Drugs of the Future 1999, 24(1): 77-116

CCC: 0377-8282/99

Information Update

Volume 1-23, Number 1

Estimated developmental phase for this month's updated products:

Preclinical

ER-30346 (antifungal; Eisai, Bristol-Myers Squibb)
PS-5 (β-lactamase inhibitor, carbapenem; Sanraku)

Phase I

FTY-720 (immunosuppressant; Yoshitomi, Novartis)
LY-333328 (glycopeptide antibiotic; Lilly)
Orazipone (treatment of IBD, cytokine modulator; Orion)
S-16020-2 (oncolytic alkaloid, topoisomerase II inhibitor; Servier)

Phase II

BTA-243 (antidiabetic, antiobesity, β_3-adrenoceptor agonist; Wyeth-Ayerst)
Decitabine (oncolytic; Teva)
Didox (anti-HIV, ribonucleotide reductase inhibitor, oncolytic; Molecules for Health)
FK-409 (antianginal, vasodilator, platelet antiaggregatory, nitric oxide donor; Fujisawa)
Flibanserin (antidepressant, 5-HT_{1A} agonist, 5-HT_{2A} antagonist; Boehringer Ingelheim)
HGP-30 (AIDS vaccine; Cel-Sci)
Mildronate (antianginal; Latvian Inst. Org. Synth., Taiho)
MKT-077 (oncolytic; Novartis, Fuji Photo Film)
Nibentan (antiarrhythmic, potassium channel blocker; Russian Acad. Med. Sci.)
Otenzepad (antiarrhythmic, muscarinic M_2 antagonist; Boehringer Ingelheim)
RMP-7 (absorption promoter, oncolytic; Alkermes, Alza)

Phase III

Dexmedetomidine (sedative/hypnotic, analgesic, α_2-adrenoceptor agonist; Orion, Abbott)
Flesinoxan hydrochloride (anxiolytic, antidepressant, 5-HT_{1A} agonist; Duphar)
Flobufen (antiarthritic; Res. Inst. Pharm. Biochem.)
GV-150526A (neuronal injury inhibitor, NMDA antagonist; Glaxo Wellcome)
Pleconaril (antiviral; Sanofi, ViroPharma)
Sabcomeline hydrochloride (cognition enhancer, muscarinic M_1 agonist; SmithKline Beecham)
Zenarestat (aldose reductase inhibitor, symptomatic antidiabetic; Fujisawa, Warner-Lambert)

Preregistered

δ-Aminolevulinic acid (treatment of acne, treatment of actinic keratoses, oncolytic, photosensitizer; Dusa, Johns Hopkins Univ.)
Loxiglumide (treatment of pancreatic disorders, treatment of IBS, CCK_A antagonist; Rotta, Kaken, Tokyo Tanabe)
Naftopidil (antihypertensive, treatment of urinary incontinence; Asahi Chem., Roche, Kanebo)
Nefiracetam (cognition enhancer; Daiichi Pharm.)
Rolipram (antidepressant, treatment of IBD; Schering AG, Meiji Seika)
Zaleplon (sedative/hypnotic; Wyeth-Ayerst)

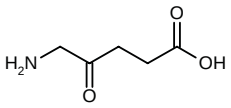
Launched/Year

Amisulpride (antipsychotic; Synthélabo)/1986
Calcipotriol (antipsoriatic, vitamin D analog; Leo Denmark, Fujisawa, Teikoku Seiyaku)/1991
Donepezil hydrochloride (cognition enhancer, acetylcholinesterase inhibitor; Eisai, Bracco, Pfizer)/1997
Fenoldopam mesilate (antihypertensive, vasodilator, dopamine D_1 agonist; SmithKline Beecham, Neurex, Crystaal)/1998
Fluoxetine hydrochloride (antidepressant, 5-HT reuptake inhibitor, treatment of premature ejaculation, treatment of premenstrual syndrome; Lilly, Pentech)/1987
Paclitaxel (taxane, microtubule inhibitor; Bristol-Myers Squibb, NaPro, Ivax, Angiotech)/1993
Rabeprazole sodium (gastric antisecretory, H^+/K^+-ATPase inhibitor; Eisai, Janssen-Cilag)/1997
Ramosetron hydrochloride (antiemetic, treatment of IBS, 5-HT_3 antagonist; Yamanouchi)/1996

δ-Aminolevulinic Acid
Levulan®

Treatment of Acne
Treatment of Actinic Keratoses
Oncolytic
Photosensitizer

EN: 191307



$C_5H_9NO_3$ **Dusa; Johns Hopkins Univ.**

Mitomycin-C and 5-aminolevulinic acid-mediated photodynamic therapy were conducted on the bladder cancer cell line, J82, and the mitomycin resistant derivative, J82MMC, to confirm if this combination is supra-additive. If used first, mitomycin C enhanced the effect of photodynamic therapy being additive in the J82 cell line and supra-additive in the J82MMC cell line. This combination in resistant bladder cancer may prove to be very useful in patient management (1).

Dusa announced that in its multicenter phase I/II clinical trial with Levulan® Photodetection (PD) of bladder cancer in high-risk patients, Levulan PD was able to detect an additional 13% of cancers that were missed with standard white light cystoscopy. In this study, all patients were examined for bladder cancer using standard white light cystoscopy as a baseline. Patients then underwent Levulan PD using blue light, as well as random biopsies, in order to compare the number of additional cancers that could be detected using these techniques. By the end of 1998, 59 patients had been enrolled and tested, with a total of 95 cancers detected, including 24 cases of carcinoma *in situ*. The baseline data show that looking inside the bladder with white light cystoscopy alone detected 72 cancers (75.8%), while missing 23 cancers (24.2%). For carcinoma *in situ*, white light cystoscopy detected 14 cancers (58%) but missed 12 cancers (42%). Levulan and blue light detected an additional 12 cancers (14.3%), including six carcinomas *in situ* (20%). One cancer detected by Levulan PD was also found by random biopsy. Therefore, Levulan PD and random biopsies appear to complement each other. There were no significant side effects reported (2).

Dusa has submitted an NDA for Levulan® Photodynamic Therapy for actinic keratoses (AKs) to the FDA. The submission covers Dusa's 20% Levulan® Kerastick™ applicator and its Blu-U™ fluorescent tube illuminator, for use in the treatment of multiple AKs of the face and scalp (3).

1. French, A.J., Allman, R., Datta, S.N., Mason, M.D., Matthews, P.N. *Mitomycin-C potentiates 5-aminolevulinic acid mediated photodynamic therapy of bladder cancer cell lines: Is this effect additive or synergistic?* 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 578.

2. *Dusa announces encouraging interim results in bladder cancer clinical trial*. Prous Science Daily Essentials Jan 11, 1999.

3. *Dusa submits NDA for Levulan PDT of actinic keratoses*. Prous Science Daily Essentials July 6, 1998.

Original monograph - Drugs Fut 1997, 22: 11.

Additional References

Curnow, A. et al. *Enhancement of 5-aminolaevulinic acid-induced photodynamic therapy in normal rat colon using hydroxypyridone iron-chelating agents*. Br J Cancer 1998, 78(10): 1278.

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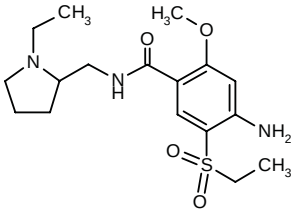
Amisulpride
Socian®
Solian®

Antipsychotic

EN: 125573



$C_{17}H_{27}N_3O_4S$ **Synthélabo**

Amisulpride (AMI) was reviewed for its efficacy in 870 acute and chronic schizophrenic patients. In four short-term studies, subjects received AMI (100-200 mg/d), haloperidol (15-20 mg), flupenthixol (15-25 mg) and risperidone (8 mg). Amisulpride was at least as effective as the comparator drugs. Chronic schizophrenic patients with predominant negative symptoms and absent or low grade of positive symptoms participated in another series of four short-term studies. Subjects received AMI (50-300 mg/d) or placebo. A 31-42% improvement from baseline was seen in the AMI groups *vs*. 8-23% in the placebo groups (1).

A pooled review of 11 clinical studies performed in schizophrenic patients (n = 1933) with predominance of positive or negative symptoms assessed the safety of amisulpride. Subjects were randomized to amisulpride, haloperidol, risperidone, flupenthixol and placebo. Extrapyramidal symptoms were the most commonly reported adverse events although at lower frequencies than comparator drugs. Amisulpride demonstrated a satisfactory safety profile that is superior to standard reference antipsychotics (2).

Synthélabo's amisulpride (Solian®) is now available in the U.K. for the treatment of acute and chronic schizophrenia in which positive and/or negative symptoms are prominent. It is available as tablets of 50 and 200 mg (3).

1. Möller, H.J. et al. *Amisulpride in schizophrenia: A review of its efficacy in acute and chronic patients*. Eur Neuropsychopharmacol 1998, 8(Suppl. 2): Abst P.2.062.

2. Coulouvrat, C., Dondey-Nouvel, L., Blanchet, S. *Safety of amisulpride (Solian®). A pooled review of 11 clinical studies*. Eur Neuropsychopharmacol 1998, 8(Suppl. 2): Abst P.2.041.

3. *Synthelabo's Solian introduced in U.K.* Prous Science Daily Essentials Nov 25, 1997.

Original monograph - Drugs Fut 1984, 9: 11.

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Genn, R.F. et al. *Amisulpride differentially attenuates effects of 7-OH-DPAT on licking microstructure*. J Psychopharmacol 1998, 12(3, Suppl. A): Abst 147.

Hamon Vilcot, B. et al. *Safety and pharmacokinetics of a single oral dose of amisulpride in healthy elderly volunteers*. Eur J Clin Pharmacol 1998, 54(5): 405.

Lesieur, P. et al. *Improvement of negative symptoms in acute schizophrenia with amisulpride*. Eur Psychiatry 1998, 13(Suppl. 4): 308s.

Möller, H.J. et al. *Amisulpride in schizophrenia: A review of its efficacy in acute and chronic patients*. Eur Psychiatry 1998, 13(Suppl. 4): 309s.

Patat, A. et al. *Effect of a low dosage regimen amisulpride (50 mg/d) on EEG, psychomotor and cognitive performance of sleep-deprived, healthy subjects*. Eur Psychiatry 1998, 13(Suppl. 4): 307s.

Perault, M.C. et al. *Lack of interaction between amisulpride and lorazepam on psychomotor performance and memory in healthy volunteers*. Hum Psychopharmacol - Clin Exp 1998, 13(7): 493.

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Smeraldi, E. *Amisulpride versus fluoxetine in patients with dysthymia or major depression in partial remission - A double-blind, comparative study*. J Affect Disord 1998, 48(1): 47.

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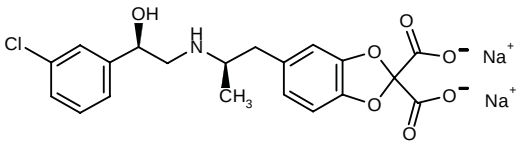
BTA-243
CL-316243

Antidiabetic
Antiobesity
β_3-Adrenoceptor Agonist

EN: 177769



$C_{20}H_{18}ClNNa_2O_7$ **Wyeth-Ayerst**

The effects on insulin action of CL-316243 have been elucidated in a randomized, double-blind, placebo-controlled trial in healthy, lean, young male volunteers. Subjects in the trial were randomized to 8 weeks treatment with CL-316243 (1500 mg/day) or placebo, and effects on splanchnic glucose output, glucose uptake and nonoxidative glucose disposal were evaluated and compared. After 4 weeks of treatment, CL-316243 increased the action of insulin in this group of healthy volunteers, primarily by stimulating glucose storage.This effect diminished, however, with prolonged administration, perhaps because β_3-adrenoceptors became downregulated (1).

1. Weyer, C., Tataranni, P.A., Danforth, E. Jr., Ravussin, E. *The effects of 8 weeks of treatment with the selective β_3-adrenoceptor agonist CL 316.243 on insulin action in man*. Diabetes 1998, 47(Suppl. 1): Abst 0379.

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Galitzky, J. et al. *Lipolytic effects of conventional β_3-adrenoceptor agonists and of CGP 12,177 in rat and human fat cells: Preliminary pharmacological evidence for a putative beta4-adrenoceptor*. Br J Pharmacol 1997, 122(6): 1244.

Hutchinson, D.S. et al. *Differential regulation of β_3-adrenoceptors (ARs) in mouse ileum and adipose tissues by the β3-AR agonist CL 316243 and the β_3-AR antagonist SR 59230A*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 6.89.

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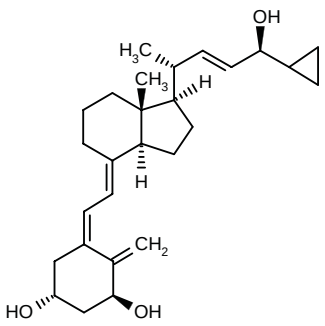
Umekawa, T. et al. *Effect of a β_3-agonist (CL-316,243) on upregulation of β_3-adrenergic receptors in OLETF rats*. J Jpn Diabetes Soc 1997, 40(Suppl. 1): Abst 2P 290.

Weyer, C. et al. *Increase in insulin action and fat oxidation after treatment with CL 316,243, a highly selective β_3-adrenoceptor agonist in humans*. Diabetes 1998, 47(10): 1555.

Calcipotriol
Daivonex®
Dovonex®
Divonex®
Psorcutan®

Antipsoriatic
Vitamin D Analog

EN: 139088



$C_{27}H_{40}O_3$ **Leo Denmark; Fujisawa; Teikoku Seiyaku**

In a double-blind, randomized study, calcipotriol ointment (50 μg/g) was compared to betamethasone dipropionate (64 mg/g) and salicylic acid (0.03 g/g) ointment to determine which was most effective in treating nail bed psoriasis. Calcipotriol was as effective as a combination of topical steroid with salicylic acid in this study and may be a safe alternative in the topical treatment of nail psoriasis (1).

In a multicenter, double-blind, parallel group study, concurrent treatment with calcipotriol (50 μg/g) and clobetasone 17-butyrate cream (0.5 mg/g) or betamethasone 17-valerate cream (1 mg/g) or placebo (vehicle of calcipotriol) was evaluated to determine which was most effective and/or resulted in less skin irritation than calcipotriol cream (50 μg/g) alone used twice a day. Subjects using concurrent corticosteroids experienced less skin irritation. Calcipotriol/vehicle treatment failed to decrease the incidence of skin irritation when compared with calcipotriol twice daily (2).

Fujisawa reached an agreement with Teikoku Seiyaku to promote and sell calcipotriol together with Teikoku's subsidiary in Japan. Upon approval, both Fujisawa and Teikoku Medix, a marketing subsidiary of Teikoku, will promote and sell calcipotriol (3).

1. Tosti, A., Piraccini, B.M., Cameli, N., Kokely, F., Plozzer, C., Cannata, G.E., Benelli, C. *Calcipotriol ointment in nail psoriasis: A controlled double-blind comparison with betamethasone dipropionate and salicylic acid*. Br J Dermatol 1998, 139(4): 655.

