monkeys following reports of its ability to prevent bone loss without inducing uterine hypertrophy in ovariectomized rats. The osteopenia developing in ovariectomized adult female cynomolgus monkeys was prevented by 24 months of daily oral treatment with either conjugated equine estrogens (Premarin) or lasofoxifene (1 or 5 mg/kg). Also, the increase in bone remodeling associated with the reduction in spinal bone mineral density induced by ovariectomy was prevented by both Premarin and lasofoxifene. However, in contrast to the uterine hypertrophy seen on Premarin, lasofoxifene maintained the reduction in uterine weight observed following ovariectomy. These results confirm the beneficial effects of lasofoxifene on bone turnover and bone loss and its lack of adverse effects on the uterus in primates (3).

1. Ke, H.Z., Qi, H., Chidsey-Frink, K.L., Crawford, D.T., Thompson, D.D. *Lasofoxifene (CP-336,156) protects against the age-related changes in bone mass, bone strength, and total serum cholesterol in intact aged male rats.* J Bone Miner Res 2001, 16(4): 765.

2. Lees, C.J., Hotchkiss, C.E., Brommage, R. *Lasofoxifene prevents ovariectomy-induced skeletal changes in macaques.* 83rd Annu Meet Endocr Soc (June 20-23, Denver) 2001, Abst P3-140.

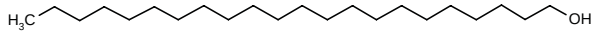
3. Brommage, R., Hotchkiss, C.E., Stancill, M.W., Lees, C.J. *Lasofoxifene inhibits bone turnover and maintains spine BMD after ovariectomy in monkeys.* Bone 2001, 28(5, Suppl.): Abst P594 S.

Original monograph - Drugs Fut 1998, 23: 1066.

Lidakol™
Docosanol
Abreva®

Anti-HSV

EN: 183153



$H_3C(CH_2)_{21}$-OH $C_{22}H_{46}O$ **Avanir; GlaxoSmithKline**

An open-label pilot study was conducted in 10 HIV-infected patients with Kaposi's sarcoma (KS). Docosanol 10% cream, applied 5 times daily over 4 weeks, was used to treat 28 cutaneous KS lesions. A partial response was obtained in 2 of 10 patients, showing 74-83% decreases in total target lesion areas. All patients chose to continue treatment for up to 35 weeks, and 2 further patients had a partial response during this period, 1 of whom showed complete visual disappearance of lesions. Symptomatic improvement was seen in addition to the decreases in total target lesion area, including lightening or fading of the color of the lesions and reductions in lesion-associated edema and pain. No disease progression was observed. Treatment with docosanol 10% cream was well tolerated, with no reports of local or systemic drug-related adverse events. The response to therapy did not appear to be dependent on antiretroviral regimens, viral load or previous KS treatments. Further investigation of docosanol as a topical treatment for KS thus appears warranted (1).

  CCC: 0377-8282/2001

SmithKline Beecham (now GlaxoSmithKline) has launched Abreva(R) in the U.S. Abreva® is the first and only nonprescription cold sore medicine approved by the FDA that shortens healing time and duration of symptoms. The launch has triggered a milestone payment from SmithKline Beecham to Avanir, the developer of the drug. Under the terms of the March 2000 agreement between the two companies, SmithKline Beecham holds exclusive rights to all sales, marketing, manufacturing and distribution of Abreva® in the U.S. and Canada (2).

1. Scolaro, M.J., Gunnill, L.B., Pope, L.E., Khalil, M.H., Katz, D.H., Berg, J.E. *The antiviral drug docosanol as a treatment for Kaposi's sarcoma lesions in HIV type 1-Infected patients: A pilot clinical study.* AIDS Res Hum Retroviruses 2001, 17(1): 35.

2. *SmithKline Beecham launches Abreva in U.S.; Avanir receives milestone payment.* DailyDrugNews.com (Daily Essentials) Dec 4, 2000.

Original monograph - Drugs Fut 1992, 17: 879.

Additional References

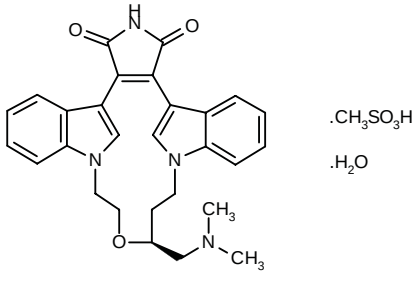
McKeough, A.B., Spruance, S.L. *Comparison of new topical treatments for herpes labialis - Efficacy of penciclovir cream, acyclovir cream, and n-docosanol cream against experimental cutaneous herpes simplex virus type 1 infection.* Arch Dermatol 2001, 137(9): 1153.

Sacks, S.L. et al. *Clinical efficacy of topical docosanol 10% cream for herpes simplex labialis: A multicenter, randomized, placebo-controlled trial.* J Am Acad Dermatol 2001, 45(2): 222.

LY-333531 Mesylate Hydrate

Treatment of Diabetic Retinopathy

EN: 252396



$C_{28}H_{28}N_4O_3.CH_4O_3S.H_2O$ **Lilly**

A new strategy for the synthesis of a key intermediate in the preparation of LY-333531 has been described: Condensation of indole (I) with the tosylate (II) by means of NaH in DMF gives 4-(1-indolyl)butane-1,2-diol (III), which is monotritylated with trityl bromide yielding ether (IV). Alkylation of compound (IV) with *tert*-butyl bromoacetate (V) and NaH in THF affords the hydroxyacetic derivative (VI), which is reduced with $LiBH_4$ in THF/EtOH to provide the carbinol (VII). Reaction of compound (VII) with Ms_2O and pyridine in THF gives the mesylate (VIII), which is condensed with oxalyl chloride (IX) in ethyl ether to yield the oxoacetyl chloride (X). The alcoholysis of (X) with NaOMe in methanol affords the oxoacetate (XI), which is finally cyclized with 2-(3-indolyl)acetamide (XII) by means of NaH in DMF to provide the target intermediate (1). Scheme 1.

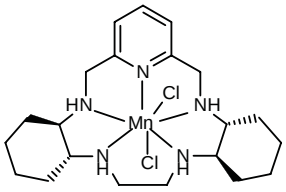
1. Faul, M.M., Kumrich, C.A. *Cyclization strategies for the synthesis of macrocyclic bisindolylmaleimides.* J Org Chem 2001, 66(6): 2024.

Original monograph - Drugs Fut 2000, 25: 1017.