2. Barnes, L., Kragballe, K., Hamberg, K.J., Hutchinson, P., Murphy, F., Moller, S., Ruzicka, T., Vandekerkhof, P.C.M. *Calcipotriol cream with or without concurrent topical corticosteroid in psoriasis: Tolerability and efficacy*. Br J Dermatol 1998, 139(4): 649.

3. *Fujisawa concludes agreement for development of calcipotriol*. Prous Science Daily Essentials Sept 28, 1998.

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Köse, O., Baloglu, H. *Calcipotriol ointment in the treatment of Mibelli porokeratosis*. J Eur Acad Dermatol Venereol 1998, 11(Suppl. 2): Abst P358.

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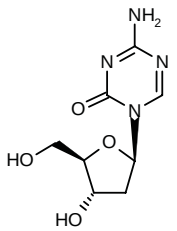
Saurat, J.-H. *Treatment of overweight psoriatic patients: Calcipotriol in skin folds*. J Eur Acad Dermatol Venereol 1998, 11(Suppl. 2): Abst ST8-2.

van de Kerkhof, P.C.M. et al. *The effect of addition of calcipotriol ointment (50 μg/g) to acitretin therapy in psoriasis*. Br J Dermatol 1998, 138(1): 84.

Decitabine

Oncolytic

EN: 125366



$C_8H_{12}N_4O_4$ **Teva**

In a phase II study, decitabine (75 mg/m^2/dose, i.v. infusion) was administered for 1 h every 8 h for 3 doses to 14 men with progressive, metastatic prostate cancer recurrent after total androgen blockade and flutamide withdrawal. The cycle of treatment was repeated every 5-8 weeks to allow resolution of toxicity. Decitabine was well tolerated with modest clinical activity against hormone-independent prostate cancer (1) (Box 1).

Box 1: Efficacy of decitabine in hormone independent metastatic prostate cancer (1) [Prous Science CSLine database].

Study Design	Open-label, phase II clinical trial
Study Population	Patients with progressive metastatic prostate cancer (n = 14)
Intervention Groups	Decitabine 75 mg/m2 i.v. as 1-h infusion q8h for 3 doses, with cycles being repeated every 5-8 weeks
Withdrawals [causes]	2/14 [not specified]
Adverse Events	Nausea and vomiting (7 pts), neutropenia (8 pts), thrombocytopenia (1 pt)
Results	2 patients with stable disease and time to progression > 10 weeks
Conclusions	Decitabine was well tolerated and had modest clinical efficacy in this indication.

The results have been reported of a phase II trial evaluating decitabine in high-risk patients with myelodysplastic syndromes. Based on promising findings obtained in an earlier phase II study, in which a response rate of 54% was obtained at higher doses, the compound was administered to 66 patients at the dose of 15 mg/m^2 t.i.d. for 3 days every 6 weeks for 4-6 courses. A total of 162 treatment courses was administered. The principal adverse event was myelotoxicity, which led to neutropenic death in 5 patients. Fever and/or infection occurred in 21 patients, and gastrointestinal disturbances and seizures occurred in 3 and 1 patient, respectively. The response rate in this study was 48%; the median duration of response was 40 weeks, and the mean survival from start of therapy was 13 months (2).

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2. Wijermans, P. et al. *A phase II study with low dose decitabine, a DNA hypomethylating pyrimidine analogue, in high risk MDS patients*. Blood 1998, 92(10, Suppl. 1): Abst 2607.

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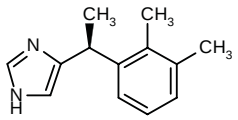
Momparler, R.L. et al. *Interesting responses in patients with advanced non-small lung cancer after treatment with the DNA-methylation inhibitor, 5-aza-2'-deoxycytidine (decitabine)*. 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 630.

Dexmedetomidine

Sedative/Hypnotic
Analgesic
EN: 145584 *α_2-Adrenoceptor Agonist*



$C_{13}H_{16}N_2$ **Orion; Abbott**

The analgesic potency and site of action of systemic dexmedetomidine was investigated in normal and neuropathic rats. Mechanical and thermal thresholds were dose-dependently increased by systemic dexmedetomidine (ED_{50} = 144 and 180 μg/kg i.p., respectively). Nerve injury augmented the analgesic potency of systemic dexmedetomidine and possibly shifted the α_2-adrenergic action to outside the blood-brain barrier but did not affect the compound's sedative potency (1).

In phase I-III studies, dexmedetomidine has been shown to produce sedation, anxiolysis, analgesia and reduced requirement for anesthesia and analgesia in a perioperative setting. The drug is also associated with good control of hemodynamic and adrenergic responses to noxious stimuli, resulting in a more favorable cardiovascular profile and a potential improvement in the oxygen supply to demand ratio. However, monotherapy with dexmedetomidine is not sufficient to achieve a clinically satisfactory anesthesia due to hemodynamic side effects that may prevent the administration of an anesthetic dose. Therefore, the drug is only useful as an adjuvant with other agents for anesthetic and analgesic purposes (2).

In a placebo-controlled, double-blinded, randomized, crossover study, the effects of atipamezole, an α_2-antagonist, on a clinically relevant dose of dexmedetomidine were studied in healthy individuals. Results indicate that intravenous atipamezole dose-dependently antagonized the sedative and sympatholytic effects of intramuscular dexmedetomidine (3).

Abbott Laboratories announced regulatory filings with U.S. and European health authorities seeking approval

for dexmedetomidine as a sedative with analgesic properties for use in patients in an intensive care setting. The submission marks the first simultaneous filing for Abbott with the FDA and the EMEA, and is the result of a global clinical trials program that included more than 3000 adult patients in 16 countries in North America and Europe (4).

1. Poree, L.R., Guo, T.Z., Kingery, W.S., Maze, M. *The analgesic potency of dexmedetomidine is enhanced after nerve injury: A possible role for peripheral α_2-adrenoceptors*. Anesth Analg 1998, 87(4): 941.

2. Jaakola, M.L. *Dexmedetomidine as a preanaesthetic agent - Phase I-III studies with a novel, specific α_2-adrenoceptor agonist*. Acta Anaesthesiol Scand 1998, 42(2): 276.

3. Scheinin, H., Aantaa, R., Anttila, M., Hakola, P., Helminen, A., Karhuvaara, S. *Reversal of the sedative and sympatholytic effects of dexmedetomidine with a specific α_2-adrenoceptor antagonist atipamezole: A pharmacodynamic and kinetic study in healthy volunteers*. Anesthesiology 1998, 89(3): 574.

4. *Abbott files for marketing approval of novel ICU sedative and analgesic compound*. Prous Science Daily Essentials Jan 11, 1999.

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Leino, T., Haapalinna, A. *Comparison of the effects of an α_2-adrenoceptor agonist, dexmedetomidine on cardiovascular functions in anaesthetised and conscious freely moving (in home cage and in open field) rats. Measurement by telemetry transmitter*. Soc Neurosci Abst 1998, 24(Part 2): Abst 567.15.

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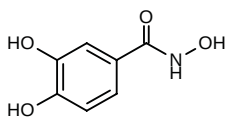
Didox

Anti-HIV
Ribonucleotide Reductase Inhibitor
Oncolytic

EN: 126587



$C_7H_7NO_4$ **Molecules for Health**

Didox and trimidox, alone and in combination with didanosine, were compared in a murine retrovirus model of AIDS. Treatments for infected mice were 5 times per week, daily, singly or in combination with didanosine. A significant increase in survival and inhibition of viremia resulted from didox or trimidox treatment alone. Although didanosine enhanced antiviral effects, toxicity was more marked and alone it demonstrated low activity. An HIV model then tested and compared these findings. Two weeks pre-infection, female mice were reconstituted with human peripheral blood monocytes. The animals were then given trimidox daily, i.p. for 7 days before HIV infection. Trimidox dose-dependently reduced the average viral titer in lymph nodes, spleen and peritoneal cells. It also decreased the titers of infectious virus by 10-fold from lymph nodes and peritoneal cells while a 3-log reduction of viral RNA copies was observed in lymph nodes and peritoneal cells (1).

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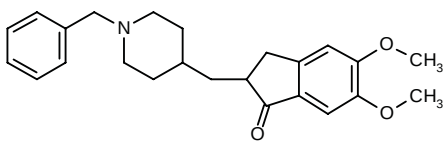
Donepezil Hydrochloride *Cognition Enhancer*
Aricept® *Acetylcholinesterase Inhibitor*
Memac®

EN: 150920



.HCl

$C_{24}H_{29}NO_3$.HCl **Eisai; Bracco; Pfizer**

Administration of donepezil 1, 3 and 10 mg/kg p.o. in 80 rats during 12 months induced pharmacological effects at all doses, without producing treatment-related mortalities. Adverse effects were not observed, as evaluated from food consumption, ophthalmologic examinations, clinical pathology studies and postmortem evaluation, demonstrating the absence of toxic effects (1).

Donepezil administered at doses of 0.6, 2 and 5 mg/kg p.o. during 12 months in 12 beagle dogs produced no chronic toxic effects, indicating the 5-mg/kg dose as the no toxic effect dose in this study model (2).

Evaluation of the reproductive toxicity of donepezil 1, 3 and 10 mg/kg in rats revealed no treatment-related effects in terms of general signs, body weight, food con-

sumption, fertility or gross pathology. The study indicated the 3-mg/kg dose as the non-toxic dose for general toxicity and reproduction in female rats and the 10 mg/kg-dose as the non-toxic dose in males (3).

A rat teratogenicity study of donepezil administered orally at doses of 1, 4 and 16 mg/kg once daily during 11 days, on days 7-17 of gestation, showed that the nontoxic dose for general toxicological effects on dams was 1 mg/kg. For the reproductive performance of dams and for fetuses, and the F1 generation, the nontoxic doses were 4 and 16 mg/kg, respectively (4).

Results from a teratogenicity study of oral donepazil in rabbits showed that nontoxic dose levels for general toxicity in dams were 3 mg/kg, and 10 mg/kg for the reproduction of dams and fetuses (5).

Evaluation of donepezil's effects on rat delivery and nursing, and growth, development, behavior and reproduction of their offspring, established the nontoxic dose level to be 3 mg/kg daily for both dams and offspring (6).

Donepezil inhibited rat brain acetylcholinesterase with an IC_{50} of 6.7 nM *in vitro*, while the IC_{50} for butyrylcholinesterase inhibition was 7.4 mM. Lineweaver-Burk analysis in brain homogenates showed that inhibition of acetylcholinesterase was noncompetitive (7).

Secretion of radiolabelled donepezil into the milk of nursing rats was evaluated following oral administration of 1-mg/kg doses. Peak concentrations of radioactivity in milk and plasma were reached after 2 h and declined rapidly. Radioactivity crossed the placenta, although levels found in the fetus were relatively low (8).

The inhibitory activity of donepezil on acetylcholinesterase was compared to that of tacrine in rats. Oral administration of donepezil and tacrine dose-dependently inhibited brain acetylcholinesterase with ID_{50}s of 2.6 and 9.5 mg/kg, respectively. The duration of action was similar for both compounds (9).

Donepezil's inhibitory activity on brain, blood and peripheral tissue cholinesterases was evaluated in rats receiving 1.25, 2.5 and 5 mg/kg p.o. of the drug. Donepezil inhibited cerebral cholinesterase more potently than its homologues in small intestine and heart. Inhibition was more effective in aged rats than in young animals (10).

Administration of donepezil 2.5, 5, 10 and 20 mg/kg orally in rats significantly increased acetylcholine synaptic content, and its effects on acetylcholine concentration were 2.4 times more potent than tacrine's. Donepezil's effects on extracellular acetylcholine concentrations were minimal or nonexistent (11).

Treatment of rats with donepezil 0.5 mg/kg significantly alleviated the impairment of memory acquisition in rats caused by lesioning the medial septum, as evaluated in the water maze test. A dose of 2 mg/kg had no significant effects as compared to saline-treated animals (12).

In rats and mice, donepezil 10 mg/kg p.o. produced transient hypothermia, increased urine volume and electrolyte excretion, decreased gastric emptying and elevated blood sugar levels. Administration of 0.3 mg/kg i.v. in anesthetized dogs produced respiratory arrest and affected the cardiovascular system. In anesthetized rats, donepezil 10-320 μg/kg i.v. intensified triceps contractions induced by sciatic nerve stimulation. No synergistic effects were observed between donepezil and furosemide, warfarin or tolbutamide (13).

The effects of (–)-huperzine A, donepezil hydrochloride and tacrine on the scopolamine-induced memory deficits in rats were compared in a radial maze. Data showed that (–)-huperzine A was the most potent and orally active acetylcholinesterase inhibitor and most closely follows the criteria for an ideal acetylcholinesterase inhibitor to be used in clinical studies (14).

Evaluation of the general toxicity of donepezil following single oral administration of 5, 10 and 15 mg/kg in 6 male and female dogs during 14 days showed that the 15-mg/kg dose was lethal in this study model (15).

The effects of donepezil were evaluated on T-cell necrosis factor-α binding in Alzheimer's disease. Patients received donepezil (5 mg/day) for the first 1 or 2 months and then 10 mg/day for more than 9 months. T-cell TNF-α binding was assessed before and during treatment. A significant difference in B_{max} values occurred after 1 month. No significant differences in K_d values were noted in patients over time. Data further support the presence of systemic T-cell activation in dementia of Alzheimer type which was partially and temporarily countered by donepezil (16).

Results from a comparative study of tremor and salivation following intraperitoneal and oral administration of tacrine, donepezil and NXX-066 in rats showed that tacrine possessed comparatively poor selectivity for centrally- (tremor) *versus* peripherally- (salivation) mediated effects. In order to achieve a similar degree of tremor, substantially higher doses of tacrine are needed when it is administered orally *versus* i.p. Donepezil's tremorogenic effect was relatively short when given orally (17).

The potency of tacrine, donepezil, rivastigmine and metrifonate to induce overt cholinergic responses after oral administration was examined as well as their duration of action in rats. Compared to the other compounds, tacrine demonstrated poor selectivity for centrally- (tremor) *versus* peripherally-mediated effects (salivation and lacrimation). Metrifonate possessed low potency and a brief duration of action (18).

The pharmacokinetics of donepezil and cimetidine separately and in combination following administration of multiple oral doses was examined. Results indicated that coadministration of donepezil (5 mg) and cimetidine (800 mg) did not result in clinically significant changes in the pharmacokinetic profiles of either drug (19).