M-40403
SC-72325

Superoxide Dismutase Mimetic

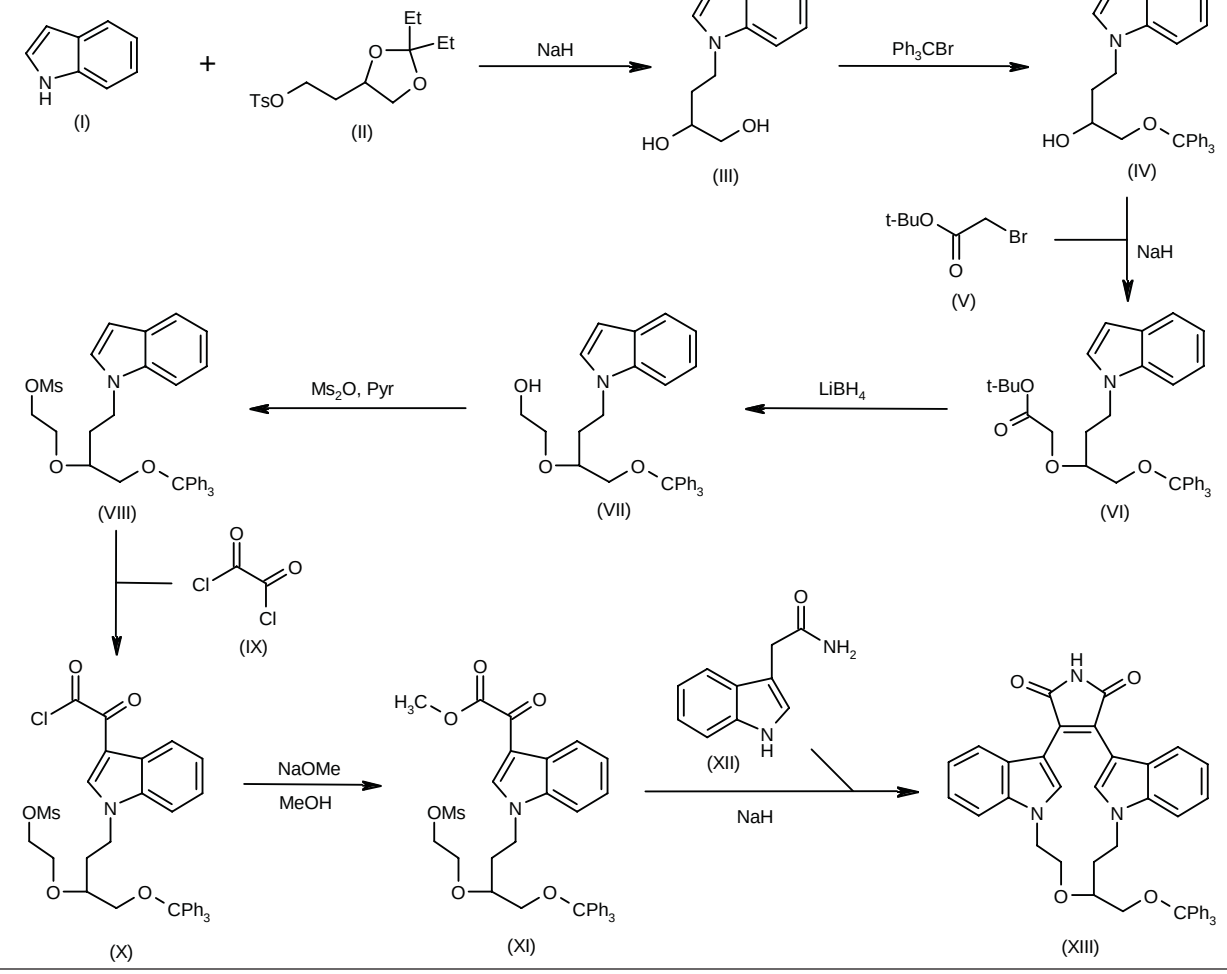
EN: 281618



$C_{21}H_{35}Cl_2MnN_5$ **MetaPhore; Pharmacia**

M-40403 may significantly improve the efficacy of IL-2 immunotherapy, currently approved for inoperable metastatic melanoma and metastatic renal cell carcinoma. The use of IL-2, which works by activating natural killer (NK) cells, in these cancers is limited by potentially life-threatening side effects, particularly hypotension at high doses. Most patients undergoing high-dose IL-2 immunotherapy require hospitalization for close monitoring and/or are unable to complete the full course of treatment. The SOD enzyme has been found to be deficient in cancer and excess free radicals, particularly superoxide anions, have been shown to deactivate catecholamines, molecules which are involved in the body's blood pressure-regulatory system. By reducing superoxide, the SOD mimetic is hypothesized to restore catecholamine levels required to constrict blood vessels and reverse hypotension. As superoxide also inhibits the activity of NK cells and thereby reduces the antitumor effect of IL-2, the SOD mimetic M-40403 is also expected to enhance the anticancer properties of IL-2. Coadministration of M-40403 (3 mg/kg b.i.d. i.p.) allowed a significant increase in the maximum tolerated dose of IL-2 in mice, providing dose-dependent reversal of IL-2-associated hypotension. *In vitro*, exposure of IL-2-activated spleen cells to M-40403 was associated with increased induction of cytolytic effector cells. Both M-40403 and IL-2 showed evidence of significant antitumor activity in a pulmonary metastasis model in mice, and they appeared to act synergistically in combination. In the Meth A ascites tumor model in mice, coadministration of IL-2 and M-40403 produced 50% complete remissions lasting for over 90 days, while untreated or M-40403-treated mice had a median survival of 15 days and IL-2-treated animals had a median survival of 21 days. Based on this evidence for a direct antitumor effect for M-40403, its ability to safely reverse

Scheme 1: Synthesis of an Intermediate of LY-333531



the hypotension associated with IL-2 and its ability to enhance the anticancer effects of IL-2, further evaluation appears warranted (1).

Preclinical studies confirmed the major role of superoxide free radicals in the development of vascular dysfunction and subsequent nerve damage using M-40403. Streptozotocin-diabetic rats treated with M-40403 at a daily s.c. dose of 10 mg/kg were compared to control rats and untreated diabetic rats. The results showed that M-40403 was able to significantly improve blood flow to the nerves and to restore the normal relaxation response to acetylcholine of vessels in the sciatic nerve region, as well as motor nerve conduction velocity. Improvements in various markers of oxidative stress were also demonstrated (2).

Data indicated that M-40403 improves heart function in rat models of heart attack. The drug acts by removing free radicals from injured heart tissues. Administered prior to reopening the blood vessels in the heart in animal models of heart attack, the compound appears to protect the heart cells from further damage. M-40403 is much smaller than the enzyme which it mimics, superoxide dismutase (SOD), allowing the drug to penetrate into tissues such as the brain and the heart that larger synthetic drugs and proteins cannot easily penetrate. Although these data suggest a role for enzyme mimetics of this type for the early treatment of stroke, additional studies are needed to evaluate the efficacy of the drug administered after rather than prior to the opening of the blood vessels (3).

M-40403 was safe and well tolerated in a phase I trial. This study was the first time that a small-molecule enzyme mimetic was tested in clinical trials. The double-blind, placebo-controlled clinical trial involved i.v. administration of single escalating doses of M-40403 in a total of 36 healthy volunteers. No dose-limiting adverse effects were observed. In the near future, MetaPhore expects to advance M-40403 in combination with IL-2 to a phase II trial involving small groups of patients with advanced skin and end-stage kidney cancer (4).

1. Samlowski, W.E., Petersen, R., McGregor, J.R., Salvemini, D. *The SOD mimetic M40403 blocks IL-2 induced hypotension and increases anticancer responses.* Proc Amer Assoc Cancer Res 2001, 42: Abst 2704.

2. Coppey, L.J., Gellet, J.S., Davidson, E.P., Dunlap, J.A., Lund, D.D., Salvemini, D., Yorek, M.A. *Effect of M40403 treatment of*

  CCC: 0377-8282/2001

diabetic rats on endoneurial blood flow, motor nerve conduction velocity and vascular function of epineurial arterioles of the sciatic nerve. Br J Pharmacol 2001, 134(1): 21.

3. *MetaPhore's enzyme mimetic shows potential as stroke treatment in animal model.* DailyDrugNews.com (Daily Essentials) May 2, 2001.

4. *MetaPhore's M-40403 successfully completes phase I evaluation.* DailyDrugNews.com (Daily Essentials) July 20, 2001.

Original monograph - Drugs Fut 2000, 25: 1027.

Additional References

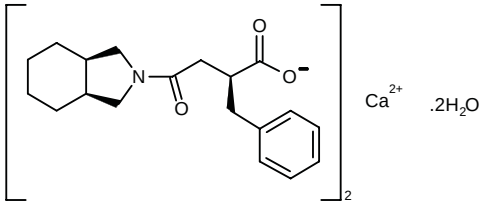
Cuzzocrea, S. et al. *Pharmacological manipulation of the inflammatory cascade by the superoxide dismutase mimetic, M40403.* 30th Congr Naz Soc Ital Farmacol (May 30-June 2, Genova) 2001, Abst A6.

Kramer, R. *The pharmaceutical potential of manganese-based superoxide dismutase mimics.* Angew Chem Int Ed 2000, 39(24): 4469.

Salvemini, D. et al. *Pharmacological manipulation of the inflammatory cascade by the superoxide dismutase mimetic, M40403.* Br J Pharmacol 2001, 132(4): 815.

Mitiglinide Calcium Hydrate *Antidiabetic*
S-21403
KAD-1229

EN: 189711



$C_{38}H_{48}CaN_2O_6.2H_2O$ **Kissei; Servier**

KAD-1229 has been compared to nateglinide and voglibose for its ability to reduce postprandial glycemia after a meal in three rat models of mild, moderate or severe streptozotocin-induced diabetes. The animals were treated with KAD-1229 (0.3, 1 or 3 mg/kg), nateglinide (25, 50 or 100 mg/kg) or voglibose (0.03, 0.1 or 0.3 mg/kg) orally just before an oral meal load. KAD-1229 proved to be the most effective hypoglycemic agent, affording significant and rapid decreases in blood glucose levels and reductions in the AUC for blood glucose in the mild and moderate models; a tendency for suppression of the meal-induced increase in blood glucose was also seen in the severely diabetic animals. KAD-1229 may thus be useful for preventing the postprandial hyperglycemia seen in type 2 diabetes (1).

KAD-1229 and gliclazide were compared for their hypoglycemic effects and insulinotropic actions in a dog model of diabetes. KAD-1229 was found to have a stronger effect on reducing the increase in plasma glucose than gliclazide and unlike the latter treatment did not produce hypoglycemia. KAD-1229 demonstrated rapid insulinotropic action. Thus, KAD-1229 appears to have potential for attenuating hyperglycemia and for improving impaired insulin secretion in the early phase of type 2 diabetes (2).

By mutual consent, a license agreement relating to Kissei's antidiabetic agent mitiglinide (KAD-1229) has been terminated with its U.S. licensee Purdue Pharma. The ongoing U.S. phase II clinical studies will be transferred to Kissei Pharma USA, Kissei's U.S. subsidiary. At present, Kissei has licensed mitiglinide in Europe, the Middle East, Africa, Oceania and some Asian countries to Servier, which is currently carrying out phase III trials with the drug. In Japan, Kissei is preparing double-blind comparative phase III studies with mitiglinide following the recent completion of phase II studies. Mitiglinide is different from conventional sulfonylurea agents in that the onset of action is rapid following dosing. In addition, the drug, which has a short duration of action, suppresses the postprandial hyperglycemia characteristic of diabetic patients and works to avoid hypoglycemia at fasting time (3).

1. Yamato, T., Ishikawa, K., Ojima, K., Tsuji, A., Ishikawa, K., Kusama, R. *Effects of KAD-1229 on post-prandial hyperglycemia after oral meal load in STZ-induced diabetic rats.* Jpn J Pharmacol 2001, 85(Suppl. I): Abst P-602.

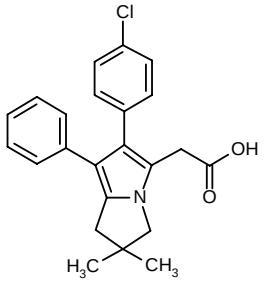
2. Misawa, K., Ichikawa, K., Ojima, K., Hamano, S., Kitamura, T., Komatsu, H. *Effect of KAD-1229, a nonsulfonylurea hypoglycemic agent, on plasma glucose and insulin in streptozotocin-induced diabetic dogs.* Pharmacology 2001, 62(2): 65.

3. *Kissei and Purdue Pharma terminate licensing agreement for mitiglinide.* DailyDrugNews.com (Daily Essentials) Feb 12, 2001.

Original monograph - Drugs Fut 2000, 25: 1034.

ML-3000 *Antiarthritic*

EN: 210861



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

In vitro studies in stimulated human polymorphonuclear leukocytes (PMNs)/platelets demonstrated the ability of ML-3000 to inhibit the production of arachidonic acid metabolites at concentrations of 10 μM or less. It was also found to inhibit PMN-platelet adhesion at concentrations below 25 μM and to concentration-dependently inhibit PMN aggregation and degranulation (1).

The inhibition of the cyclooxygenase pathway of arachidonic acid metabolism by NSAIDs results in increased activity of 5-lipoxygenase-mediated arachidonic acid metabolism, the products of which (LTB_4, peptidoleukotrienes) are suggested to contribute to the gastrointestinal mucosal damage associated with these drugs. ML-3000 is a potent inhibitor of both COX-1/COX-2 and 5-lipoxygenase which has proved effective in animal models of inflammation, pain, fever, asthma and thromboembolism while being devoid of GI toxicity, and is currently in phase III clinical trials for the treatment of osteoarthritis. In the rat carrageenan-induced paw edema model, it gave an ED_{50} of 17 mg/kg p.o. In contrast to indomethacin, ML-3000 as single or multiple oral doses of up to 300 mg/kg produced no gastric mucosal damage (2).

Experiments demonstrated that while both ML-3000 and indomethacin significantly reduced PGE_2 levels in the stomach and inflamed rat paw, ML-3000, unlike indomethacin, did not increase gastric mucosal LTB_4 levels, significantly reduced paw LTB_4 levels and did not induce leukocyte adherence to rat mesenteric venules. These findings confirm that the gastric-sparing properties of ML-3000 are related to its ability to inhibit 5-LO (3).

The therapeutic effects of ML-3000 were evaluated in a canine model of osteoarthritis induced by sectioning the anterior cruciate ligament of the right joint. The animals were treated with placebo or ML-3000 at doses of 2.5 and 5 mg/kg/day p.o. starting on the day after surgery and continued for 8 weeks. Serum levels considered therapeutic were measured in ML-3000-treated dogs. The compound significantly decreased the size and grade of cartilage lesions both macroscopically and histologically compared to placebo-treated dogs. Although no significant differences were seen among treatment groups as regards synovial inflammation, ML-3000 produced a significant decrease in PGE_2 levels in synovial fluid and in LTB_4 production in synovial membranes, as well as a marked decrease in collagenase 1 levels in cartilage and IL-1β levels in synovial membrane (4).

1. Rotondo, S., Dell'Elba, G., Manarini, S., Martelli, N., Simone, V., Evangelista, V., Cerletti, C. *ML3000, a balanced inhibitor of cyclooxygenase and lipoxygenase, inhibits PMN/platelet transcellular metabolism and PMN adhesion and degranulation.* Thromb Haemost 2001, (Suppl.): Abst P2835.

2. Tries, S., Laufer, S. *Pharmacological profile of ML3000: A new gastric mucosa sparing anti-inflammatory drug with COX/5-LOX inhibitory activity.* Inflamm Res 2001, 50(Suppl. 3): Abst W25/02.

3. Tries, S., Neupert, W., Laufer, S. *ML3000, a novel anti-inflammatory compound without the potential for causing gastric damage.* Inflamm Res 2001, 50(Suppl. 3): Abst 063.

4. Pelletier, J.-P., Fernandes, J.C., Jolicoeur, F.-C., Reboul, P., Laufer, S., Tries, S. *The in vivo dual inhibition of cyclooxygenase and lipoxygenase by ML-3000 reduces the progression of experimental osteoarthritis: Suppression of collagenase-1 and interleukin-1beta synthesis.* Osteoarthritis Cartilage 2001, 9(Suppl. B): Abst PP13.

Original monograph - Drugs Fut 1995, 20: 1007.

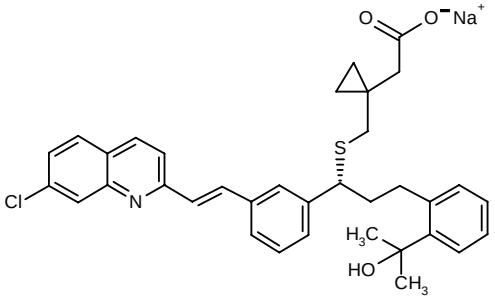
Additional Reference

Gay, R.E. et al. *Dual inhibition of 5-lipoxygenase and cyclooxygenases 1 and 2 by ML3000 reduces joint destruction in adjuvant arthritis.* J Rheumatol 2001, 28(9): 2060.

Montelukast Sodium
Singulair®

Antiallergy/Antiasthmatic
Treatment of Allergic Rhinitis

EN: 205402



$C_{35}H_{35}ClNaNO_3S$ **Merck & Co.**

Patients with continuing asthma symptoms and/or impaired lung function despite the use of inhaled corticosteroids and additional medications were entered in a double-blind, randomized, placebo-controlled, crossover study of add-on therapy with montelukast sodium. The additional bronchodilating effect of montelukast, together with its approved indication as add-on therapy for asthma not controlled by inhaled corticosteroids and β_2-agonists, led a group of U.K. investigators to examine its potential as add-on therapy in 100 such difficult-to-treat outpatients at a dose of 10 mg for 14 days. However, no additional benefit was seen in these patients, as evaluated by symptom scores, rescue inhaled β_2-agonists or peak expiratory flow measurements, and no evidence for a subgroup of responding patients was obtained (1).

Montelukast was assessed in 6 children with both asthma and migraine in a prospective, open-label trial. All patients were administered montelukast at a dose of 5 mg at night for 24 weeks and showed a decrease in asthma attacks without significant side effects. Moreover, headache frequency was reduced from 3-8 attacks per month during the 4 weeks before treatment to 1-3 attacks per month during the first 8 weeks and to 0-2 attacks per month by the end of the study. According to this small study, montelukast is a safe and effective treatment for comorbid asthma and migraine (2).

Health Canada has approved montelukast sodium (Singulair®) in 4-mg tablets for the prevention and treatment of asthma in children aged 2-5 years. Results from a double-blind, placebo-controlled clinical study involving 689 patients with asthma aged 2-5 supported the approval. In the trial, 461 patients received montelukast 4 mg and 228 received placebo over 12 weeks of therapy. Patients in this study had a history of physician-diagnosed asthma with at least 3 episodes (such as coughing,

  CCC: 0377-8282/2001

wheezing and shortness of breath) within the year prior to the study. Data indicate that montelukast 4 mg improved the ability of children with asthma as young as 2 years of age to continue their daily activities. The tolerability profile in children of this age group was similar to placebo. Furthermore, the percent of patients using oral corticosteroids for serious asthma attacks was significantly reduced (3).

1. Robinson, D.S., Campbell, D., Barnes, P.J. *Addition of leukotriene antagonists to therapy in chronic persistent asthma: A randomised double-blind placebo-controlled trial.* Lancet 2001, 357(9273): 2007.

2. de Souza Carvalho, D., Fragoso, Y.D., Coelho, F.M., Pereira, M.M. *Asthma + migraine in childhood and adolescence: Prophylactic benefits with leukotriene receptor antagonist.* Cephalalgia 2001, 21(4): Abst P2-I17.

3. *Singulair approved for treatment of children with asthma as young as two years.* DailyDrugNews.com (Daily Essentials) April 23, 2001.

Original monograph - Drugs Fut 1997, 22: 1103.

Additional References

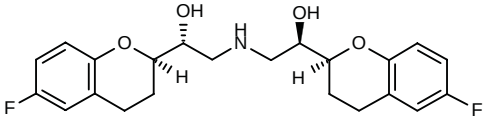
Philip, G. et al. *Improvement in rhinoconjunctivitis quality of life in the treatment of spring allergic rhinitis by montelukast in a multicenter, double-blind, randomized, placebo-controlled study.* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A190.

Philip, G. et al. *Reduction of eosinophil counts by montelukast in a large, double-blind, randomized, placebo-controlled study of spring allergic rhinitis.* Allergy 2001, 56(Suppl. 68): Abst 235.

Nebivolol
Lobivon®
Nevilet®

Antihypertensive

EN: 116585



$C_{22}H_{25}F_2NO_4$

Janssen; Menarini; Meiji Seika; Bertek

Bertek Pharmaceuticals has obtained exclusive U.S. and Canadian rights to nebivolol. Bertek will initially evaluate the drug in essential hypertension followed by a clinical program in heart failure. The company expects to submit an NDA for hypertension in late 2003. Nebivolol, currently available in 30 countries in Europe and Central America, was developed by Janssen in the late 1980s (1).

1. *Bertek licenses β-blocker nebivolol; new indications to be evaluated.* DailyDrugNews.com (Daily Essentials) April 9, 2001.

Original monograph - Drugs Fut 1989, 14: 957.

Additional References

Belousov, Y.B., Leonova, M.V. *Clinical efficacy of a novel beta-blocker nebivolol in patients with hypertension. Results of a multicenter study.* Kardiologiya 2000, 40(9): 27.

Cazzola, M. et al. *Comparison of the effects of single oral doses of nebivolol and celiprolol on airways in patients with mild asthma.* Chest 2000, 118(5): 1322.

Cleophas, T.J. et al. *Long-term efficacy of nebivolol monotherapy in patients with hypertension.* Curr Ther Res 2001, 62(6): 451.

Cleophas, T.J. et al. *Nebivolol monotherapy in 3,747 patients with hypertension. Efficacy continues to improve during the first 6 months of treatment.* J Hypertens 2001, 19(Suppl. 2): Abst 43.

Conrady, A. et al. *A randomized study comparing nebivolol and nadolol in obese essential hypertensive patients: Effects on lipid and glucose metabolism and NO production.* Eur Heart J 2001, 22(Suppl.): Abst P632.

Davletyants, G.L. et al. *Clinical and hemodynamic efficacy of nebivolol in patients with essential hypertension and heart failure.* Kardiologiya 2000, 40(12): 64.

De Marchi, S. et al. *Modifications of arm microcirculatory flux in hypertensive patients treated with nebivolol and atenolol.* J Hypertens 2001, 19(Suppl. 2): Abst P3.50.

López-Vidriero Tejedor, E. et al. *Hemodynamic effects of nebivolol in essential hypertensive patients vs healthy non hypertensive controls.* J Hypertens 2001, 19(Suppl. 2): Abst 110.

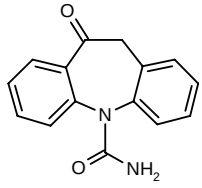
Morizzo, C. et al. *Nebivolol selectively improves endothelium-dependent vasodilation at peripheral microcirculatory level in hypertensive patients with basally depressed response to acetylcholine.* J Hypertens 2001, 19(Suppl. 2): Abst P2.188.

Tzemos, N. et al. *Nebivolol reverses endothelial dysfunction in essential hypertension: A randomized, double-blind, crossover study.* Circulation 2001, 104(5): 511.