Results obtained during the largest single trial of donepezil hydrochloride to date confirm benefits of the drug for the improvement of cognition, global functioning and activities of daily living among patients with mild to moderate Alzheimer's disease. Data confirmed a significant beneficial effect already observed with the drug in clinical practice on the overall functioning of patients in their everyday activities. Patients treated with 10 mg of donepezil hydrochloride once daily showed significant

improvements in the more complex activities of daily living scores as compared to placebo. In all, 818 patients were randomized to receive placebo, 5 mg or 10 mg of donepezil hydrochloride daily for 24 consecutive weeks, followed by a 6-week period during which all patients received placebo. Results indicated that patients in the groups receiving 5 mg or 10 mg donepezil exhibited mean improvements over placebo of 1.48 and 2.92, respectively, for ADAS-cog. Clinically statistically significant improvements in global function were demonstrated. Twenty-one percent of the 5-mg daily and 25% of the 10-mg daily donepezil hydrochloride-treated patients improved compared to 14% in the placebo group. Significant improvements were observed in the IDDD Complex Activities Scores for patients receiving 10 mg of the drug daily *versus* placebo. The study confirmed that donepezil hydrochloride is well tolerated, with 86% of active drug-treated patents completing the study as compared to 90% for the placebo group (20).

Administration of donepezil 5 and 10 mg/day in 40 patients with Alzheimer's disease produced improvements in cognitive and neuropsychiatric symptoms; however, 25% of the patients experienced a reduction in neuropsychiatric symptoms without measurable effects on cognitive symptoms. In addition, an association was observed between neuropsychiatric symptoms and caregiver distress (21).

Administration of donepezil in 867 patients with Alzheimer's disease at an initial dose of 5 mg/day, which was then raised to 10 mg/day, during a study period of 12 weeks produced improvements, as compared to baseline, in Standardized Mini-Mental State Exam scores of 1.14 and 1.5, for the 5 and 10 mg/day doses, respectively. Adverse events and discontinuation rates were very similar in donepezil- and placebo-treated groups (22).

The effects of donepezil on cerebral glucose metabolism were evaluated in 28 patients with mild to moderate Alzheimer's disease. Administration of donepezil 10 mg during 24 weeks reduced disease-related loss of functional brain activity by 77% (23).

Results from a multicenter double-blind study evaluating the efficacy and safety of donepezil (5 and 10 mg/day) in 473 subjects with mild to moderate Alzheimer's disease indicate that the agent was well tolerated and that cognitive function, as assessed by ADAS-cog, improved significantly in donepezil-treated patients at weeks 12, 18 and 24, as compared to the placebo-treated group (24).

A long-term extension study evaluated the efficacy and safety of donepezil hydrochloride in 133 patients with mild to moderate Alzheimer's disease who had completed a 14-week trial of the drug. Patients were evaluated at 3-week intervals for 12 weeks, then at 12-week intervals for a period of 192 weeks. After 98 weeks of therapy, donepezil improved cognition, which remained superior to baseline for 38 weeks. CDR-SB also showed improvement, with scores similar to baseline values for a period of 26 weeks. Donepezil was well tolerated in this group of patients and showed no evidence of hepatotoxicity. The data indicate no loss of treatment benefit over the 98-week period, even though the absence of a placebo group does not allow conclusions regarding donepezil's potential to attenuate disease progression (25).

The efficacy of donepezil in the treatment of Alzheimer's type dementia was evaluated in 6 patients receiving doses of 5 or 10 mg/day for up to 2 years. Patients reported either a modest but clinically significant cognitive improvement, no change or less than expected cognitive decline, or lack of response to treatment (26).

The effects of donepezil (5 and 10 mg/day p.o.) on cognition and global function were evaluated in two 30-week, randomized, placebo-controlled studies in 473 Alzheimer's patients. Significant improvements were found in both treatment groups in ADAS-cog and CIBIC-plus scores, compared to placebo. Adverse events were similar in both studies and included nausea, diarrhea and vomiting. No clinically significant treatment-related effects on vital signs and laboratory values were observed (27) (Box 2).

Eisai has filed a new drug application with the Japanese Ministry of Health and Welfare requesting marketing approval for donepezil hydrochloride as a treatment for cognition disorders (28).

Pfizer's Aricept® has been launched in Spain for the treatment of mild to moderate Alzheimer's disease (29).

Eisai and Pfizer have launched Aricept® in France for the symptomatic treatment of mild to moderate Alzheimer's disease (30).

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Box 2: Efficacy and safety of donepezil in patients with mild to moderately severe Alzheimer's disease (27) [Prous Science CSLine]

Study Design	Two multinational, randomized, placebo-controlled phase III clinical trials
Study Population	Patients with mild to moderate Alzheimer's disease (n = 1291)
Intervention Groups	Donepezil (D), 5 mg/day p.o. x 24 weeks Donepezil, 10 mg/day p.o. x 24 weeks Placebo (P) x 24 weeks Treatment phase followed by a 6-week, single-blind placebo washout period
Withdrawals [causes]	2/14 [not specified]
Adverse Events	Nausea, diarrhea and vomiting, which were low in frequency and generally mild
Results	ADAS-cog score improvement: D10 > D5 > P CIBIC-plus score improvement: D10 > D5 > P
Conclusions	Donepezil was effective and well tolerated, with the magnitude and extent of improvement being similar in both trials

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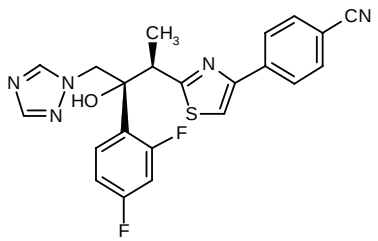
ER-30346
BMS-207147

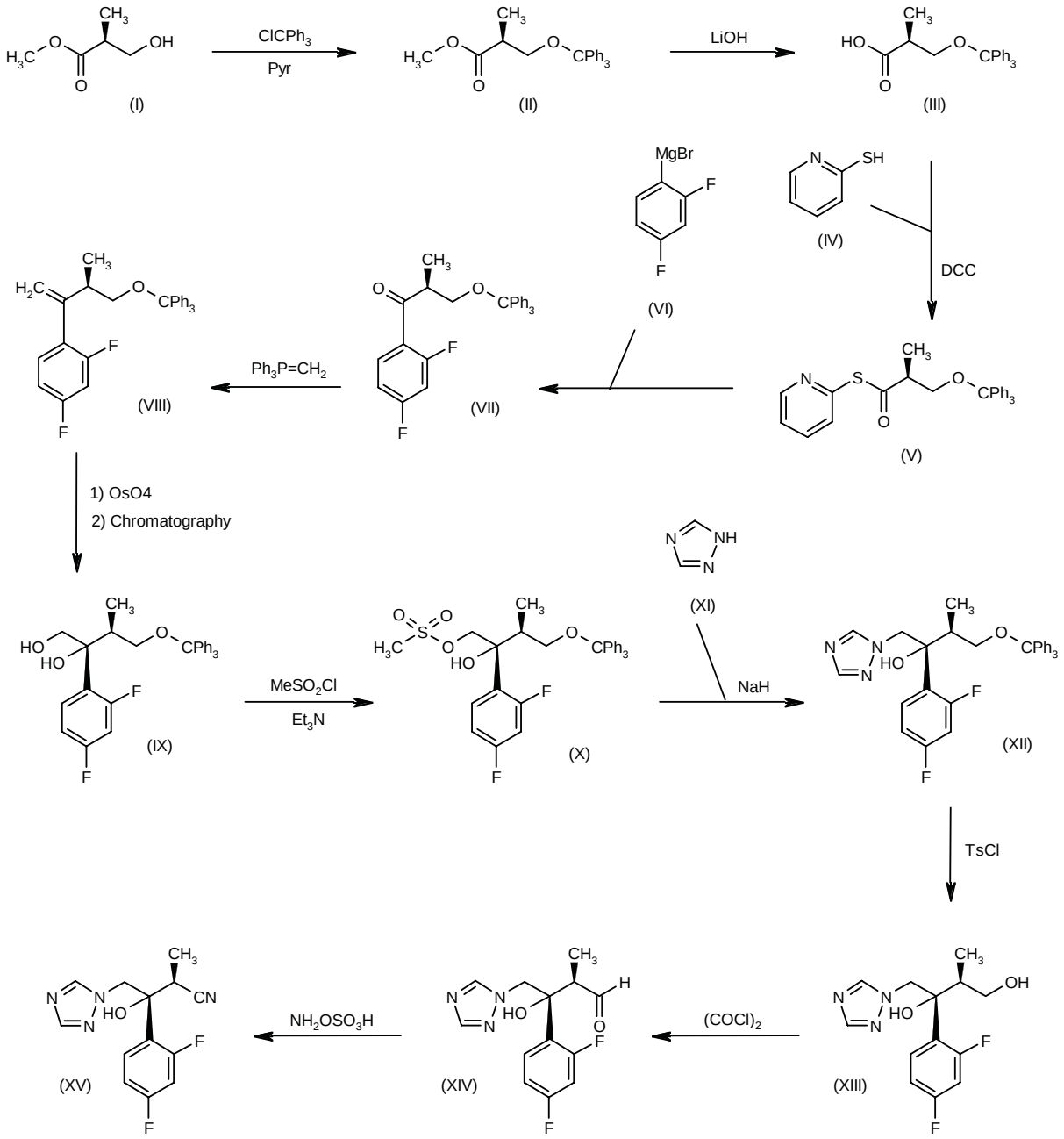
Antifungal

EN: 226621



$C_{22}H_{17}F_2N_5OS$ **Eisai; Bristol-Myers Squibb**

Scheme 1: Synthesis of Intermediate (XV)



The synthesis of (2*S*,3*S*)-3-(2,4-difluorophenyl)-3-hydroxy-2-methyl-4-(1,2,4-triazol-1-yl)butyronitrile (XV), a key intermediate in the synthesis of ER-30346, has been described: The tritylation of 3-hydroxy-2(*S*)-methylpropionic acid methyl ester (I) with trityl chloride in hot pyridine gives the trityl ether (II), which is hydrolyzed with LiOH in H_2O/THF/methanol yielding the free acid (III). The esterification of (III) with 2-mercaptopyridine (IV) by means of dicyclohexylcarbodiimide (DCC) in dichloromethane gives the thioester (V), which is treated with 2,4-difluorophenylmagnesium bromide (VI) in THF yielding the propiophenone (VII), which by treatment with methyltriphenylphosphonium bromide/NaH in THF is converted into the methylene derivative (VIII). The oxidation of (VIII) with OsO_4 and *N*-methylmorpholine oxide in acetone affords, after column chromatography, the chiral diol (IX), which is

monomesylated with mesyl chloride/triethylamine in dichlormethane giving the monoester (X). The reaction of (X) with 1,2,4-triazol (XI) and NaH in DMF yields (2*R*,3*S*)-2-(2,4-difluorophenyl)-3-methyl-1-(1,2,4-triazol-1-yl)-4-(triphenylmethoxy)-2-butanol (XII), which is detritylated with *p*-toluenesulfonic acid in methanol affording the diol (XIII). The oxidation of (XIII) with oxalyl chloride/DMSO in dichloromethane gives the aldehyde (XIV), which is finally treated with hydroxylamine-*O*-sulfonic acid in water yielding the desired bytyronitrile intermediate (XV) already referenced (1). Scheme 1.

Results from an *in vitro* comparison of the antifungal activities of BMS-207147, amphotericin, fluconazole, itraconazole and SCH 56592 against 23 *Candida albicans* and *C. krusei* (including susceptible dose-dependent and resistant strains), 42 *Aspergillus* spp. and 23 *Acremonium* spp., *Fusarium* spp., *Scopulariopsis brevicaulis* and *Scytalidium* spp. showed that BMS-207147 was similar to SCH 56592 and superior to itraconazole for *Aspergillus fumigatus*. In addition, the 3 azoles showed similar activity against the other species and the activity of BMS-207147 based on MICs was better than that of SCH 56592 for both fluconazole- and itraconazole-susceptible and resistant *Candida* spp. Thus, BMS-207147 may have therapeutic potential in treating human mycoses (2).

In a rabbit model of invasive aspergillosis employing a sublethal challenge, BMS-207147 was effective and showed activity similar to that of amphotericin B (3).

Several thiazole-containing triazole antifungals were synthesized and evaluated for activity against a variety of clinically isolated pathogenic fungi *in vitro* and against systemic candidosis *in vivo*. These compounds showed potent *in vivo* and *in vitro* activity. ER-30346 was especially active and demonstrated well balanced *in vitro* and *in vivo* efficacy with a good safety profile (4).

The antifungal activities of BMS-207147, itraconazole and fluconazole were compared against 250 strains of fungi representing 44 fungal species. BMS-207147 was more potent than itraconazole and substantially more potent than fluconazole against yeasts. BMS-207147 and itraconazole were fungicidal to cryptococci, inhibitory to most aspergilli in which activity against half of the isolates was cidal, active against most hyaline *Hyphomycetes*, dermatophytes, and the dematiaceous fungi yet ineffective against *Sporothrix schenckii* and zygometes. All three compounds showed activity against about half of the *Candida glabrata* strains and against all the tested *Cryptococcus neoformans* strains (5).

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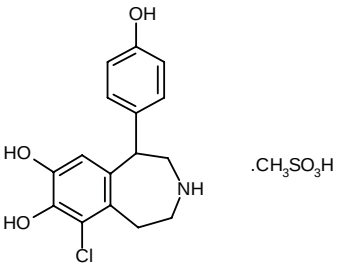
Fenoldopam Mesilate
Corlopam®

Antihypertensive
Vasodilator
Dopamine D_1 Agonist

EN: 090634



$C_{16}H_{16}ClNO_3.CH_4O_3S$

SmithKline Beecham; Neurex; Crystaal

Twelve healthy human subjects received fenoldopam (0.2, 0.5 and 1.9 μg/kg/min, 2h) to assess its effects on intraocular pressure, aqueous humor outflow facility and gonioscopy. Findings indicated that systemic administration of a selective dopamine-1 receptor agonist caused a significant dose-dependent increase in intraocular pressure partly explainable by diminished outflow capacity. Results supported a role for the dopamine-1 receptor in the modulation of intraocular pressure in general and suggested modulation of aqueous humor outflow by dopaminergic receptors (1).

The pharmacokinetic parameters of fenoldopam after a single dose were determined in hypertensive patients at various doses ranging from 0.1-0.8 μg/kg/min for 48 h along with placebo. The elimination half-life was 12 min with a clearance rate of 3.3 l/min. Pharmacokinetic parameters showed high interindividual variation (>100%);

however, there was no lag time between racemic fenoldopam and hemodynamic effects (2).

Fenoldopam (0.04-0.8 μg/kg/min) was administered to hypertensive patients by i.v. infusion as defined by dosing instructions analyzed by NONMEM. 0.1 μg/kg/min was determined to be a good starting dose. The clearance of the drug was 2.6 l/min with an elimination half-life of 4.6 min. The minimally effective infusion rate was determined to be 0.1 μg/kg/min (3).

The pharmacokinetic parameters of fenoldopam after a single dose were determined in hypertensive patients at various doses ranging from 0.04-8.0 μg/kg/min for 48 h along with placebo. The first E_{max} was achieved by low concentrations whereas the second E_{max} was seen with high concentrations. The half-life of tolerance factor was about 100 h. The clearance of fenoldopam was 2.6 l/min with an elimination half-life of 4.6 min. The volume of distribution was 17.4 l (4).