Oxcarbazepine
Trileptal®

Antiepileptic

EN: 117845



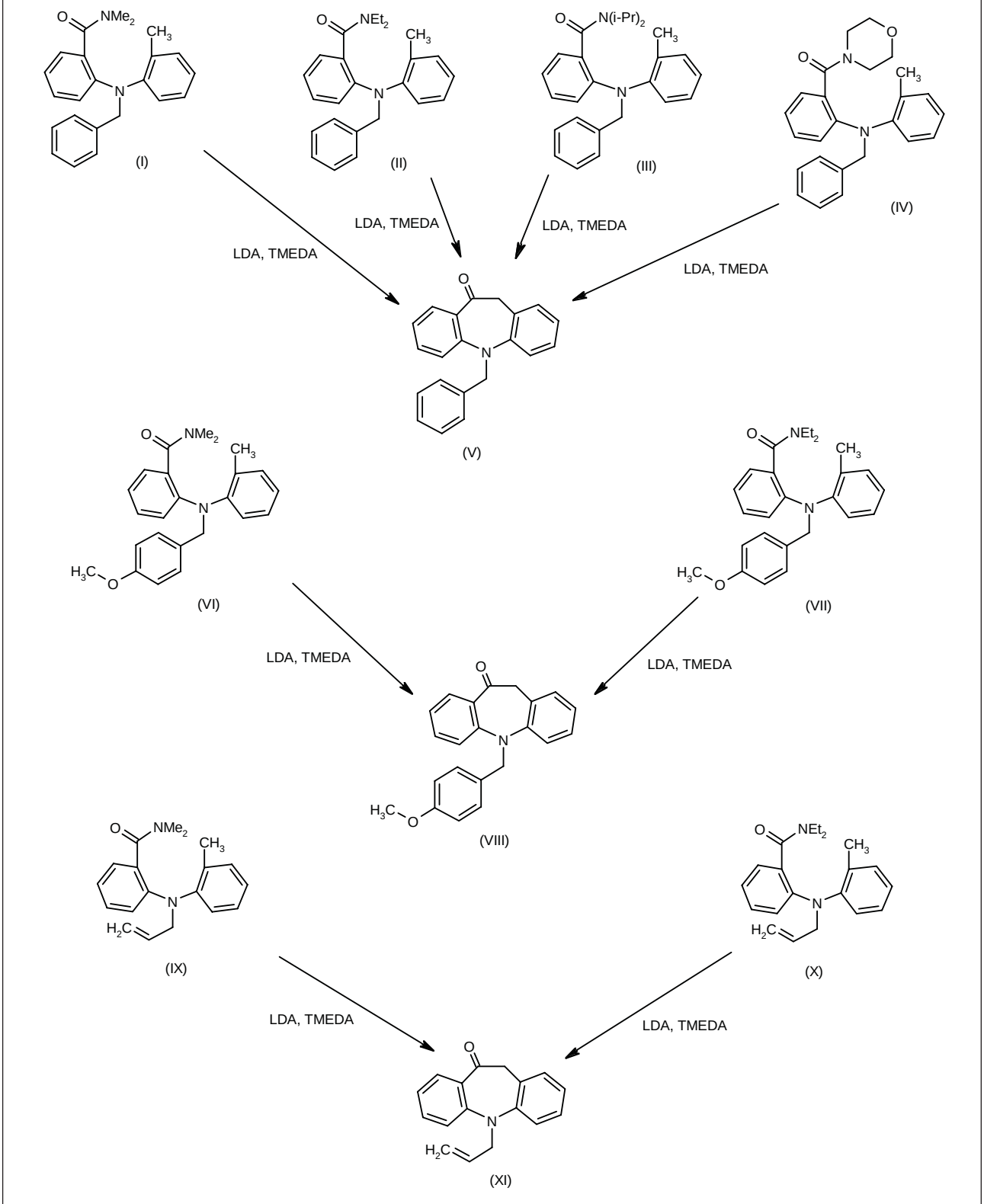
$C_{15}H_{12}N_2O_2$

Novartis; Kissei

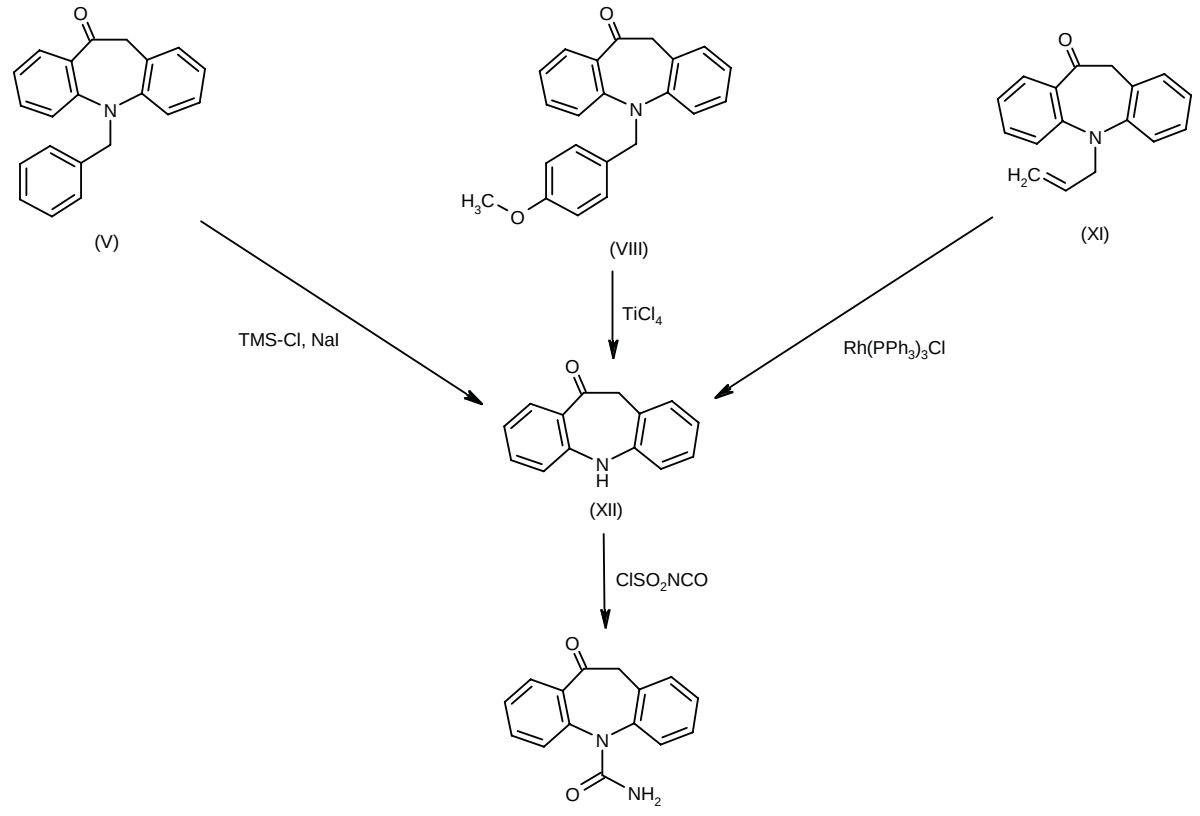
Several novel similar syntheses of oxcarbazepine have been reported (1):

1) Syntheses of intermediate (V), 5-benzyl-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepin-10-one: Cyclization of either 2-[*N*-benzyl-*N*-(2-methylphenyl)amino]-*N*,*N*-dimethylbenzamide (I), 2-[*N*-benzyl-*N*-(2-methylphenyl)-ami-no]-*N*,*N*-diethylbenzamide (II), 2-[*N*-benzyl-*N*-(2-methylphenyl)amino]-*N*,*N*-diisopropylbenzamide (III) or the morpholine derivative (IV) by means of LDA and TMEDA in THF. Scheme 2.

Scheme 2: Synthesis of Intermediates (V), (VIII) and (XI) of Oxcarbazepine



Scheme 3: Synthesis of Oxcarbazepine



2) Syntheses of intermediate (VIII), 5-(4-methoxybenzyl)-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepin-10-one: Cyclization of 2-[*N*-(4-methoxybenzyl)-*N*-(2-methylphenyl)amino]-*N*,*N*-dimethylbenzamide (VI) or 2-[*N*-(4-methoxybenzyl)-*N*-(2-methylphenyl)amino]-*N*,*N*-diethylbenzamide (VII)) by means of LDA and TMEDA in THF. Scheme 2.

3) Syntheses of intermediate (XI), 5-allyl-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepin-10-one: Cyclization of 2-[*N*-allyl-*N*-(2-methylphenyl)amino]-*N*,*N*-dimethylbenzamide (IX) or 2-[*N*-allyl-*N*-(2-methylphenyl)amino]-*N*,*N*-diethylbenzamide (X) by means of LDA and TMEDA in THF. Scheme 2.

4) Finally, deprotection of either intermediate (V) with TMS-Cl and NaI, intermediate (VIII) with $TiCl_4$ or intermediate (XI) with $Rh(PPh_3)_3Cl$ give, in all cases, 10,11-dihydro-5*H*-dibenz[*b*,*f*]azepin-10-one (XII), which is finally treated with chlorosulfonyl isocyanate to afford oxcarbazepine. Scheme 3.

The European Mutual Recognition Procedure has been completed for the oral suspension formulation of Trileptal®, which is indicated for monotherapy and as adjunctive therapy in children and adults with partial epileptic seizures, with or without secondary generalization. The oral suspension was approved by the FDA in the U.S. in May of this year (2).

1. Lohse, O., Beutler, U., Funfschilling, P., Furet, P., France, J., Kaufmann, D., Zaugg, W. *New synthesis of oxcarbazepine via remote metalation of protected N-o-tolyl-anthranilamide derivatives.* Tetrahedron Lett 2001, 42(3): 385.

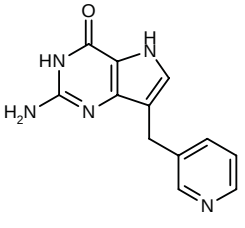
2. *Oral suspension formulation of Trileptal soon to be available in Europe.* DailyDrugNews.com (Daily Essentials) Aug 28, 2001.

Original monograph - Drugs Fut 1986, 11: 844.

Peldesine

Treatment of Lymphoma

EN: 193376



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

In vitro studies of the delivery of peldesine by mixed and self-emulsifying creams and hydrophobic ointment formulations into and across cryopreserved human

cadaver skin have indicated that creams containing propylene glycol and petrolatum-base formulations are the most effective. Petrolatum- and lanolin-based ointments prepared with propylene glycol were evaluated along with oil-in-water cream formulations with 1% radiolabeled peldesine and propylene glycol, glycerin, isopropyl myristate, oleic acid and capric-caprylic esters. Drug diffusion of 4-6 mg of a formulation sample was allowed for 12 and 24 h periods after application to the epidermal surface of skin sections. *In vitro* flux and skin-vehicle partition coefficients correlated well with drug quantities found in the skin samples. The formulation containing propylene glycol delivered more drug into the skin than the glycerin formulation. The isopropyl myristate self-emulsifying cream formulation delivered more drug into the dermis than the oleic acid and capric-caprylic esters formulations. Six times as much drug entered the epidermis with the petrolatum ointment as compared to the lanolin ointment (1).

A pharmacokinetic study of peldesine in cancer patients revealed that intravenous infusion of the drug results in the elevation of endogenous inosine (INO) and 2'-deoxyguanosine (dGUO), with longer infusions having potentially greater therapeutic benefit. Patients received either a 30-min infusion of peldesine 80, 106 and 141 mg/m^2, or a 30-min infusion of peldesine 175 mg/m^2 plus a 4-h infusion of peldesine 168 mg/m^2. A dose response in plasma C_{max} and $AUC_{0-\infty}$ between the 30-min peldesine doses of 80-175 mg/m^2 was observed. The elimination half-life was 2.3-3.9 h and clearance was 22-36 l/h. Pharmacodynamic evaluation revealed a drug dose response for dGUO. Elimination half-lives of 2.1 and 14.5 h were calculated for dGUO and INO, respectively. Higher plasma levels of dGUO, but not INO, resulted from the 4-h infusion regimen as compared to the 30-min regimen (2).

A randomized, placebo-controlled, double-blind study was conducted to determine the efficacy of peldesine in the treatment of cutaneous T-cell lymphoma. Patients with patch and plaque phase disease were randomized to peldesine 1% dermal cream or placebo vehicle cream twice daily for up to 24 weeks. Of the 90 patients enrolled in the study, 1 withdrew, 43 received peldesine and 46 received placebo. Response rates in the active drug and placebo groups were 28% and 24%, respectively, with efficacy defined as clearing of 50% or more of patches and plaques. It was unclear whether the vehicle cream had more than a placebo therapeutic effect (3).

1. Viegas, T.X., Van Winkle, L.L., Lehman, P.A., Franz, S.F., Franz, T.J. *Evaluation of creams and ointments as suitable formulations for peldesine.* Int J Pharm 2001, 219(1-2): 73.

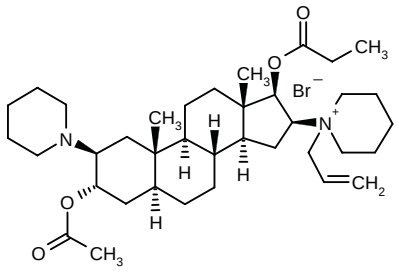
2. Viegas, T.X., Omura, G.A., Warren, T.S., Herring, J.B., Kilpatrick, J.M. *Pharmacokinetics and pharmacodynamics of peldesine (BCX-34), a purine nucleoside phosphorylase inhibitor, following single intravenous infusions in cancer patients.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 3514.

3. Duvic, M., Olsen, E.A., Omura, G.A. et al. *A phase III, randomized, double-blind, placebo-controlled study of peldesine (BCX-34) cream as topical therapy for cutaneous T-cell lymphoma.* J Am Acad Dermatol 2001, 44(6): 940.

Original monograph - Drugs Fut 1993, 18: 887.

Rapacuronium Bromide *Neuromuscular Blocker*
Raplon®

EN: 203872



$C_{37}H_{61}BrN_2O_4$ **Organon**

Based on reports of safety issues related to the association of rapacuronium bromide with bronchospasm, including 5 fatalities, Organon has announced the voluntary withdrawal of the agent from the U.S. market. Rapacuronium bromide was approved by the FDA in August 1999 as an adjunct to general anesthesia to facilitate tracheal intubation and to provide skeletal muscle relaxation during short surgical procedures. The company contacted the FDA and sent a letter beginning on March 27, 2001 to all anesthesiologists, hospital pharmacists and other consignees of the drug, notifying them of the withdrawal (1).

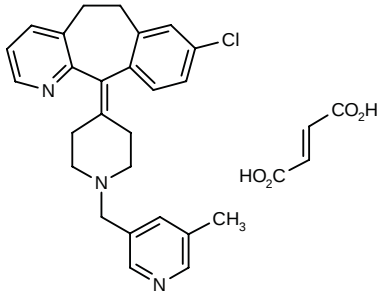
1. *Voluntary withdrawal of injectable anesthesia drug by Organon.* DailyDrugNews.com (Daily Essentials) March 30, 2001.

Original monograph - Drugs Fut 1994, 19: 916.

Rupatadine Fumarate

Treatment of Allergic Rhinitis

EN: 204914



$C_{26}H_{26}ClN_3.C_4H_4O_4$ **Uriach**

  CCC: 0377-8282/2001

A study in guinea pigs with histamine (400 μg)-, PAF (10 μg)- or ovalbumin-induced experimental conjunctivitis demonstrated the efficacy of topical rupatadine (0.0005-0.1% solution) as compared to loratadine and levocabastine (0.001-0.1% solution). Treatment was administered ocularly 15 min prior to exposure to histamine, PAF or ovalbumin. Rupatadine was well tolerated and significantly and dose-dependently prevented histamine-induced conjunctivitis. Loratadine at doses of 0.01% or higher also prevented histamine conjunctivitis although levocabastine (0.001%) was the most active agent. Treatment with rupatadine also prevented PAF-induced conjunctivitis at doses of 0.05 and 0.1% while loratadine and levocabastine had no significant effects. Similarly, although levocabastine had no effect, rupatadine (0.03-0.1%) inhibited ovalbumin-induced conjunctivitis (1).

The efficacy and safety of rupatadine and ebastine were compared in a multicenter, randomized, double-blind, placebo-controlled study of outpatients with seasonal allergic rhinitis. Patients were randomized to rupatadine 10 mg/day, ebastine 10 mg/day or placebo once daily for 2 weeks. Statistically significant differences were found between rupatadine and placebo for mean Daily Total Symptom Score. The lowest mean Daily Symptom Scores were found with rupatadine, while for ebastine and placebo these values were only statistically significant for runny nose. Both ebastine and rupatadine were significantly better than placebo according to patient and investigator assessments. Both agents were well tolerated, with headache being the most common adverse event reported overall (2).

1. Merlos, M., Ferrando, R., Giral, M., Ramis, I., Forn, J. *Effect of topical rupatadine in experimental conjunctivitis in guinea pigs: Macroscopic evaluation of ocular lesions.* J Allergy Clin Immunol 2001, 107(2, Part 2): Abst 1016.

2. Izquierdo, I., Lurigados, C., Pérez, I., Forn, J. *Rupatadine exhibits a better profile than ebastine in patients with seasonal allergic rhinitis.* Allergy 2001, 56(Suppl. 68): Abst 635.

Original monograph - Drugs Fut 1996, 21: 1032.

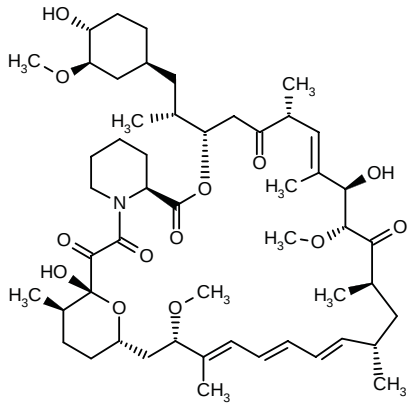
Additional Reference

Izquierdo, I. et al. *Lack of electrocardiographic effects of rupatadine, new nonsedating selective histamine H_1-receptor and PAF antagonist.* Allergy 2001, 56(Suppl. 68): Abst 637.

Sirolimus
Rapamune®

Treatment of Transplant Rejection

EN: 175652



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

Sirolimus (Rapamune®), the first in a new class of immunosuppressants developed for the prevention of organ rejection following renal transplantation, is now commercially available in Canada. Sirolimus is marketed by Wyeth-Ayerst (American Home Products) and is recommended for use in combination with ciclosporin and corticosteroids for the prevention of acute organ rejection in kidney transplant patients. Results from clinical trials demonstrated that the agent, when used in this combination, reduces acute rejection rates by up to 60% when compared to control regimens containing ciclosporin and corticosteroids in combination with either azathioprine or placebo. Graft loss and patient survival rates at 6 and 12 months were similar in both groups. Studies also show that patients treated with sirolimus experienced a reduction in the incidence of all grades of acute rejection episodes. Rapamune® was approved in the U.S. in September 1999 and has also been approved in other countries including the countries of the E.U., Argentina, Brazil, Chile, Mexico, Switzerland, Taiwan and Venezuela (1).

Wyeth-Ayerst has announced that the first solid formulation of sirolimus is now available in the U.S. This new 1-mg tablet provides easier administration and storage than the oral solution (2).

1. *Health Canada approves Rapamune for immunosuppression following renal transplantation.* DailyDrugNews.com (Daily Essentials) June 6, 2001.

2. *New tablet form of Rapamune for kidney transplants now available in the U.S.* DailyDrugNews.com (Daily Essentials) Aug 6, 2001.

Original monograph - Drugs Fut 1977, 2: 692.

Additional References

Campistol, J.M. et al. *Sirolimus (Rapamune®) maintenance therapy: Therapeutic drug monitoring and dosing considerations.* Am J Transplant 2001, 1(Suppl. 1): Abst 987.

Flechner, S.M. et al. *A prospective randomized trial of sirolimus vs. cyclosporine in kidney transplantation: Impact of calcineurin inhibitor elimination on renal function.* Am J Transplant 2001, 1(Suppl. 1): Abst 147.

Johnson, R.W.G. et al. *Sirolimus allows early cyclosporine withdrawal in renal transplantation resulting in improved renal function and lower blood pressure.* Transplantation 2001, 72(5): 777.

Kahan, B.D. *Two-year safety and efficacy of sirolimus in renal transplantation.* Am J Transplant 2001, 1(Suppl. 1): Abst 144.

MacDonald, A.S. *A worldwide, phase III, randomized, controlled, safety and efficacy study of a sirolimus/cyclosporine regimen for prevention of acute rejection in recipients of primary mismatched renal allografts.* Transplantation 2001, 71(2): 271.

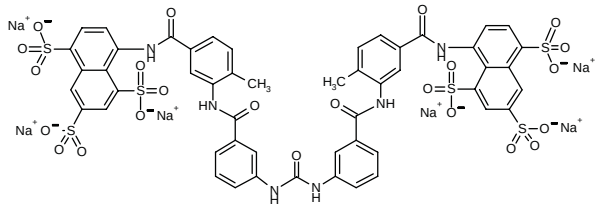
Ponticelli, C. et al. *Phase III trial of Rapamune versus placebo in primary renal allograft recipients.* Transplant Proc 2001, 33(3): 2271.

Yoo, S.J., Kahan, B.D. *Combination treatment with sirolimus and ciclosporin in clinical renal transplantation: A comprehensive review.* Drugs Today 2001, 37(6): 385.