A review mongraph has been published dealing with fenoldopam mesylate, a novel, peripherally acting dopamine-1 receptor agonist that induces potent arteriolar vasodilation of renal, mesenteric, coronary and skeletal muscle vasculature. Clinical studies indicate that fenoldopam reduces blood pressure in a linear, dose-dependent fashion in healthy subjects and in patients with mild, moderate or severe hypertension. The reduction in blood pressure is attributable primarily to a reduction in peripheral vascular resistance. In hypertensive subjects with and without renal insufficiency, fenoldopam tends to increase renal blood flow and has significant natriuretic and diuretic properties, as indicated by substantial increases in sodium and free water excretion and urine flow. Fenoldopam has a rapid onset of action (5 min) and short duration of action (30 min) when administered intravenously. Little if any tachyphylaxis is observed in blood pressure reduction with up to 24 h of infusion, and no rebound hypertension occurs upon abrupt cessation of therapy. Fenoldopam is metabolized quickly, with no accumulation of toxic degradation products. Fenoldopam is well tolerated. The most common adverse events associated with the compound, flushing and headache, are attributable to its vasodilator action. In heart failure patients, fenoldopam reduces systemic vascular resistance while increasing cardiac output. Unlike nitroprusside, fenoldopam is not a venodilator, and does not consistently reduce pulmonary capillary wedge pressure. Interestingly, the natriuretic/diuretic properties of fenoldopam observed in hypertensive patients have not been consistently observed in heart failure patients. Fenoldopam has been shown to safely reduce postoperative hypertension in patients undergoing both cardiac and noncardiac surgery. In a study of patients recovering from coronary artery bypass grafting, decreases in urine flow associated with nitroprusside were not seen with use of fenoldopam. In these same postoperative patients, nitroprusside use was associated with reductions in pulmonary capillary wedge pressure while fenoldopam was not. Fenoldopam is a promising alternative to nitroprusside for intravenous reduction of blood pressure. Clinical comparisons indicate antihypertensive efficacy and safety similar to nitroprusside. Fenoldopam has a rapid but not abrupt onset of action such that use of an intraarterial line to monitor blood pressure can be avoided. Compared with nitroprusside, fenoldopam tends to increase renal blood flow and to increase sodium and free water excretion, which may be clinically advantageous in certain subsets of patients. Fenoldopam will likely be more convenient to use than nitroprusside as it is not photosensitive and none of its metabolites are toxic (5).

Neurex has launched fenoldopam mesylate (Corlopam®) in the U.S., where it is indicated for the in-hospital, short-term (up to 48 h) management of severe hypertension when rapid, but quickly reversible, emergency reduction of blood pressure is clinically indicated, including malignant hypertension with deteriorating end-organ function. Corlopam® is available in 5-ml single-dose ampules containing 10 mg/ml (6).

Biovail's wholly owned subsidiary Crystaal has entered into a licensing agreement with Neurex for the marketing of Corlopam® in Canada for the in-hospital management of hypertension when emergency reduction in blood pressure is required (7).

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7. *Crystaal in-licenses Neurex's Corlopam*. Prous Science Daily Essentials April 27, 1998.

Original monograph - Drugs Fut 1982, 7: 32.

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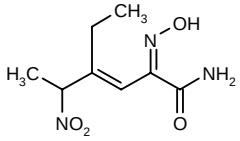
FK-409

Antianginal
Vasodilator
Platelet Antiaggregatory
EN: 150837 *Nitric Oxide Donor*



$C_8H_{13}N_3O_4$ **Fujisawa**

The contribution of nitric oxide by FK-409 on acute renal failure (ARF) was studied in rats. After contralateral nephrectomy, occlusion of the left renal artery and vein for 45 min induced ARF. Untreated ARF rats showed a marked decrease in renal functioning at 24 h after reperfusion and later recovered gradually within 7 days. FK-409 at 1 mg/kg, i.v. preocclusion lessened the decrease in renal function much like verapamil (1 mg/kg, i.v.); moreover, the protective effect was greater at a higher dose (3 mg/kg, i.v.). Morphological protection against tubular necrosis and development of tubular casts was additionally observed. These findings suggest that FK-409 may be clinically useful to treat ischemic ARF (1).

The effects of peripherally administered FK-409, a spontaneous nitric oxide releaser, and its interaction with peripheral morphine analgesia were studied during a rat formalin test. Peripherally administered nitric oxide itself possessed no analgesic effect; however, it enhanced the analgesic effects of peripherally administered morphine in inflammation induced by an injection of formalin in the rat paw (2).

The influence of FK-409 on the endothelium-dependent relaxation of aorta from streptozotocin-induced diabetes was studied in rats. Animals received FK-409 (10 or 20 mg/kg/day, p.o.) for 4 weeks. Results indicate that chronic administration of the 20 mg dose normalized the attenuated relaxation of the endothelium. The impaired function of the endothelium in diabetic animals may be improved by chronic administration of a nitrous oxide donor such as FK-409 (3).

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Original monograph - Drugs Fut 1993, 18: 9.

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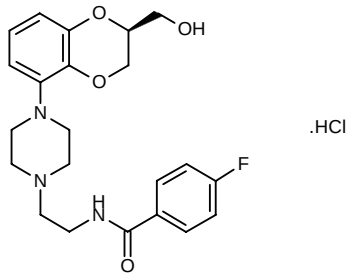
Ohmori, H. et al. *Beneficial effects of FK409, a novel nitric oxide donor, on reperfusion injury of rat liver*. Transplantation 1998, 66(5): 579.

Tadano, K. et al. *Effects of FK409, a nitric oxide donor, on renal responses to renal nerve stimulation in anesthetized dogs*. Eur J Pharmacol 1998, 341(2-3): 191.

Flesinoxan Hydrochloride

Anxiolytic
Antidepressant
EN: 124142 *5-HT_{1A} Agonist*



$C_{22}H_{26}FN_3O_4.HCl$ **Duphar**

The effects of an acute injection of flesinoxan on mineralocorticoid and glucocorticoid receptors in the hippocampus using *in situ* hybridization histochemistry showed that flesinoxan can exert an effect on glucocorticoid receptors in the absence of an intact HPA-axis and in the presence of a stable continuous release of corticosterone (1).

The antidepressant potential of flesinoxan (1 and 3 mg/kg s.c), a full agonist of the 5-HT_{1A} receptor, and eltoprazine (1 mg/kg i.p.), a partial agonist of the 5-HT_{1A} and 5-HT_{1B} receptors with weak 5-HT_{2C} antagonsim, was studied in Sprague-Dawley rats. Flesinoxan showed potential antidepressant properties. Eltoprazine demonstrated little antidepressant potential at this dose but it has been suggested to have antiaggressive properties. These studies highlight the role of the 5-HT_{1A} receptor in the pathogenesis of depression and indicate that the antidepressive and antiaggressive action of psychotropic drugs may be linked to different 5-HT receptor subtypes (2).

Sequential rectal temperature measurements of singly-housed male mice in a stress-induced hyperthermia paradigm showed an increased body temperature. This increase represents stress-induced hyperthermia and putatively reflects a stress-induced anxiogenic response. Stress-induced hyperthermia was reduced by the full 5-HT_{1A} receptor agonist flesinoxan ((+)-enantiomer), its (–)-enantiomer and the racemic mixture. Their potency in receptor binding affinities reflected the ratio of their potencies to reduce stress-induced hyperthermia. WAY 100635 and DU 125530, two 5-HT_{1A} receptor antag-

onists, antagonized the anti-stress-induced hyperthermia effects of flesinoxan. Thus, anxiolytic effects of flesinoxan were mediated by the 5-HT_{1A} receptor (3).

No relationship was observed between neurophysins and temperature responses to flesinoxan as assessed in relation to suicidal behavior in 24 patients with major depression. Subjects were subgrouped into suicidal attempters (n = 13) and nonattempters (n = 11) and were evaluated after a drug-free period of at least 3 weeks. Data indicated that hormonal and temperature responses to a $5HT_{1A}$ receptor agonist are mediated by other $5HT_{1A}$ receptors, that there may be a dysfunction in neurophysin secretion in depression and that a blunted temperature response to flesinoxan could indicate a risk factor for suicide (4).

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3. Olivier, B., Zethof, T.J.J., Ronken, E., vander Heyden, J.A.M. *Anxiolytic effects of flesinoxan in the stress-induced hyperthermia paradigm in singly-housed mice are 5-HT_{1A} receptor mediated*. Eur J Pharmacol 1998, 342(2-3): 177.

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Original monograph - Drugs Fut 1988, 13: 31.

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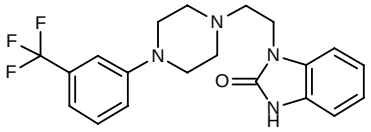
Flibanserin
BIMT-17

Antidepressant
5-HT_{1A} Agonist
5-HT_{2A} Antagonist

EN: 197146



$C_{20}H_{21}F_3N_4O$ **Boehringer Ingelheim**

The effects of 2- and 7-day flibanserin administration on the dorsal raphe nucleus, the medial prefrontal cortex and the CA3 region of the hippocampus of the rat show that flibanserin may possess an accelerated onset of antidepressant action given that it rapidly enhanced 5-HT transmission (1).

BIMT-17 was evaluated in three animal paradigms sensitive to antidepressants: olfactory bulbectomy (OB), differential-reinforcement-of-low rate 72-s (DRL 72-s) and learned helplessness (LH). OB rats, given BIMT-17 10 mg/kg i.p. once daily for 14 consecutive days, showed a reduced increase in ambulation at 24 h after the last administration. BIMT-17 showed a different profile than imipramine in the DRL 72-s test. One dose of BIMT-17 at 5, 10, 15, mg/kg i.p. failed to affect response and reinforcement rate in DRL 72-s by 1 h postdose. Interresponse time distribution showed shorter duration with BIMT-17 whereas duration was longer with imipramine. BIMT-17 at acute oral doses of 36, 48 or 60 mg/kg 30 min before LH testing, decreased the number of escape failures and did not alter the intertrial crossings. A repeated dose of imipramine at 8 or 16 mg/kg achieved the same effect. These data indicate that BIMT-17 acts via different mechanisms than imipramine and may possess faster therapeutic action (2).

Flibanserin's potential to alleviate psychomotor depression associated with amphetamine withdrawal has been evaluated in rats. Amphetamine withdrawal resulted in a significant reduction in exploratory locomotor activity which was attenuated dose-dependently by flibanserin during the final 60 min of testing (3).

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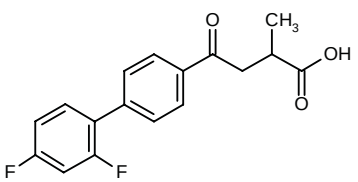
Original monograph - Drugs Fut 1998, 23: 9.

Flobufen

Antiarthritic

EN: 144185



$C_{17}H_{14}F_2O_3$ **Res. Inst. Pharm. Biochem (CZ)**

The chiral aspects of pharmacokinetics of flobufen were evaluated in rats after intravenous administration. A 5 mg/kg dose was employed to compare elimination and distribution parameters of flobufen racemate and the individual enantiomers. The total plasma clearance value of *S*-(–)-flobufen in rats was more than 10-fold lower than that of *R*-(+)-flobufen; the other pharmacokinetic parameters of the enantiomers were also significantly different. These findings present unidirectional conversion in flobufen and different pharmacokinetics for its individual enantiomers which could be significant in practical use of the drug (1).

The Research Institute for Pharmacy & Biochemistry has informed Prous Science that flobufen is now in phase III testing for the treatment of rheumatoid arthritis. When administered as a single daily dose of 25 mg, flobufen was at least as effective as piroxicam and superior in efficacy to diclofenac and ibuprofen. Gastric and overall tolerance of flobufen was reported to be excellent, being better than that of diclofenac and significantly better than that of piroxicam (2).

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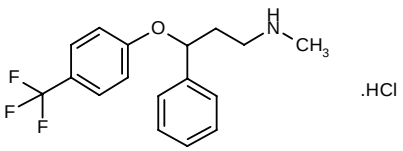
Original monograph - Drugs Fut 1989, 14: 24.

Fluoxetine Hydrochloride *Antidepressant*
Prozac® *5-HT Reuptake Inhibitor*
Treatment of Premature Ejaculation

EN: 131699 *Treatment of Premenstrual Syndrome*



.HCl

$C_{17}H_{18}F_3NO.HCl$ **Lilly; Pentech**

A prospective, double-blind, placebo-controlled, crossover trial has assessed the effects of fluoxetine on sexual function in men with premature ejaculation and/or erectile dysfunction. Four groups of patients/subjects – 9 with premature ejaculation, 9 with premature ejaculation and erectile dysfunction, 7 with erectile dysfunction and 15 healthy subjects – received fluoxetine (5 mg/day for 2 weeks followed by 10 mg/day for 2 weeks) and placebo for 4 weeks, treatment periods being separated by a 4-week washout period. Fluoxetine treatment was associated with a significant increase in latency to ejaculation in patients with both premature ejaculation and erectile dysfunction, but not in patients with only premature ejaculation, although a significant increase was also observed when the premature ejaculation and premature ejaculation/penile dysfunction groups were evaluated together. As assessed in the laboratory, fluoxetine stimulated subjectively but not objectively measured erectile response. No serious side effects were observed (1).

Interneuron received a milestone payment from Lilly under a 1997 license agreement between the companies related to the development of Prozac® for the treatment of premenstrual syndrome. The milestone payment marked the completion of a clinical trial with Prozac® for the treatment of this condition. Interneuron received an upfront payment from Lilly under the agreement and could receive future payments and royalties if additional milestones are met (2).

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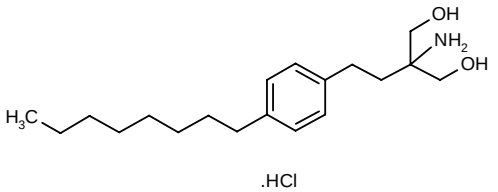
FTY-720 *Immunosuppressant*

EN: 210392



.HCl

$C_{19}H_{33}NO_2.HCl$ **Yoshitomi; Novartis**

Evaluation of oral administration of FTY-720 (0.03-1 mg/kg) in rats showed that the drug sequesters circulating mature lymphocytes into peripheral lymph nodes, mesenteric lymph nodes and Peyer's patches by accelerating lymphocyte homing and thus decreasing the number of lymphocytes in peripheral blood, thoracic duct lymph and spleen (1).

The molecular mechanism of FTY-720-induced apoptosis was evaluated in lymphocytes transfected with human Fas cDNA. The results indicated that activation of caspases, but not cell lysis, is required for the induction of apoptotic cell damage. Target cell nuclei are not required for membrane damage (2).

The immunosuppressive action of FTY-720 was evaluated in a renal allograft rat model. Administration of daily doses of 5 mg/kg p.o. produced marked increases in peripheral lymphocytes and significantly enhanced allograft survival. The treatment also reduced IL-2 mRNA expression and the levels of CD4-positive infiltrating cells within allografts. The results indicate that FTY-720 may have clinical application in renal transplantation (3).

FTY-720 administered at a dose of 5 mg/kg s.c. or p.o., in conjunction with cyclosporine 10 mg/kg, was evaluated for its efficacy as a rescue drug for acute rejection in dogs with renal transplants. The treatment prevented acute rejection in 3/5 dogs but had no effect in dogs with ongoing rejection. White cell count, T and B lymphocytes in particular, was depressed in peripheral blood in FTY-720-treated dogs (4).

Evaluation of FTY-20 (0.1-10 mg/kg) in combination with cyclosporine in several experimental rat allograft models showed that the combination produces synergistic effects in the prolongation of allograft survival. The drug thus appears to be a good candidate for immunosuppressive therapy in clinical organ transplantation (5).

The immunosuppressive mechanism of FTY-720 (0.1 mg/kg) was evaluated in WKAH skin allografts. The drug markedly inhibited CD3 mRNA elevation, but only slightly inhibited mRNA elevations of IL-2 and IFN-γ. Thus, the immunosuppressive effects of FTY-720 appear to be mediated by the reduction of T cell infiltration into grafts, but not cytokine production (6).

The immunosuppressive effects of FTY-720 were assessed in combination with intrathymic injection of splenic cells on a rat whole pancreas allotransplantation model. FTY-720 with intrathymic injection of splenic cells induced long acceptance of pancreaticoduodenal allografts (7).

FTY-720 was evaluated for its ability to prolong islet allograft survival. The donors were inbred Lewis rats and the recipients were ACI rats made hyperglycemic with intravenous streptozotocin. Graft survival time in the study group was significantly longer than that in the control group which indicated that the agent retained a potent effect on the prolongation of islet allograft survival (8).

A DA donor-to-LEW recipient rat combination was employed to assess the efficacy of peritransplant FTY-720 alone or in combination with posttransplant tacrolimus on the survival of cardiac allografts. FTY-720 was a powerful immunosuppressive agent when used as induction therapy and may possess an additive effect – possibly synergistic – with posttransplant tacrolimus (9).

Administration of FTY-720 (0.1-10 mg/kg) orally and intravenously, dose-dependently prolonged cardiac allograft survival in rats. Synergistic effects were observed when FTY-720 was administered in combination with either FK-506 or cyclosporine. Doses of 30 mg/kg/day induced lethal toxicity (10).

The immunosuppressive potential and toxicity of FTY-720 was evaluated in a canine renal allograft model. Oral administration of 0.05-10 mg/kg produced immunosuppressive effects, although not very potent, without significant toxicity (11).

Evaluation of the synergistic interactions between FTY-720 and ciclosporin or sirolimus in a rat model of heart transplant showed that the combination of FTY-720 with either adjuvant produced important synergistic effects in terms of graft survival (12).

The effect of FTY-720 on the expression of apoptotic molecules such as perforin, granzymes, Fas and FasL, was evaluated in a rat heterotopic heart transplantation model. Upregulation of perforin, granzyme B and FasL was observed in relation to the advance of acute rejection. Oral administration of FTY-720 (1, 5 and 10 mg/kg/day) dose-dependently inhibited the mRNA expression of these proteins and produced prolonged graft survival (13).

In rats undergoing heterotopic cardiac transplantation, administration of FTY-720 (5 mg/kg) significantly prolonged graft survival as compared to control animals. The effect was more pronounced in animals treated before and on the day of grafting, than in animals treated on days 2 and 3 after transplantation. The effects were comparable to those observed following treatment with FK-506 (1 mg/kg) administered at early stages following grafting but not at late stages (14).

The therapeutic effects of FTY-720 were evaluated to determine if they induce autoimmune type I diabetes or if the induction of autoimmune type I diabetes is prevented in rats. Thymectomies were performed at 6-8 weeks of age followed by sublethal irradiation 3 weeks later. The first day of blood sugar level over 200 mg/dl or positive urine sugar defined diabetic state. The drug did not induce autoimmune diabetes in thymecotmized rats in spite of lymphocytopenia. FTY-720 pretreatment did not thwart the onset of diabetes following irradiation (15).

FTY-720 was administered to dogs with acute rejection after renal allotransplantation to assess its efficacy as a rescue drug. Results indicated that parenteral administration of FT-Y720 should be effective in rescue therapy for acute rejection in dog renal transplantation and possibly so in human organ transplantation (16).

The immunosuppressive activity of FTY-720 was analyzed in concordant xenotransplantation. FTY-720 showed cytotoxicity to B and T lymphocytes and apoptosis may play an important role in this cytotoxicity. When combined with FK-506, FTY-720 can inhibit both the cellular and hormonal response and shows a synergistic effect on skin xenograft survival (17).

The metabolites of FTY-720 were isolated and identified. Rats were orally administered FTY-720; then, 3 metabolites were isolated from urine and 2 from feces and identified by nuclear magnetic resonance spectrum and mass spectrum. ω-Oxidation of the octyl side chain of FTY-720 produced an alcohol compound that was in turn metabolized to ω-carboxylic acid compound M1 by oxidation. The M1 was metabolized to M2, M3, and M4 by β-oxidation. A pathway was discovered whereby carboxylic acid of M3 combines with taurine to form M5 (18).

FTY-720 at 3-10 μM nonspecifically increased the membrane permeability of thymocytes causing necrotic cell death; FTY-720 was described to induce apoptosis of spleen cells at micromolar concentrations (19).

FTY-720 at 0.03 mg/kg i.v. or orally dose-dependently increased skin allograft survival time and possessed greater immunosuppressive activity than cyclosporine or tacrolimus in MHC-incompatible rat strains of WKAH donors and F344 recipients. FTY-720 up to 1000 nM failed to alter IL-2 production in allogeneic MLC. Three to 24 h post FTY-720 dose at 0.1-1 mg/kg, lymphocyte count was reduced in the peripheral blood and thoracic duct lymph and partially in the spleen while the count was increased in peripheral lymph nodes (PLN), mesenteric lymph nodes (MLN) and Peyer's patches (PP). Calcein-labeled rat lymphocytes indicated that FTY-720 accelerated lymphocyte homing to PLN, MLN, and PP. Thus, the sequestration of circulating mature lymphocytes presents itself as the main mechanism of FTY-720 immunosuppression (20).

Short-term administration of FTY-720 with antigen-presenting cells appeared to induce immunological tolerance in heterotopic heart transplant recipient rats (21).

FTY-720 is known to induce apoptosis, mainly via disruption of cell membranes. Further studies indicated that its apoptotic effect may be at least partially independent of caspases (22).

In vivo studies in mice and rats provided further evidence that the immunosuppressive effects of FTY-720, *i.e.*, reduction in peripheral lymphocytes, are the consequence of an enhancement of their accumulation in lymph nodes and Peyer's patches (23).

The immunosuppressant FTY-720 was reported to accelerate peripheral lymphocyte elimination. Recent *in vitro* studies indicated that the compound enhanced adhesion of lymphocytes to HEV cells in lymph nodes and Peyer's patches (24).

In a homologous skin graft model in rats, repeated oral administration of FTY-720 (0.1 mg/kg) markedly suppressed T-cell infiltration, whereas Th1 cytokine expression was not affected; median graft survival was prolonged from 7.0 days to 10.5 days. Combination of FTY-720 (0.1 mg/kg) and ciclosporin (10 mg/kg) synergistically suppressed both T-cell infiltration and Th1 cytokine production, and median graft survival was prolonged to over 70 day (25).

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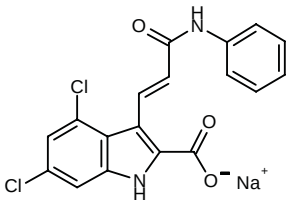
GV-150526A
Gavestinel Sodium

Neuronal Injury Inhibitor
NMDA Antagonist

EN: 202359



$C_{18}H_{11}Cl_2N_2NaO_3$ **Glaxo Wellcome**

The neuroprotective effects of GV-150526A were compared to those of DL-2-amino-5-phosphonopentanoic acid (AP5), ifenprodil, 7-chlorokynurenic acid and NBQX on glutamate-induced changes in resting and electrically stimulated cells. GV-150526A was the most potent compound with it and 7-chlorokynurenic acid being 2-3 times more active in stimulated neurons than in resting neurons. These results indicated a major involvement of the glycine site in the protection of cells maintained in an active state (1).

Evaluation of GV-150526 in rats and rhesus monkeys did not produce discriminative stimulus effects characteristic of MK801/PCP-like noncompetitive antagonists. In addition, PCP-preexposed rhesus monkeys did not self-administer the drug, indicating that GV-150526 may have a lower potential for abuse than MK801/PCP-like noncompetitive antagonists (2).

The safety and efficacy of GV-150526 administered within 12 h of symptom onset were evaluated in 29 patients with ischemic stroke and primary intracerebral hemorrhage. Administration of 800 mg followed by 200 mg b.i.d. during 3 days was discontinued due to elevated bilirubin levels reported from a different investigation (3).

The safety and tolerability of GV-150526A were tested in a double-blind, randomized, placebo-controlled phase II study. The agent was administered as a bolus infusion of 800 mg, followed by 5 maintenance doses of 400 mg b.i.d. or placebo, to 128 patients within 12 h of onset of stroke symptoms. Overall incidence of adverse events consistent with those generally observed in stroke victims was greater with GV-150526A than with placebo, although adverse CNS effects were less frequent with the active drug. A dose of 800 mg followed by 200 mg b.i.d. x 5 was generally well tolerated (4) (Box 3).

Box 3: Safety and tolerability of GV-150526 in acute stroke (4) [Prous Science CSLine database].

Study Design	Double-blind, randomized, placebo-controlled phase II clinical trial
Study Population	Patients treated within 12 h of stroke symptom onset (n = 128)
Intervention Groups	GV-150526 (GV), 800 mg i.v. bolus + 200 mg b.i.d. x 5 (n = 48) GV 800 mg i.v. bolus + 400 mg b.i.d. x 5 (n = 38) Placebo (P) (n = 42)
Adverse Events	Total: GV200, 75%; P, 54% CNS: GV200, 21%; P, 33% Hepatic: GV200, 40%; GV400, 50%
Results	Entry NIH: P, 8.0; GV200, 11.5; GV400, 10.0 Hemorrhage on CT: P, 5%; GV200, 15%; GV400, 3% Mortality at 30 days: P, 10%; GV200, 17%; GV400, 18%
Conclusions	GV-150526 was generally well tolerated, with no excess of CNS adverse events. Transient bilirubin abnormalities were dose-limiting. The higher mortality after active treatment was not statistically significant

Gavestinel sodium is the new proposed international nonproprietary name for GV-150526A (5).

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HGP-30

AIDS Vaccine

EN: 159052

H-Tyr-Ser-Val-His-Gln-Arg-Ile-Asp-Val-Lys-Asp-Thr-Lys-Glu-Ala-Leu-Glu-Lys-Ile-Glu-Glu-Glu-Gln-Asn-Lys-Ser-Lys-Lys-Lys-Ala-OH

$C_{154}H_{259}N_{45}O_{52}$ **Cel-Sci**

It has been reported that HGP-30 immunization in mice can induce cross-reacting antibodies (Th1 and Th2) which can efficiently recognize HIV-1 p17-related peptide sequences that represent clades B, C and E sequences. These findings on cross-clade recognition by HGP-30-induced antibodies, as well as prior demonstration of significant protection against HIV infection in hu-PBL-SCID mice, suggested that HPG-30 may be an important vaccine antigen for inducing cross-clade-protective cellular and humoral immune responses. Induction of such cross-clade-recognizing cellular and humoral immune responses may be useful for a polypeptide HIV vaccine intended for global use (1).

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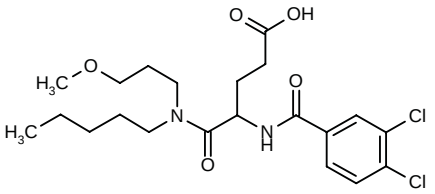
Loxiglumide

Treatment of Pancreatic Disorders
Treatment of IBS
CCK_A Antagonist

EN: 135822



$C_{21}H_{30}Cl_2N_2O_5$ **Rotta; Kaken; Tokyo Tanabe**

A biochemical and pharmacological profile was conducted to assess the selectivity of loxiglumide to CCK-A (rat pancreas, bovine gallbladder) and CCK-B/gastrin receptors (guinea pig cerebral cortex and gastric parietal cell). A tissue bioassay evaluated the effect of loxiglumide on contractions of the guinea pig gallbladder and ileum. Loxiglumide showed inhibitory effects with respect to ^{125}I-CCK-8 binding to rat pancreatic and bovine gallbladder membranes, ^{125}I-CCK-8 binding to guinea pig cerebral cortex membranes and parietal cells, and ^{125}I-gastrin binding to guinea pig parietal cells. Results indicated that the affinity of loxiglumide to CCK-A receptors was at least 63 times greater than that to CCK-B/gastrin receptors. In addition, loxiglumide functions as a competitive CCK antagonist with a high affinity to guinea pig gallbladder and ileum tissues (1).

The effects of loxiglumide and gabexate mesilate were assessed in three experimental acute pancreatitis models in mice induced by caerulein, sodium taurocholate + caerulein and closed duodenal loop. Loxiglumide, but not gabexate mesilate, at 3 and 10 mg/kg by i.v. injection at 6-h intervals suppressed an increase in serum amylase activity cause by caerulein. Loxiglumide at 18 and 60 mg/kg/h evinced a life-prolonging effect in the lethal necrotizing pancreatitis induced by caerulin after an injection of sodium taurocholate into the common bile duct. Gabexate mesilate (180 mg/kg/h) showed a lower cumulative survival rate. Loxiglumide at 6, 18 and 60 mg/kg/h suppressed a rise in total ascitic lipase activity and plasma amylase and lipase activity of rats with closed duodenal loop. Thus, cholecystokinin has an important role in the development of acute pancreatitis and loxiglumide may possess therapeutic potential for pancreatitis (2).

Administration of loxiglumide to rats at a low dose for 7 days revealed no significant effect on exocrine or endocrine pancreatic function. A high dose of this agent, however, reduced pancreatic enzyme output without provoking insulin resistance or diabetes mellitus (3).

The effects of loxiglumide were tested on pancreatic exocrine secretion stimulated by CCK and intraduodenal casein in male Wistar rats. The results of these studies indicate that loxiglumide inhibits pancreatic exocrine secretion stimulated by exogenous or endogenous CCK thus being a potent CCK receptor antagonist (4).

The effects of loxiglumide on pancreatic exocrine secretion stimulated by CCK-8 were tested in conscious dogs with chronic pancreatic fistula. CCK-8 at 0.06 µg/kg/h i.v. infusion increased pancreatic exocrine secretion. Loxiglumide at doses of 1, 3, 10 mg/kg/h i.v. suppressed CCK-8-increased outputs of trypsin and amylase and at 10 mg/kg/h inhibited pancreatic juice volume. Thus, loxiglumide arrested the rise of CCK-8-stimulated pancreatic exocrine secretion through selective blockade of receptor binding of CCK in dogs (5).