Suramin Sodium

Oncolytic

EN: 116051



$C_{51}H_{34}N_6Na_6O_{23}S_6$ **Pfizer**

The tolerability and potential efficacy of suramin in patients with recurrent high-grade gliomas were demonstrated in a trial of 12 patients. Adverse effects were modest and reversible. Although no partial or complete responses were observed at 12 weeks, 1 patient had a reduction in tumor size and a stable partial response for more than 2 years with no other therapy, and 2 patients had disease stabilization and lived for 16 and 27 months. Based on the results of this study, suramin and radiation administered concurrently are now being investigated in patients with newly diagnosed glioblastoma multiforme (1).

The efficacy and toxicity of suramin were evaluated in 50 metastatic hormone-refractory prostate cancer patients. Along with hydrocortisone, patients received a test i.v. infusion of suramin 200 mg and then 24-h i.v. administration of suramin 500 mg/m^2 for 5 days. Weekly 2-h infusions of suramin 350 mg/m^2 were then given for 12 weeks and repeated after 3 months if there was no disease progression or significant toxicity. There were no complete responses to therapy, although 54% of patients had a partial response. Of these, 32% had a decrease in PSA levels of more than 75%. Analgesic use was reduced in 72.9% of patients with bone pain. The high activity of the suramin regimen lasted a median of 13 weeks before progression. The median overall survival time was 11 months. The drug also had a good tolerance profile (2).

1. Grossman, S.A., Phuphanich, S., Lesser, G., Rozental, J., Grochow, L.B., Fisher, J., Piantadosi, S. *Toxicity, efficacy, and pharmacology of suramin in adults with recurrent high-grade gliomas.* J Clin Oncol 2001, 19(13): 3260.

2. Calvo, E., Cortes, J., Rodriguez, J. et al. *Fixed dose schedule of suramin in hormone-refractory metastatic prostate cancer: A multicenter phase II study.* Ann Oncol 2000, 11(Suppl. 4): Abst 338P.

Original monograph - Drugs Fut 1986, 11: 860.

Additional References

Kruger, E.A., Figg, W.D. *Protein binding alters the activity of suramin, carboxyamidotriazole, and UCN-01 in an ex vivo rat aortic ring angiogenesis assay.* Proc Amer Assoc Cancer Res 2001, 42: Abst 3145.

Schroder, L.E. et al. *Phase II evaluation of suramin in advanced adrenal carcinoma: Southwest Oncology Group (SWOG) trial 9427.* Proc Am Soc Clin Oncol 2001, 20(Part 2): Abst 2361.

Song, S. et al. *Suramin enhances the antitumor activity of doxorubicin in mice bearing lung metastasis of human prostate tumors.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 2662.

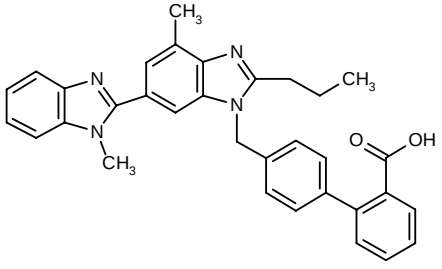
Walsh, C.T. et al. *Suramin enhances the antitumor activity of paclitaxel in mice bearing lung metastasis of human prostate tumors.* Proc Amer Assoc Cancer Res 2001, 42: Abst 4374.

Zhang, Y. et al. *Suramin enhances doxorubicin efficacy in human prostate xenograft tumors in mice.* Proc Amer Assoc Cancer Res 2001, 42: Abst 4360.

Telmisartan
Micardis®
Pritor®

Antihypertensive

EN: 195173



$C_{33}H_{30}N_4O_2$ **Boehringer Ingelheim; Abbott; GlaxoSmithKline**

Boehringer Ingelheim has reported plans for the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) study to evaluate the role of telmisartan (Micardis®), an

  CCC: 0377-8282/2001

angiotensin II receptor blocker, and ramipril, an angiotensin-converting enzyme (ACE) inhibitor, alone or in combination, compared to ramipril alone for the prevention of stroke, myocardial infarction, cardiovascular death and hospitalization for congestive heart failure (CHF). The composite cardiovascular endpoint will be the reduction of risk of cardiovascular mortality, stroke, myocardial infarction and hospitalization for CHF. The trial is a multicenter, double-blind, randomized study that will involve approximately 28,000 patients at about 700 sites in North and South America, Europe, Asia, Australia and South Africa over a 5-year period. Patients will be divided into three treatment groups. One group will receive 80 mg of telmisartan daily, another group will receive 10 mg of ramipril daily and the third group will receive the combination of 80 mg telmisartan plus 10 mg ramipril daily. Patient enrollment will begin in the second half of 2001 and the study is expected to be completed in 2007. Patients in the study will be at least 55 years of age with a history of coronary artery disease, stroke, peripheral vascular disease or diabetes. Specifically, patients with diabetes also will have at least one other cardiovascular risk factor, including hypertension, elevated total cholesterol, low HDL cholesterol levels, cigarette smoking or microalbuminuria (1).

Boehringer Ingelheim has announced plans to begin the largest cardiovascular protection trial ever conducted in patients intolerant to angiotensin-converting enzyme (ACE) inhibitors. The trial, referred to as the TRANSCEND (Telmisartan Randomized AssessmeNt Study in aCE iNtolerant subjects with cardiovascular Disease) trial, will examine the effects of telmisartan in a total of approximately 5000 patients who are intolerant to ACE inhibitors; patients over the age of 55 years with a history of coronary artery disease, stroke, peripheral vascular disease or type 1 or 2 diabetes with end-organ damage will be eligible for enrollment. The double-blind, parallel-group trial will begin in 2001 and will be completed in approximately 5.5 years. The TRANSCEND trial will evaluate telmisartan 80 mg *versus* placebo in patients who are intolerant to ACE inhibitors. The primary goal of the trial is to compare treatments with respect to the composite endpoint of cardiovascular mortality, stroke, acute myocardial infarction and hospitalization for congestive heart failure. The secondary objective of the trial is the comparison of treatment with respect to incidence of revascularization procedures, newly diagnosed diabetes, dementia, new-onset atrial fibrillation and microvascular complications of diabetes (2).

1. *Boehringer Ingelheim prepares large international study for prevention of cardiovascular disease.* DailyDrugNews.com (Daily Essentials) March 15, 2001.

2. *Boehringer Ingelheim announces TRANSCEND trial in ACE-intolerant patients.* DailyDrugNews.com (Daily Essentials) June 18, 2001.

Original monograph - Drugs Fut 1997, 22: 1112.

Additional References

Lacourcière, Y. et al. *Comparison of the antihypertensive effects of a fixed-dose combination of telmisartan and hydrochlorothiazide versus telmisartan monotherapy in mild-to-moderate hypertension.* J Renin-Angiotensin-Aldosterone Syst 2001, 2(1): Abst PC.9.

Lacourcière, Y., Poirier, L. *Comparison of a fixed-dose combination of telmisartan 40 mg + hydrochlorothiazide 12.5 mg with telmisartan 40 mg in the control of mild-to-moderate hypertension.* J Renin-Angiotensin-Aldosterone Syst 2001, 2(1): Abst PC.31.

Laws, D. *Safety and efficacy of long-term exposure to monotherapy or combination therapy with telmisartan.* J Renin-Angiotensin-Aldosterone Syst 2001, 2(1): Abst PC.35.

McGill, J.B., Reilly, P.A. *Combination treatment with telmisartan and hydrochlorothiazide in black patients with mild to moderate hypertension.* Clin Cardiol 2001, 24(1): 66.

McGill, J.B., Reilly, P.A. *Telmisartan plus hydrochlorothiazide versus telmisartan or hydrochlorothiazide monotherapy in patients with mild to moderate hypertension: A multicenter, randomized, double-blind, placebo-controlled, parallel-group trial.* Clin Ther 2001, 23(6): 833.

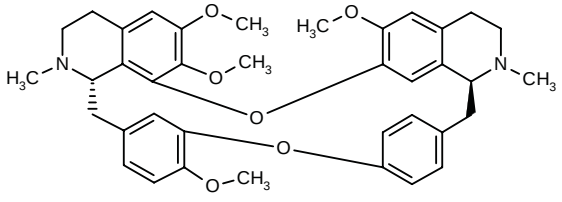
McGill, J.B., Reilly, P.A. *Telmisartan reverses the potassium loss associated with high doses of hydrochlorothiazide.* J Renin-Angiotensin-Aldosterone Syst 2001, 2(1): Abst PC.22.

Yong, C.-L., Dias, V.C., Stangier, J. *Multiple-dose pharmacokinetics of telmisartan and of hydrochlorothiazide following concurrent administration in healthy subjects.* J Clin Pharmacol 2000, 40(12, Part 1): 1323.

Tetrandrine

Oncolytic
Antihypertensive

EN: 090703



$C_{38}H_{42}N_2O_6$ **Kaken; Chin. Acad. Med. Sci.**

A study was conducted to compare the cardioprotective effects of radix stephaniae tetrandrae (RST) extract and its individual components tetrandrine and fangchinoline with those of verapamil. Rat hearts were treated with the compounds or vehicle and subjected to regional ischemia and reperfusion. RST and tetrandrine were equally effective in ameliorating arrhythmia and infarct and did not inhibit ischemia-reduced heart rate or coronary artery flow. Verapamil also had ameliorating effects on arrhythmia and infarct, with a 1 μM dose further inhibiting heart rate during ischemia. Fangchinoline induced S-T segment elevation and reduced heart rate and coronary artery flow during ischemia. RST and tetrandrine thus showed equal benefit and an advantage over verapamil for the treatment of arrhythmia and infarct (1).

1. Yu, X.C., Wu, S., Wang, G.Y., Shan, J., Wong, T.M., Chen, C.F., Pang, K.T. *Cardiac effects of the extract and active components of radix stephaniae tetrandrae II. Myocardial infarct, arrhythmias, coronary arterial flow and heart rate in the isolated perfused rat heart.* Life Sci 2001, 68(25): 2863.

Original monograph - Drugs Fut 1979, 4: 749.

Additional References

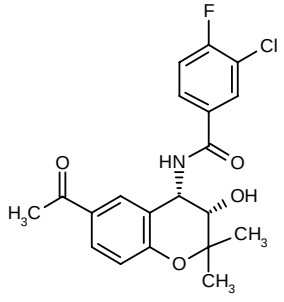
Kang, C. et al. *Effects of tetrandrine on mRNA expression of inflammatory molecules induced by focal cerebral ischemic damage in rats.* Soc Neurosci Abst 2000, 26(Part 1): Abst 183.9.

Zhang, Y.H., Fang, L.H. *Antagonism of morphine-induced antinociception by tetrandrine is dependent on serotonergic mechanisms.* Life Sci 2001, 69(12): 1429.