The effects of loxiglumide on pancreatic blood flow response to an intraduodenal milk infusion were evaluated and compared to those of the stomach and the intestine in 4 conscious beagle dogs. Pancreatic blood flow quickly rose after the intraduodenal administration of milk. Loxiglumide did not affect the resting pancreatic branch of the splenic, left gastric or superior mesenteric artery blood flow while it did suppress pancreatic blood flow response to the intraduodenal milk infusion. Milk-induced pancreatic vasodilation is suggested to be at least partially mediated by the CCK-A receptor (6).

Conscious dogs with chronic pancreatic fistula were administered 10 mg/kg/h i.v. of loxiglumide to assess its effects on pancreatic secretion stimulated by meal. Loxiglumide at this dose suppressed outputs of amylase and bicarbonate but did not apparently inhibit pancreatic juice volume or trypsin output. Thus, loxiglumide may suppress pancreatic exocrine secretion by selective blockade of receptor binding of CCK endogenously induced by meal in dogs (7).

Evaluation of the effects of loxiglumide (30 mg/kg/h during 10 min followed by 10 mg/kg/h during 3 h) on lower esophageal sphincter motor events and gastric relaxation induced by duodenal infusion of a liquid meal in 12 healthy volunteers showed that transient lower esophageal sphincter relaxations and fundic relaxation occur simultaneously after the infusion of a meal. Both events are blocked by loxiglumide indicating that cholecystokinin is involved in the response (8).

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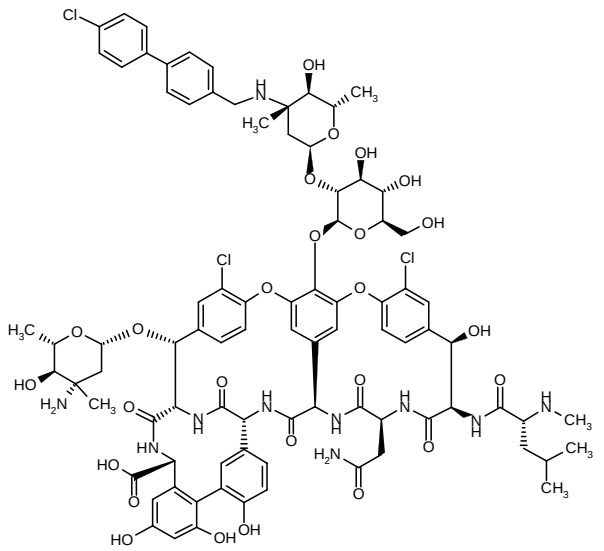
LY-333328 *Glycopeptide Antibiotic*

EN: 226450



$C_{86}H_{97}Cl_3N_{10}O_{26}$ **Lilly**

Using a colony count method, vancomycin and LY-333328 were tested against 8 strains of *Staphylococcus aureus* having various susceptibilities to methicillin and ciprofloxacin. Vancomycin was bacteriostatic against all the tested extracellular staphylococci while LY-333328 was bactericidal at 10 MIC. Regardless of the concentration, vancomycin showed nearly no activity against ingested staphylococci as compared with controls. LY-333328 at concentrations of 1 MIC and above was active against ingested staphylococci regardless of their susceptibility pattern. These findings indicated that LY-333328 is active against intracellular *S. aureus* (1).

Evaluation of MICs of LY-333328 in penicillin susceptible, intermediate and resistant strains of *Streptococcus pneumoniae* showed that the drug possesses excellent antipneumococcal activity regardless of the resistance phenotype of the strains (2).

The activity of LY-333328 in the treatment of *Staphylococcus aureus* infection associated with central venous catheter was evaluated in rats. Administration of 2.5, 5, 10 and 20 mg/kg doses produced overall infection rates of 100, 40, 80 and 30%, respectively. The results

suggest that LY-333328 has excellent antistaphylococcal activity, being most efficient at doses of 20 mg/kg administered every 96 h (3).

In a multicenter study, 195 individual vancomycin-resistant *Enterococcus faecium* isolates were studied for antimicrobial susceptibilities to LY-333328, quinupristin-dalfoprisitin, teicoplanin, ampicillin and gentamicin. LY-333328 was the most active and was rapidly bactericidal against vancomycin-resistant *E. faecium*. The susceptibilities to LY-333328 varied with media and study methods. The PAE was prolonged. Bacterista-tic synergy with LY-333328 occurred with ampicillin, quinupristin-dalfopristin and gentamicin (4).

LY-333328, linezolid, CL-331,002, CL-329,998, moxifloxacin, trovafloxacin and quinupristin-dalfopristin were tested against 274 clinical isolates of enterococci to assess these agents' activities. No vancomycin resistance or β-lactamase production was seen. These agents showed promising *in vitro* antienterococcal activity with the exception of 12 isolates (all non-*Enterococcus faecalis*) which showed decreased susceptibility to quinupristin-dalfopristin (MIC ≥ 4 μg/ml) (5).

In vitro, LY-333328 demonstrated reduced antibacterial activity against vancomycin-intermediate strains of *Staphylococcus aureus*, as compared to a vancomycin-susceptible strain. In the presence of albumin, the activity of LY-333328 against the vancomycin-intermediate strains was further reduced. The results indicate that LY-333328 doses above 3 mg/kg/day may be necessary for the treatment of infections with vancomycin-intermediate strains of *S. aureus* (6).

Evaluation of monotherapy with LY-333328, or combination therapy of LY-333328 with ceftriaxone and/or dexamethasone in a rabbit meningitis model demonstrated that LY-333328 alone is an excellent treatment for cephalosporin-resistant pneumococcal meningitis. In combination with ceftriaxone, the antibacterial activity of LY-333328 was improved, although without statistical significance and synergistic effects. Combination therapy of LY-333328 and dexamethasone was also bactericidal, however, therapeutic failures were reported (7).

The antibacterial activity of LY-333328 was evaluated in vancomycin-resistant strains of *Enterococcus faecium* and *Enterococcus faecalis* both ingested and noningested by polymorphonuclear leukocytes. LY-333328 was at least as active as vancomycin against extracellular enterococci, regardless of their susceptibility phenotype, and showed activity against both strains at clinically achievable concentrations. However, the drug seemed to be more efficient against *E. faecialis* than *E. faecium* (8).

LY-333328 demonstrated excellent inhibitory activity *in vitro* against the following anaerobic Gram-positive strains of bacteria isolated from human infections; peptostreptococci (0.016-1.0 mg/l), *Propionibacterium acnes* (0.032-0.125 mg/l) and *Clostridium perfringens* (0.016-2.0 mg/ml) (9).

The MICs and MBCs of 15 antibiotics were determined with two strains of *Staphylococcus aureus* in Mueller-Hinton broth and 90% serum-10% Mueller-Hinton broth. Results indicate that highly protein-bound antibiotics like LY-333328 demonstrated higher MICs and MBCs, less bactericidal activity during an 8-h period and decreased postantibiotic effects in 90% serum-10% Mueller-Hinton broth than in Mueller-Hinton broth alone. Albumin was shown to be almost completely responsible for changes in the above pharmacodynamic parameters of LY-333328 (10).

The *in vitro* activities of LY-333328, vancomycin and teicoplanin were compared against 425 Gram-positive clinical isolates including various strains with multiple resistance. LY-333328 was active against all microorganisms tested, including methicillin- and teicoplanin-resistant staphylococci, glycopeptide-resistant enterococci, penicillin- and multiply resistant pneumococci, and viridans and β-hemolytic streptococci (11).

Optimal dosing regimen and pharmacokinetics of LY-333328 were evaluated in a neutropenic mouse thigh model of *Staphylococcus* infection. CFU/thigh were reduced by a factor of 4.8 following administration of a single 2 mg/kg dose. Dose increments and dose divisions did not improve efficacy. Administration of a 2 mg/kg dose produced a peak plasma concentration of 27 mg/l and a concentration of 10 mg/l 1 h after dosing. Total plasma concentration of LY-333328 was sustained above MIC during 7 h (12).

The *in vitro* activity of LY-333328 was compared to vancomycin and teicoplanin against clinical isolates of *Staphylococcus aureus*, coagulase-negative staphylococci, vancomycin/teicoplanin-resistant enterococci and vancomycin-sensitive and -resistant enterococci. LY-333328 displayed comparable or superior activity (MIC and MBC = 0.25-4 mg/l) relative to the reference compounds. Microbial regrowth was observed after 4-8 h of exposure to LY-333328. In light of the emergence of glycopeptide resistance in the clinic, LY-333328 appears to represent a useful therapeutic option, although the dosage regimen may have to be carefully adjusted to ensure successful treatment (13).

LY-333328 and vancomycin were compared in a rabbit model of left-sided methicillin-resistant *Staphylococcus aureus* endocarditis. Animals were administered 25 mg/kg every 24 or 8 h, respectively, for 4 days. Results indicated that LY-333328 was microbiologically effective and is a possible alternative to vancomycin (14).

Safety and pharmacokinetics evaluation of LY-333328 in 8 healthy male subjects receiving single doses of 0.5-3.0 mg/kg produced C_{max} values of 13.1-23.6 mg/ml and AUC values of 120-305 mg·h/ml. Both parameters increased in a dose-dependent and linear manner. The area under the terminal phase represented approximately 50% of $AUC_{(0-\infty)}$, and $t_{1/2}$ observed was 10.5 days. The drug was safe and well tolerated at all doses tested (15).

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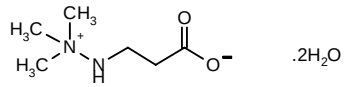
Mildronate *Antianginal*
MET-88

EN: 145694



$C_6H_{14}N_2O_2.2H_2O$ **Latvian Inst. Org. Synth. (LV); Taiho**

The potential protective effect of a reduction in carnitine content on hypoxic cardiac damage was explored in isolated perfused rat hearts using MET-88. Rats, divided into 4 groups, received vehicle, pretreatment with MET-88 (100 mg/kg p.o. once daily for 10 days), insulin in the perfusate or both pretreatment with MET-88 and insulin in the perfusate, followed by 10-min perfusion under normoxic conditions and 30-min perfusion under hypoxic conditions. Pretreatment with MET-88 was associated

with cardioprotective effects on contractile function and energy metabolism under hypoxia; insulin also improved cardiac function and combination of the two treatments further improved cardiac function during hypoxia (1).

Male Wistar rats received mildronate i.p. for 12 days at 60 mg/kg. The animals did not eat for 48 h. While plasma glucose and nonesterified fatty acid levels were higher in rats receiving mildronate, this drug greatly decreased plasma glucose and myocardial glycogen content and prevented raised liver triglycerides caused by fasting. In addition, mildronate prevented palmitate oxidation, a decrease in skeletal muscle and myocardial lipolytic activity. Thus, mildronate modulates some effects of fasting on lipid and glucose metabolism by likely increasing the peripheral utilization of fatty acids and liver gluconeogenesis (2).

Evaluation of the effects of mildronate 1000 mg/day on platelet and erythrocyte membrane lipid peroxidation, platelet aggregation and erythrocyte deformability in 30 patients with coronary heart disease demonstrated the antioxidant activity of the drug. In addition, a reduced platelet aggregation and improved erythrocyte deformability was observed (3).

1. Asaka, N., Muranaka, Y., Kirimoto, T., Miyake, H. *Cardioprotective profile of MET-88, an inhibitor of carnitine synthesis, and insulin during hypoxia in isolated perfused rat hearts*. Fundam Clin Pharmacol 1998, 12(2): 158.

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3. Koroleva, L. et al. *The possibilities of mildronate as antioxidant and its influence on platelets aggregation and erythrocytes deformability in patients with coronary heart disease*. 2nd Int Congr Coron Artery Dis (Oct 18-21, Florence) 1998, Abst 184.

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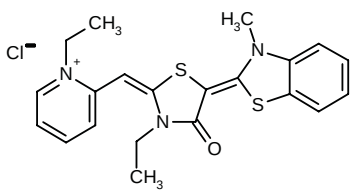
MKT-077
SDZ-MKT-077

Oncolytic

EN: 237755



$C_{21}H_{22}ClN_3OS_2$ **Novartis; Fuji Photo Film**

The *in vivo* antitumor activity of MKT-077 against human tumor xenografts was evaluated in nude mice. Five xenografts were inoculated subcutaneously and MKT-077 treatment began when exponential growth started. Antitumor activity positively correlated with exposure time and MKT-077 concentration (7.5-40 mg/kg/day) via Osmotic Micropump™. The maximum tolerated dose was 20 mg/kg/day for 7 days. Human colon, gastric and pancreatic cancers showed sensitivity to MKT-077 in 5 test strains (1).

MKT-077 was tested against fresh human tumor specimens from the human tumor cloning system. The compound was assessed at 3 different exposures to replicate potential dosing regimens. MKT-077 was active against a wide variety of tumors showing a concentration-response effect as confirmed by the chi-squared test at 24 h, 2-24-2 h and continuous exposure ($p < 0.001$). These findings with toxicity results, may help guide selection of proper dose and treatment schedules for clinical evaluation of the drug against solid tumors (2).

The pharmacokinetic parameters of MKT-077 after a single dose were determined to evaluate its tolerability. The compound was assessed at various doses ranging from 42-126 mg/m^2/wk as an i.v. infusion over 2 h weekly for 4 weeks and thereafter every 6 weeks. The peak plasma levels achieved (2.64 and 6.64 μM at 42 and 56 mg/m^2/wk, respectively) were similar to IC_{50} values of MKT-077 (0.3-93 μM). MKT-077 follows a three compartmental model with $t_{1/2\gamma}$ of 25-30 h. It appears from preliminary studies that dose has no significant effect on clearance (40 l/h/m^2) (3).

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2. Izbicka, E., Lawrence, R., Davidson, K., Cerna, C., Gomez, L., Bair, K.W., Nalin, C.M., Von Hoff, D.D. *Anticancer activity of MKT077, a novel rhodacyanine dye, against human tumor specimen taken directly from patients*. 10th NCI-EORTC Symp New Drugs Cancer Ther (June 16-19, Amsterdam) 1998, Abst 140.

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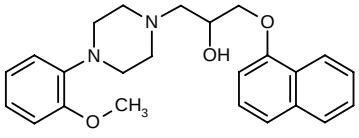
Naftopidil
Flivas™

Antihypertensive
Treatment of Urinary Incontinence

EN: 105012



$C_{24}H_{28}N_2O_3$ **Asahi Chem.; Roche; Kanebo**

A registration dossier for Asahi Chemical's antidysuria agent naftopidil is under review in Japan and the company expects to receive marketing approval shortly (1).

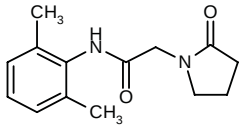
1. *Asahi expects approval of dysuria Rx in near future*. Prous Science Daily Essentials Oct 14, 1998.