Tonabersat
SB-220453

Antimigraine

EN: 231735



$C_{20}H_{19}ClFNO_4$ **GlaxoSmithKline**

The contractile properties of SB-220453 were investigated in human coronary artery, saphenous vein, middle meningeal artery and atrial and ventricular cardiac trabeculae and compared to those of sumatriptan. Only sumatriptan induced contractions in blood vessels, and neither SB-220453 nor sumatriptan had any inotropic effect in atrial and ventricular cardiac trabeculae. The antimigraine effects of SB-220453 did not appear to be due to direct cerebral vasoconstriction. Since SB-220453 had no activity on isolated blood vessels, the compound is not expected to cause cardiac side effects (1).

The effects of SB-220453 and sumatriptan on cGMP were investigated in the setting of KCl-induced cortical spreading depression in anesthetized rats. Cortical spreading depression produced a significant elevation in cGMP concentration in the brainstem, which was completely abolished by pretreatment with SB-220453 (10 mg/kg i.p.) but not with sumatriptan (300 μg/kg i.v.) (2).

The effects of SB-220453 on nitric oxide release associated with cortical spreading depression were investigated in anesthetized cats. Doses of 1, 3 and 10 mg/kg were found to dose-dependently inhibit changes in extracellular direct current field potential and nitric oxide release induced by KCl application to the cortical surface (3).

SB-220453 demonstrated marked inhibition of repetitive cortical spreading depression in a study in anesthetized cats administered SB-220453 (1, 3 or 10 mg/kg) or vehicle i.p. After 90 min, spreading depression was induced in the suprasylvian gyrus and changes in d.c. potential were recorded in the suprasylvian gyrus and marginal gyrus. SB-220453 was shown to dose-dependently reduce the number of events and the period of repetitive spreading depression induced by brief exposure to KCl. Repetitive pial vasodilatation induced by spreading depression was also reduced by SB-220453, although resting hemodynamics were unaffected. Furthermore, metabolic coupling was not affected when spreading depression events occurred in the presence of SB-220453 (4).

The effects of SB-220453 on trigeminal nerve ganglion stimulation-induced sensory-autonomic neurovascular reflexes have been evaluated in anesthetized cats. The effects of intravenous carabersat and intraduodenal sodium valproate, gabapentin and lamotrigine were also evaluated in this model. None of the compounds tested produced any effect on resting blood pressure, heart rate, carotid blood flow or carotid vascular resistance. Intravenous tonabersat and carabersat caused time-related reductions in trigeminal nerve-induced neurovascular reflexes. Tonabersat administered at 3.4 μmol/h produced a maximal inhibition as compared to controls of 30 ± 7% at 240 min, and similar inhibition was achieved at 120 min when tonabersat was administered at 11.5 μmol/h. Carabersat (3.4 μmol/h) achieved a maximal inhibition of 33 ± 4% at 180 min of infusion. Intraduodenal tonabersat produced a maximal inhibition of nerve stimulation-induced response of 55 ± 4% at 120 min after a dose of 10 mg/kg and of 24 ± 2% at 180 min after a dose of 1 mg/kg. Intraduodenal lamotrigine produced a maximal inhibition of 52 ± 12% at 150 min after a dose of 50 mg/kg and of 22 ± 11% at 180 min after 10 mg/kg. Intraduodenal gabapentin (100 mg/kg) led to a maximal inhibition of 17 ± 13% at 150 min and intraduodenal sodium valproate had no effect on neurovascular reflexes. Based on these results, the researchers concluded that blockade of trigeminal parasympathetic reflexes with anticonvulsant agents such as tonabersat and carabersat may indicate potential in the treatment of conditions such as migraine (5).

1. Maassen van den Brink, A., van den Broek, R.W.M., De Vries, R., Upton, N., Parsons, A.A., Saxena, P.R. *The potential antimigraine compound SB-220453 does not contract human isolated blood vessels or myocardium: A comparison with sumatriptan.* Cephalalgia 2000, 20(6): 538.

2. Read, S.J. et al. *Cortical spreading depression produces increased cGMP levels in cortex and brain stem that is inhibited by tonabersat (SB-220453) but not sumatriptan.* Brain Res 2001, 891(1-2): 69.

3. Read, S.J., Smith, M.I., Hunter, A.J., Upton, N., Parsons, A.A. *SB-220453, a potential novel antimigraine agent, inhibits nitric oxide release following induction of cortical spreading depression in the anaesthetized cat.* Cephalalgia 2000, 20(2): 92.

4. Smith, M.I., Read, S.J., Chan, W.N., Thompson, M., Hunter, A.J., Upton, N., Parsons, A.A. *Repetitive cortical spreading depression in a gyrencephalic feline brain: Inhibition by the novel benzoylamino-benzopyran SB-220453.* Cephalalgia 2000, 20(6): 546.

5. Parsons, A.A., Bingham, S., Raval, P., Read, S., Thompson, M., Upton, N. *Tonabersat (SB-220453) a novel benzopyran with anticonvulsant properties attenuates trigeminal nerve-induced neurovascular reflexes.* Br J Pharmacol 2001, 132(7): 1549.

Original monograph - Drugs Fut 1999, 24: 1078.

Additional References

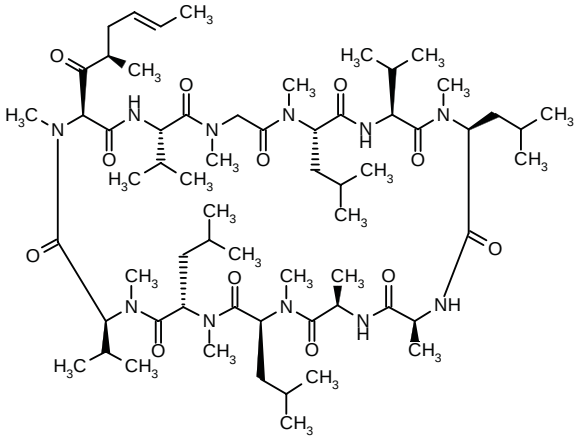
Bradley, D.P. et al. *Inhibition of cortical spreading depression (CSD) initiation by tonabersat, but not sumatriptan, detected with MRI.* J Cereb Blood Flow Metab 2001, 21(Suppl. 1): Abst 84.

Tvedskov, J.F. et al. *Experience with SB-220453 in the glyceryl-trinitrate (GTN) migraine model, interaction with GTN.* Cephalalgia 2001, 21(4): Abst P1-H15.

Valspodar
Amdray®

Multidrug Resistance Modulator

EN: 182411



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

A study evaluating the cause of transient neurological symptoms associated with ciclosporin and PSC-833 has been reported. Concentrations of 0.1, 1, 10 and 20 μM of each drug were investigated for 24 and 48 h in primary cultures of rat neuronal and glial cells. The 10 μM concentration of PSC-833 was not cytotoxic in either cell type, did not inhibit proliferation in astrocytes 24 h after incubation, resulted in significantly increased glucose consumption and lactate production in both cell types and decreased levels of Krebs cycle intermediates. Glucose consumption and lactate formation increased 60-83% and 54-78%, respectively, when both cells type were treated with 10 μM PSC-833. These increases were similar to those seen with 20 μM ciclosporin. It was concluded that energy depletion and acidosis may result from impaired tricarboxylic acid cycle activity and this may be responsible in part for the neurological symptoms observed with the two agents (1).

The cytotoxicity of the cyclosporines alone and in combination with other agents has been reevaluated in defined cell lines. At clinically relevant concentrations, ciclosporin and PSC-833 demonstrated cytotoxic activity in leukemia, breast and prostate cell lines. The combination of PSC-833 and estramustine, etoposide, ketoconazole, suramin and vinorelbine demonstrated synergistic or additive effects in prostate cancer cell lines. Additive and synergistic effects were found in specific cell lines with bicalutamide, carboplatin, cisplatin, *cis*-retinoic acid, dexamethasone, 5-fluorouracil, liarozole and *trans*-retinoic acid. It was concluded that the anticancer effects of PSC-833 and ciclosporin alone or in combination with other drugs may be independent of their action on the MDR pump (2).

The modulator activity of PSC-833 and ciclosporin was studied in murine T-cell leukemia cell lines made resistant by treatment with doxorubicin (LBR-D160) or vincristine (LBR-V160). In the absence of either doxorubicin or vincristine, multidrug resistant phenotype reversal was obtained in LBR-D160 but not in LBR-V160. PSC-833 was more effective than ciclosporin in producing reversal of resistance when the two drugs were used together with vincristine or doxorubicin, whereas ciclosporin had a greater cytotoxic effect than PSC-833 in sensitive and resistant cells. Cross-resistance with vincristine, doxorubicin and other antineoplastic agents was also observed (3).

The ability of PSC-833 to inhibit cancer development was evaluated in several P-glycoprotein (Pgp)-expressing cancer cell lines, including 4 astrocytomas (U87, U251, U343 and SF126), mouse mammary tumor cell lines (EMT6 and EMT6/AR1.0) and a human colorectal cancer cell line (Caco-2bbe). PSC-833 (10-60 μM) inhibited cell proliferation and induced cell death in all of the cell lines in a dose- and time-dependent manner, ranging from 30-85%. In the U87 and Caco-2bbe cell lines, C6-ceramide and PSC-833 induced 100% cell death. At 10 μM, the caspase inhibitor Z-VAD-fmk reversed PSC-833-induced cell death by 50%. The results suggest that overexpression of Pgp sustains cancer cell growth by protecting against ceramide-mediated apoptosis (4).

The effect of various doses of PSC-833 on doxorubicin chemotherapy was studied in CT26 colon tumors grown in Balb/c mice. PSC-833 25 mg/kg p.o. given 1 h prior to doxorubicin had peak plasma levels of 7 μM, while repeated dosing of PSC-833 (12.5 mg/kg) resulted in plasma levels between 3-5 μM. In both cases, the plasma AUC of doxorubicin was increased approximately 3-fold. Treatment of tumors with doxorubicin 15 mg/kg was effective but highly toxic. Although doxorubicin (5 mg/kg) plus PSC-833 (25 mg/kg) resulted in a similar plasma AUC as doxorubicin, the combination was much less effective. Animals receiving PSC-833 with doxorubicin 5 mg/kg had tumor levels of doxorubicin as high as or higher than 15 mg/kg doxorubicin alone at 24 and 48 h. The tumor level of doxorubicin at 4 h, however, was 3-fold higher with 15 mg/kg doxorubicin alone. It was

concluded that Pgp inhibitors with minimal nonspecific effects should be used to avoid the loss of benefit from chemotherapy dose reduction (5).

The efficacy of the Pgp inhibitors ciclosporin, PSC-833 and GF-120918 on the brain penetration of paclitaxel was determined in wild-type mice, with knockout mice used as a reference for complete Pgp inhibition. All of the inhibitors increased drug intake into the brain of wild-type mice, with GF-120918 most effective, followed by PSC-833 and ciclosporin. In knockout mice ciclosporin was most efficacious, followed by PSC-833 and GF-120918. Ciclosporin and PSC-833 treatment resulted in 6- and 4-fold higher AUC paclitaxel levels, respectively. Penetration was enhanced by ciclosporin and PSC-833 via increased plasma levels and inhibition of Pgp in the blood-brain barrier, whereas only the latter mechanism was true for GF-120918. After the increase in paclitaxel in knockout mice, brain levels remained constant but plasma levels declined. Peak plasma levels therefore appear to be more important than plasma AUC for maintaining paclitaxel brain levels (6).

The effects of PSC-833 on paclitaxel metabolism and the pharmacokinetics of the major paclitaxel metabolite 6alpha-hydroxypaclitaxel were investigated in a phase I study in patients with refractory cancer. In the first cycle, paclitaxel 35 mg/m^2/day was administered for 4 days without PSC-833. In the second cycle, escalating doses of paclitaxel (13.1, 17.5 or 21.3 mg/m^2/day for 4 days) were administered together with PSC-833 (5 mg/kg every 6 h for 7 days). Plasma levels showed a metabolite peak in 21 of the 22 patients in the second cycle, whereas the metabolite was not detectable in the first cycle. The concentration of the metabolite in the second cycle was higher than that of paclitaxel. Total bilirubin and 6α-hydroxypaclitaxel concentrations were moderately associated. The production of the metabolite was not affected by PSC-833 concentrations as high as 10 mM. Further investigation in HL60 and K562 human leukemia cells revealed that the cytotoxicity of paclitaxel was increased in the presence of noncytotoxic concentrations of the metabolite (7).

The pharmacokinetics of paclitaxel with and without valspodar were studied in 31 patients with advanced breast cancer. Patients received paclitaxel alone (175 mg/m^2 as a 3-h infusion) or paclitaxel (70 mg/m^2) in combination with oral valspodar (5 mg/kg q.i.d.) starting 1 day before paclitaxel and continuing for 21 days. The addition of valspodar had little effect on the clearance of unbound paclitaxel. In the presence of valspodar, the volume of distribution and the terminal disposition half-life of unbound paclitaxel were slightly higher. Cremophor EL clearance varied substantially between patients (8).

A phase I trial in 23 patients with refractory solid tumors was conducted to determine the maximum tolerated dose (MTD) of Doxil (liposomally encapsulated anthracycline) followed by paclitaxel and the combination followed by PSC-833, as well as the pharmacokinetic interactions of these agents. Doxil was administered by i.v. bolus and paclitaxel by 1-h infusion. After 4 weeks, the Doxil and paclitaxel doses were reduced and PSC-833 was added. The MTD of the Doxil/paclitaxel combination was 40/150 mg/m^2 and was due to neutropenia. Grade 3/4 nonhematological toxicities included mucositis, fatigue and arthralgias. The PSC-833 dose was reduced from 5 to 4 mg/kg when the drug induced significant but reversible ataxia. Responses included 1 complete response, 1 partial response, 1 minor response and 4 stable disease (9).

The effects of coadministration of PSC-833 with doxorubicin and paclitaxel have been evaluated in a phase I trial. In patients with various refractory malignancies, a 15-min doxorubicin infusion was followed by a 1-h paclitaxel infusion for the first cycle. Patients then received reduced doses of doxorubicin and paclitaxel with PSC-833 (5 mg/kg p.o. q.i.d. for 12 doses). The MTD of doxorubicin plus paclitaxel without PSC-833 was found to be 35 mg/m^2 doxorubicin and 150 mg/m^2 paclitaxel. The MTD of doxorubicin plus paclitaxel combined with PSC-833 without filgrastim was 12.5 mg/m^2 doxorubicin and 70 mg/m^2 paclitaxel. Neutropenia and thrombocytopenia were the dose-limiting toxicities for both the with- and without-PSC-833 treatments. The MTD of doxorubicin plus paclitaxel combined with PSC-833 with filgrastim was 20 mg/m^2 doxorubicin and 90 mg/m^2 paclitaxel. There were no grade 4 nonhematological toxicities. Treatment resulted in 5 partial and 2 minor tumor remissions. PSC-833 interacted substantially with both doxorubicin and paclitaxel, necessitating dose reductions (10).

In a phase I/II study comparing PSC-833, daunorubicin and cytarabine in patients with poor-risk acute myeloid leukemia, MTDs of 10 mg/kg/day and 45 mg/m^2 were established for PSC-833 and daunorubicin, respectively. Treatment combining PSC-833 and daunorubicin was also found to be well tolerated and active in these patients (11).

1. Cruz, F., Wolf, A. *Effects of the novel cyclosporine derivative PSC 833 on glucose metabolism in rat primary cultures of neuronal and glial cells.* Biochem Pharmacol 2001, 62(1): 129.

2. Kreis, W., Budman, D.R., Calabro, A. *A reexamination of PSC 833 (valspodar) as a cytotoxic agent and in combination with anticancer agents.* Cancer Chemother Pharmacol 2001, 47(1): 78.

3. Lopes, E.C., Scolnik, M., Alvarez, E., Hajos, S.E. *Modulator activity of PSC 833 and cyclosporin-A in vincristine and doxorubicin-selected multidrug resistant murine leukemic cells.* Leuk Res 2001, 25(1): 85.

4. Kankassan, K., Sadanard, V., Sitaraman, S.V., Yusuf, A., Thiessen, J., Rao, P.M., Rutka, J.T., Ling, C.V., Srinivassan, R. *The effect of PSC 833, a potent inhibitor of P-glycoprotein on the growth of several cancer cell lines.* Proc Amer Assoc Cancer Res 2001, 42: Abst 4357.

5. van Tellingen, O., Kemper, M., Neijnen, J.H. *P-glycoprotein inhibition in tumors by PSC 833: Impact of dose adjustments on the efficacy of doxorubicin chemotherapy.* Proc Amer Assoc Cancer Res 2001, 42: Abst 5107.

6. Kemper, M., Cleypool, C., van Zandbergen, E., Boogerd, W., Beijnen, J.H., van Tellingen, O. *The efficacy of P-glycoprotein inhibitors to increase the brain penetration of paclitaxel in mice.* Proc Amer Assoc Cancer Res 2001, 42: Abst 5110.

7. Kang, M.H., Figg, W.D., Ando, Y., Blagosklony, V., Liwerhr, D., Fojo, T., Bates, S.E. *The P-glycoprotein antagonist PSC 833 increases the plasma concentrations of 6α-hydroxypaclitaxel, a major metabolite of paclitaxel.* Proc Amer Assoc Cancer Res 2001, 42: Abst 2881.

8. Sparreboom, A., Spicer, D., Verweij, J., Loss, W.J., Doroshow, J.H., Synold, T.W. *Effect of valspodar (PSC 833) on the pharmacokinetics of unbound paclitaxel.* Proc Amer Assoc Cancer Res 2001, 42: Abst 2884.

9. Advani, R., Fisher, G., Lum, B., Halsey, J., Sikic, B.I. *A phase I trial of Doxil, paclitaxel and valspodar (PSC 833).* Clin Cancer Res 2000, 6(Suppl.): Abst 192.

10. Advani, R., Fisher, G.A., Lum, B.L., Hausdorff, J., Halsey, J., Litchman, M., Sikic, B.I. *A phase I trial of doxorubicin, paclitaxel, and valspodar (PSC 833), a modulator of multidrug resistance.* Clin Cancer Res 2001, 7(5): 1221.

11. Dorr, R., Karanes, C., Spier, C. et al. *Phase I/II study of the P-glycoprotein modulator PSC 833 in patients with acute myeloid leukemia.* J Clin Oncol 2001, 19(6): 1589.

Original monograph - Drugs Fut 1995, 20: 1010.

Additional References

Baekelandt, M. et al. *Phase I/II trial of the multidrug-resistance modulator valspodar combined with cisplatin and doxorubicin in refractory ovarian cancer.* J Clin Oncol 2001, 19(12): 2983.

Bardelmeijer, H.A. et al. *Cyclosporin A increases the oral bioavailability of docetaxel in mice.* Clin Cancer Res 2000, 6(Suppl.): Abst 188.

Chauncey, T.R. et al. *A phase I study of induction chemotherapy for older patients with newly diagnosed acute myeloid leukemia (AML) using mitoxantrone, etoposide, and the MDR modulator PSC 833: A Southwest Oncology Group Study 9617.* Leuk Res 2000, 24(7): 567.

Chica, I., Kang, M.H., Bergan, R. et al. *Phase I study of infusional paclitaxel in combination with the P-glycoprotein antagonist PSC 833.* J Clin Oncol 2001, 19(3): 832.

Fracasso, P.M. et al. *A phase I accelerated dose escalation and pharmacokinetic study of Doxil® and valspodar (PSC 833) in patients with advanced malignancies.* Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 286.

Fracasso, P.M. et al. *Phase II study of paclitaxel and valspodar (PSC 833) in refractory ovarian carcinoma: A Gynecologic Oncology Group study.* J Clin Oncol 2001, 19(12): 2975.

Lopes de Menezes, D.E., Mayer, L.D. *Combination of Bcl-2 antisense oligodeoxynucleoside (G3139), P-glycoprotein inhibitor (PSC 833) and liposomal doxorubicin can suppress the growth of drug-resistant human breast cancer xenografts in SCID mice.* Proc Amer Assoc Cancer Res 2001, 42: Abst 2018.

Lum, B.L. et al. *A phase I trial of Doxil, paclitaxel, and valspodar (PSC 833) in refractory malignancies.* Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 285.

Minami, H., Ohtsu, T., Fuji, H. et al. *Phase I study of intravenous PSC-833 and doxorubicin: Reversal of multidrug resistance.* Jpn J Cancer Res 2001, 92: 220.

Stein, W.D. et al. *Measurements, ex vivo in human plasma, of the effectiveness of blockers of multidrug resistance.* Proc Amer Assoc Cancer Res 2001, 42: Abst 5118.