Original monograph - Drugs Fut 1987, 12: 31.

Nefiracetam
Translon®

Cognition Enhancer

EN: 105128



$C_{14}H_{18}N_2O_2$ **Daiichi Pharm.**

The effects of nefiracetam (1-10 mg/kg) on amyloid β-peptide(1-42)-induced learning and memory deficits were assessed in rats. The drug (administered p.o. 1 h before testing) significantly improved learning and memory deficits in amyloid β-peptide(1-42)-infused rats. Nefiracetam (3 mg/kg) increased choline acetyltransferase activity in the hippocampus of these animals. These data indicated that the drug would be useful in treating Alzheimer's disease (1).

Nefiracetam interacted with cAMP-dependent protein kinase (PKA) and Ca^{2+}-dependent protein kinase (PKC) pathways which resulted in the PKC phosphorylation of Torpedo californica nicotinic acetylcholine receptors presented in *Xenopus laevis* oocytes. In addition, nefiracetam produced short-term and long-term depression of ACh-evoked currents at submicromolar (0.01-0.1 μM) and micromolar (1.10 μM) concentrations, respectively. These results provide a possible cellular mechanism for the action of cognition-enhancing agents (2).

Nefiracetam was assessed for its effects on synaptic transmission *in vivo* in mouse dentate gyrus and *in vitro* in the rat hippocampal CA1 region. Results indicate that nefiracetam is associated with a long-lasting facilitation of hippocampal synaptic transmission via an effect on neuronal nicotinic acetylcholine receptors, which may be the mechanism for its cognition-enhancing effects (3).

The effects of nefiracetam on the motivational properties of phencyclidine (PCP) were investigated based on its ability to increase intracellular cAMP levels and to attenuate the development of morphine dependence. Results from this study using the conditioned place preference task in mice indicate the potential of nefiracetam for treating PCP addiction (4).

In an *in vivo* microdialysis study, nefiracetam (10 mg/kg p.o.) elevated extracellular acetylcholine (ACh) levels in the frontal cortex of rats with cerebral cholinergic dysfunctions. This effect was additionally noted when scopolamine (1 mg/kg i.p.) was administered at 45 min post nefiracetam treatment. The extracellular ACh level in the frontal cortex of basal forebrain (BF)-lesioned rats was increased by perfusion of nefiracetam at 10 μM. By increasing cortical ACh levels, nefiracetam may thus produce an antiamnesic effect on learning deficits induced by scopolamine or BF lesion in rats (5).

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3. Matsuyama, S., Nishizaki, T. *The nootropic nefiracetam induces a long-lasting facilitation of hippocampal synaptic transmission mediated by neuronal nicotinic ACh receptors*. Jpn J Pharmacol 1998, 76(Suppl. 1): Abst O-292.

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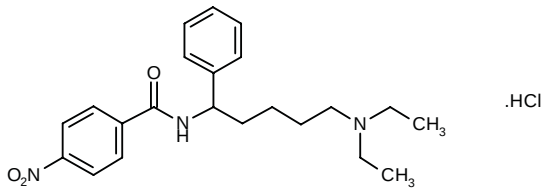
Nibentan

Antiarrhythmic
Potassium Channel Blocker

EN: 226458



$C_{22}H_{29}N_3O_3.HCl$ **Russian Acad. Med. Sci.**

In a preclinical study designed to determine the mechanism of antiarrhythmic activity of nibentan, the effects of his compound on acetylcholine-activated potassium current (IK.ACh) were studied *in vitro* in rat and human atrial myocytes. Nibentan (7.5 μM) did not affect action potential or K^+ current in control rat cells; in the presence of carbachol (CCh), however, nibentan partially reversed CCh-induced shortening of action potentials and decreased IK.ACh by 73 ± 12%. Nibentan (7.5 μM) also produced 45 ± 3% inhibition of GTPγS-activated IK.ACh, indicating that its anticholinergic activity is the result of both direct IK.ACh channel inhibition and muscarinic receptor antagonism. To test this theory, the effects of nibentan on the specific binding affinity of [^{3}H]-QNB were tested in human cardiac membranes and nibentan, at therapeutic concentrations, was shown to compete with [^{3}H]-QNB for sites on muscarinic cholinoreceptors. In human atrial myocytes obtained from patients, nibentan inhibited the CCh-induced increase in IK.ACh by 84 ± 11%. These results indicate that nibentan suppresses the shortening of wavelengths for reentry during vagal stimulation, leading to elimination of cholinergic atrial fibrillation (1).

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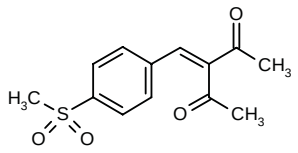
Orazipone
OR-1384

Treatment of IBD
Cytokine Modulator

EN: 251434



$C_{13}H_{14}O_4S$ **Orion**

Orazipone was shown to inhibit the production of inflammatory cytokines in LPS-stimulated human peripheral blood mononuclear cells. This effect possibly contributes to orazipone's protective action in colitis models (1).

1. Serkkola, E., Aho, P., Nissinen, E. *Inhibition of LPS-induced cytokine production in mononuclear cells by orazipone (OR-1384)*. 9th Int Conf Inflamm Res Assoc (Nov 1-5, Hershey) 1998, Abst P37.

Original monograph - Drugs Fut 1998, 23: 28.

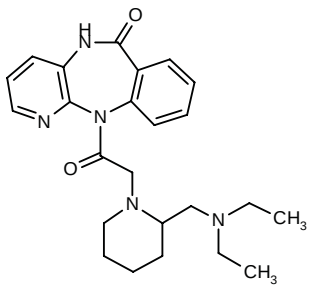
Additional Reference

Nissinen, E. et al. *Inhibition of neutrophil activation by a novel thiol modulating compound OR-1384*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 23.18.

Otenzepad

Antiarrhythmic
Muscarinic M_2 Antagonist

EN: 112381



$C_{24}H_{31}N_5O_2$ **Boehringer Ingelheim**

The effects of AF-DX 116 were assessed on ventricular arrhythmias induced by two-stage coronary ligation, digitalis or adrenaline in beagle dogs. AF-DX 116 (0.3 mg/kg i.v.) raised the sinus rate of conscious dogs but showed no antiarrhythmic effects on ligation-induced ventricular tachycardia (VT). AF-DX 116 did not affect the blood pressure, suppress digitalis-induced VT, nor did it increase the atrial rate previously raised to about 210 beats/min by ouabain. The drug did reduce the arrhythmic ratio at 9 min post bolus injection and raised the atrial rate in adrenaline-induced VT. The maximum plasma concentration was 1 μg/ml at 1 min post bolus injections in the digitalis and adrenaline tests. It was concluded that the overdrive suppression mechanism fails to explain the late onset of the antiarrhythmic effect of this drug on adrenaline-induced arrhythmia (1).

Long-term control of mild to moderate bradyarrhythmia and temporary treatment until pacemaker implantation may be achieved through oral administration of otenzepad. Fifty patients with sick sinus syndrome (SSS), atrioventricular block (AVB), SSS with AVB or bradycardic atrial fibrillation were investigated. Initial dosage was increased weekly from 270 mg/day to 540 mg/day up to 810 mg/day. Otenzepad caused dose-dependent increases of 24-h total heartbeats in SSS and AVB and dose-dependent decreases in the maximum RR interval. Nineteen SSS and 10 AVB patients experienced signifi-

cant electrocardiographic improvement. Adverse events were clinically mild and tolerable (2).

1. Naito, H., Furukawa, Y., Hashimoto, K. *Effects of a cardioselective M-2 receptor antagonist, AF-DX 116, on ventricular arrhythmias in dogs*. Heart Vessels 1997, 12(5): 229.

2. Katoh, T., Hayakawa, H., Katoh, K. *Anti-bradycardic effects of AF-DX 116, a new selective M_2-muscarinic blocker*. J Am Coll Cardiol 1998, 31(2, Suppl. A): Abst 1225-37.

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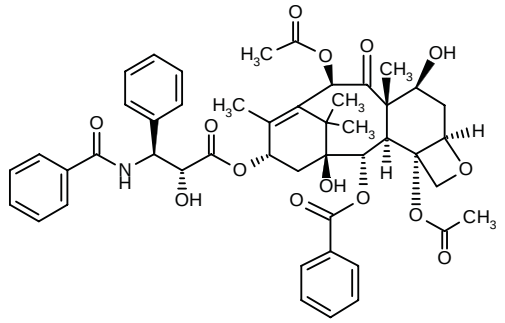
Zhang, L. et al. *Muscarinic receptor subtypes and their signaling pathways in colonic longitudinal smooth muscle*. Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 1): Abst P 5.3.

Paclitaxel
Taxol®
Anzatax®
Yewtaxan®
Paxene®

Taxane
Microtubule Inhibitor

EN: 101438



$C_{47}H_{51}NO_{14}$

Bristol-Myers Squibb; NaPro; Ivax; Angiotech

A new synthesis of paclitaxel has been reported: The esterification of (2*R*,3*S*)-2,3-epoxy-3-phenylpropionic acid (I) with 2-(trimethylsilyl)ethanol (II) by means of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in hot toluene gives the expected ester (III), which is treated with LiBr in acetic acid to yield the (2*R*,3*R*)-3-bromo-2-hydroxy ester (IV). The reaction of (IV) with sodium azide in hot DMF affords the corresponding azido derivative (V), which is reduced with ammonium formate or H_2 over Pd/C giving the (2*R*,3*S*)-3-amino-2-hydroxy ester (VI). The amidation of (VI) with benzyl chloroformate (VII) yields the corresponding benzyloxycarbonylamino compound (VIII), which is esterified with benzoyl chloride (IX) and triethylamine affording (2*R*,3*S*)-2-(benzoyloxy)-3-(benzyloxycarbonylamino)-3-phenylpropionic acid 2-(trimethylsilyl)ethyl ester (X). The condensation of the ester (X) with 7-*O*-(triethylsilyl)baccatin (XI) by means of 4-(1-pyrrolidinyl)-piperidine (4-PP) and dicyclohexylcarbodiimide (DCC) in hot toluene gives the mixed ester (XII). Finally, this compound is hydrogenated with ammonium formate and Pd/C to obtain a free amino group to which the benzoyl group of the α-position is transferred by a treatment with formic acid yielding pure paclitaxel (1). Scheme 2.

In an *in vitro* study, paclitaxel showed antiinflammatory effects through inhibition of neutrophil chemiluminescence, reduced superoxide generation and inhibition of degranulation of stimulated human plasma neutrophils as well as inhibition of antigen-induced T-cell activation. Paclitaxel (1% topical gel) significantly inhibited swelling and erythema in oxazolone or phorbol-12-myristol-acetate-induced skin inflammation in mice ears when administered at the same time as or 24 h following irritant exposure. Given that paclitaxel showed antiinflammatory and antiprolifertive activity, inhibition of angiogenesis and of MMP production, the drug may effectively treat psoriasis (2).

Angiotech has completed enrollment in a clinical study evaluating the safety and pharmacological activity of micellar paclitaxel as a treatment for secondary progressive multiple sclerosis. All 30 patients enrolled in the study have begun treatment with the company's formulation of paclitaxel, and no significant adverse events have been reported. The study involves 6 monthly treatments with micellar paclitaxel at 2 different dose levels, with 18 months of follow-up (3).

NaPro BioTherapeutics and Baker Norton, a wholly owned subsidiary of Ivax, have terminated their paclitaxel development and marketing agreement established in 1993 (4).

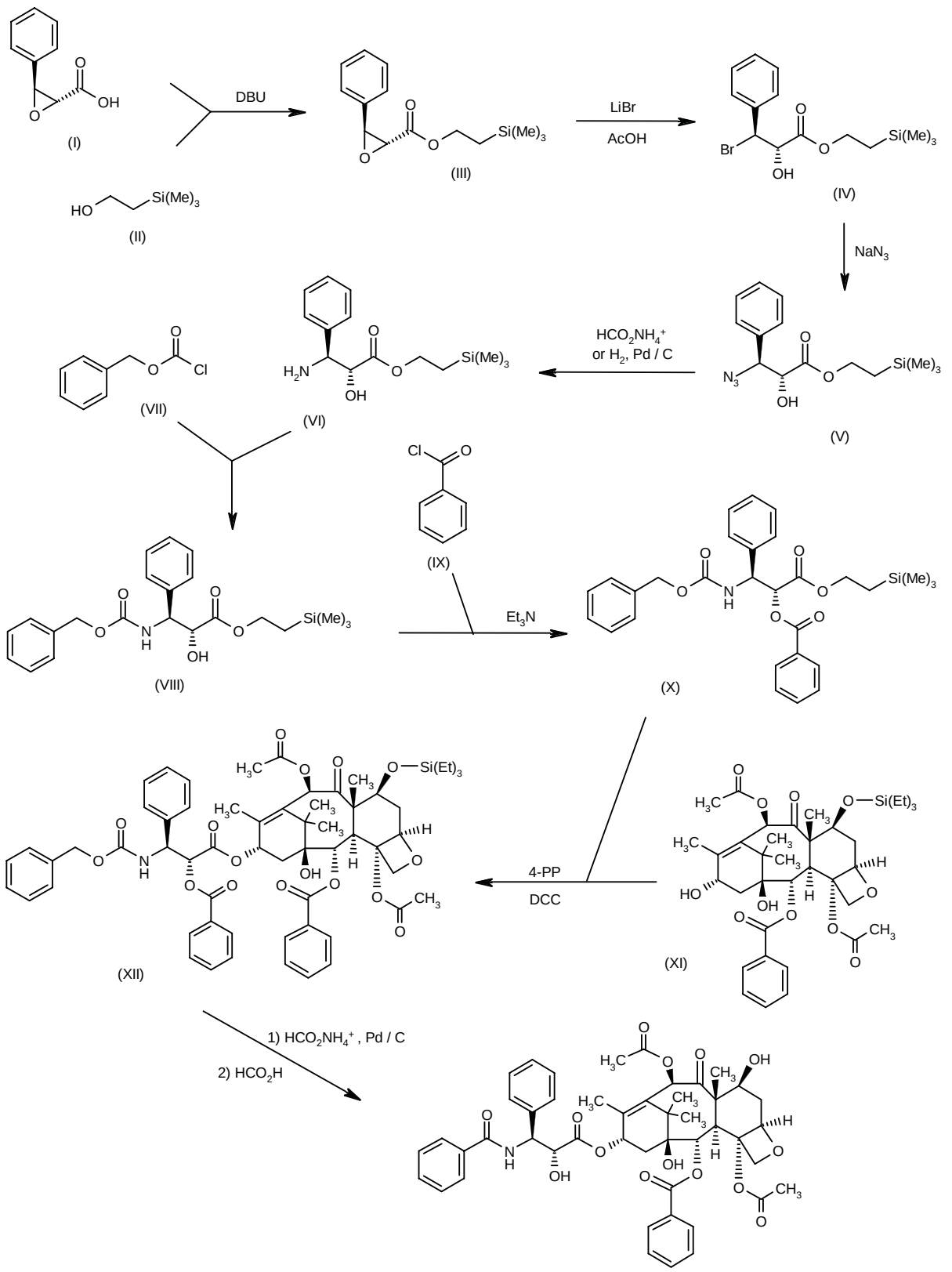
The Oncologic Drugs Advisory Committee has recommended that the FDA approve Taxol® Injection in combination with a platinum agent for the first-line treatment of advanced ovarian cancer and non-small cell lung cancer (5).

Angiotech has been cleared by the FDA to begin a phase I clinical trial of micellar paclitaxel for the treatment of rheumatoid arthritis. The double-blind trial will be conducted at the University of California at Los Angeles and will assess the safety and pharmacological effects of paclitaxel in 15 patients with class I-III rheumatoid arthritis who have failed treatment with at least 1 disease-modifying antiarthritic drug, such as methotrexate. Treatment will consist of a dose of paclitaxel at monthly intervals for a total of 6 treatments, with 6-month follow-up (6).

The French health authorities have authorized Bristol-Myers Squibb to market Taxol® in combination with cisplatin for the treatment of advanced non-small cell lung cancer (7).

Angiotech Pharmaceuticals has initiated a phase I/II clinical study to assess the safety and pharmacological

Scheme 2: Synthesis of Paclitaxel



activity of topical paclitaxel gel in patients with mild to moderate psoriasis. The 20-patient study is being conducted at the University of British Columbia (8).

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3. *Angiotech study of micellar paclitaxel in MS well under way*. Prous Science Daily Essentials Nov 5, 1998.

4. *NaPro and Ivax terminate paclitaxel agreement*. Prous Science Daily Essentials March 24, 1998.

5. *FDA advisory committee recommends Taxol for new indications*. Prous Science Daily Essentials March 27, 1998.

6. *Angiotech's micellar paclitaxel enters clinic for arthritis*. Prous Science Daily Essentials June 18, 1998.

7. *Taxol combination therapy approved in France for NSCLC indication*. Prous Science Daily Essentials Oct 16, 1998.

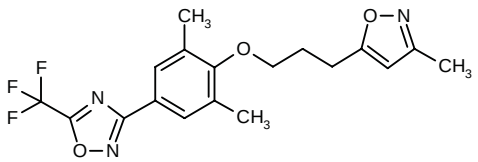
8. *Angiotech initiates another clinical trial with paclitaxel for treatment of psoriasis*. Prous Science Daily Essentials Dec 16, 1998.

Original monograph - Drugs Fut 1986, 11: 45.

Pleconaril
VP-63843

Antiviral

EN: 202115



$C_{18}H_{18}F_3N_3O_3$ **Sanofi; ViroPharma**

ViroPharma announced positive preliminary results from the second of 4 studies of pleconaril (2 in adults and 3 in children) for the treatment of viral meningitis. In this double-blind, placebo-controlled trial, 130 adults with viral meningitis received either pleconaril 200 mg or placebo t.i.d. Those treated with pleconaril showed a statistically significant and clinically beneficial reduction in the duration of headache, the primary endpoint in the study. Pleconaril-treated patients experienced clinical benefit within 24 h after beginning therapy. The median duration of headache in patients receiving pleconaril was reduced by 2 days in cases of confirmed enteroviral meningitis and by 1 day in the entire group. The median duration of headache in placebo-treated patients was 9 days. The primary endpoint was achieved 3-4 days earlier in 75% of pleconaril-treated patients, both those with confirmed enteroviral meningitis and all randomized patients, compared to placebo-treated patients. Adverse events were reported in fewer patients treated with pleconaril than with placebo, and the majority of the events were similar to disease symptoms. In addition to these patients, 68 patients received a higher dose of 400 mg t.i.d. pleconaril and they showed a slight increase in adverse events compared to placebo. Data from this group will be included in the safety analysis. The company plans to have a complete report of results ready for presentation at the annual meeting of the American College of Physicians in April 1999 (1).

1. *Positive adult meningitis study results reported for pleconaril*. Prous Science Daily Essentials Jan 8, 1999.

Original monograph - Drugs Fut 1997, 22: 40.

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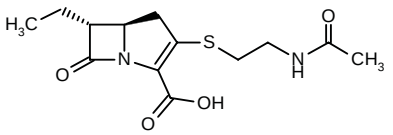
Kearns, G.L. et al. *Pharmacokinetics of pleconaril in children*. Clin Pharmacol Ther 1998, 63(2): Abst PII-81.

Preliminary results announced for pleconaril pediatric study: Other trials in progress. Prous Science Daily Essentials Nov 26, 1998.

PS-5

β-Lactamase Inhibitor
Carbapenem

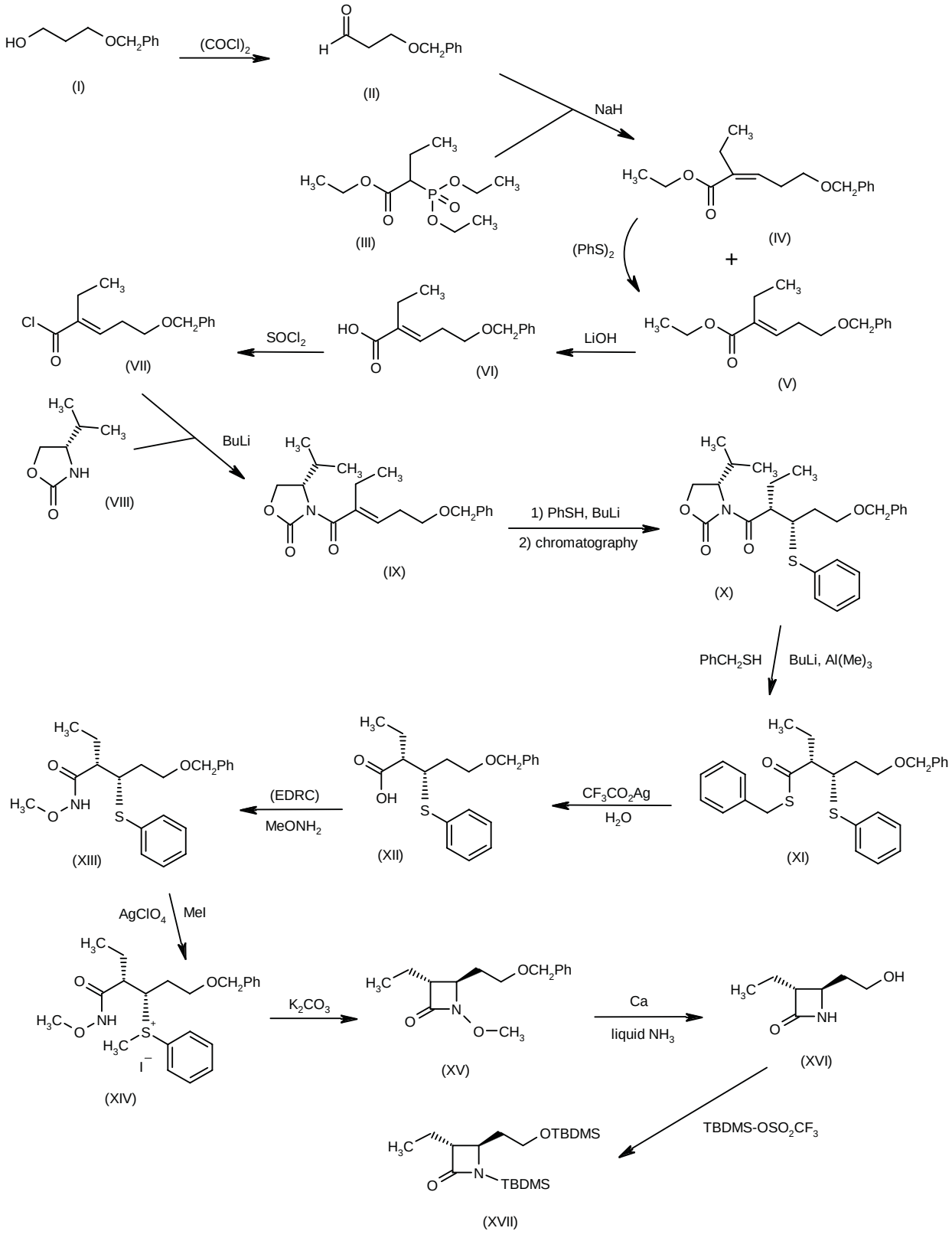
EN: 090641



$C_{13}H_{18}N_2O_4S$ **Sanraku**

A new and stereoselective synthesis of (3*R-trans*)-3-ethyl-1-(*tert*-butyldimethylsilyl)-4-[2-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-one (XVII), a key intermediate in the synthesis of PS-5 has been developed: The oxidation of 3-benzyloxy-1-propanol (I) with oxalyl chloride in DMSO gives the corresponding aldehyde (II), which is condensed with the phosphonate (III) by means of NaH yielding a mixture of the (*Z*)- and (*E*)-isomers of 5-benzyloxy-2-ethyl-2-pentenoic acid ethyl ester (IV) and (V). The undesired (*Z*)-isomer (IV) is isomerized by treating the mixture with diphenyldisulfide in refluxing THF. The hydrolysis of (V) with LiOH in THF/methanol/ water gives the expected free acid (VI), which is treated with $SOCl_2$ in refluxing benzene to afford the acid chloride (VII). The condensation of (VII) with the chiral oxazolidinone (VIII) by means of butyl lithium in THF gives the acylated compound (IX), which is treated with benzenethiol and butyl lithium in THF to give the addition compound (X) that is purified by medium pressure column chromatography to eliminate the undesired diastereomer. The elimination of the oxazolidinone group of (X) by reaction with trimethylaluminum, benzylthiol and butyl

Scheme 3: Synthesis of Intermediate (XVII)



lithium in THF yields the thioester (XI), which is treated with silver trfluoroacetate and water to afford the corresponding free acid (XII). The reaction of (XII) with methoxyamine and 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide (EDPC) in water affords the methoxyamide (XIII), which is methylated by means of methyl iodide and silver perchlorate to give the sulfonium salt (XIV). The cyclization of (XIV) by means of K_2CO_3 yields the azetidinone (XV), which is debenzylated by means of calcium in liquid ammonia affording (3*R-trans*)-3-ethyl-4-(2-hydroxyethyl)azetidin-2-one (XVI). Finally, this compound is silylated with *tert*-butyldimethylsilyl (TBDMS) trifluoromethanesulfonate affording (3*R-trans*)-3-ethyl-1-(*tert*-butyldimethylsilyl)-4-[2-(*tert*-butyldimethylsilyloxy)-ethyl]azetidin-2-one (XVII), the desired target key intermediate in the synthesis of PS-5 (1). Scheme 3.

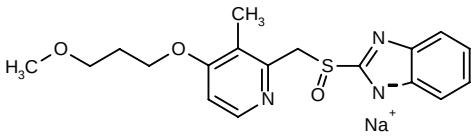
1. Miyata, O., Fujiwara,Y., Ninomiya, I., Naito, T. *Efficient stereoselective route to β-lactams and their application to the stereoselective synthesis of a key intermediate for carbapenem antibiotic (+)-PS-5*. J Chem Soc Perkins Trans I 1998, 14: 2167.

Original monograph - Drugs Fut 1980, 5: 41.

Rabeprazole Sodium
Pariet®
Aciphex®

Gastric Antisecretory
H^+/K^+-ATPase Inhibitor

EN: 143151



$C_{18}H_{20}N_3NaO_3S$ **Eisai; Janssen-Cilag**

Rabeprazole, like omeprazole, did not impact hepatic lysosomal function in rats. Animals received chloroquine (50 mg/kg), rabeprazole (5 mg/kg) or omeprazole (5 mg/kg) i.p. for 6 days. Bile was collected for 5 h and hepatic and biliary lysosomal enzyme activities were measured. Rabeprazole and omeprazole did not change lysosomal enzyme activities, lysosomal enzyme latency, protein content in liver or liver weight. Chloroquine did not influence lysosomal enzyme latency, hepatic and biliary protein content or bile flow but it raised hepatic and biliary lysosomal enzyme activities (1).

A slight statistically significant change in biological half-life was observed in fasted subjects taking rabeprazole (20 mg). Detailed pharmacokinetic evaluation of rabeprazole in young healthy, elderly and renally impaired subjects showed no need for adjustment. Half-life values ranged from 1-2 h with peak plasma values of 250-670 ng/ml (2).

Rabeprazole interactions with digoxin (increased absorption) and ketoconazole (reduced absorption) were found to be significant (3).

The pharmacokinetic parameters of rabeprazole after a single dose were determined in healthy human volunteers as well as in patients at a dose of 20 mg. In the Japanese population, it has been shown that either food or concomitant administration of antacid has no effect on the bioavailability of rabeprazole (4).

Data presented at the recent American College of Gastroenterology Annual Meeting in Boston demonstrate the efficacy of rabeprazole sodium in the treatment of gastroesophageal reflux disease (GERD) and duodenal and gastric ulcers. In a multicenter U.S. trial, 285 patients with healed erosive or ulcerative GERD were treated with rabeprazole (10 or 20 mg) or placebo once daily for 1 year. Both doses of rabeprazole were significantly more effective than placebo in maintaining healing: 86% and 77% of patients, respectively, receiving 20 mg and 10 mg remained healed at 52 weeks *versus* only 29% in the placebo group. All treatments were well tolerated. The effects of short-term treatment (4-6 weeks) with rabeprazole and omeprazole (both 20 mg/day) on ulcer healing and symptom relief were compared in 2 controlled clinical trials, 1 in 205 patients with duodenal ulcers and the other in 227 patients with gastric ulcers. In the duodenal ulcer patients, rabeprazole induced healing in 98% *versus* 93% for omeprazole, and symptoms were effectively relieved on both drugs. In those with gastric ulcers, rabeprazole was as effective as omeprazole, both giving 91% healing rates. However, rabeprazole was associated with significantly greater improvement in pain frequency, daytime pain and nighttime pain (5).

The therapeutic efficacy of rabeprazole 10, 20 or 40 mg was assessed in male and female patients with duodenal or gastric ulcers or gastroesophageal reflux. All dosing levels were superior to placebo in healing acid-related lesions, although no effects were observed on *Helicobacter pylori* status (6).

In a single-center, double-blind, randomized, pilot study, 75 *Helicobater pylori*-infected patients were administered RAC, RAM, RCM or RC (R = rabeprazole 20 mg b.i.d., A = amoxycillin 1 g b.i.d., C = clarithromycin 500 mg b.i.d., M = metronidazole 400 mg b.i.d.) in one of four 7-day treatment regimens. At 4 and 8 weeks posttreatment, *H. pylori* eradication was evaluated by the urea breath test. Results indicated that rabeprazole effectively eradicated *H. pylori* in PPI-based triple therapy regimens (7).

Rabeprazole (20 mg) has shown faster onset of antisecretory activity when compared to omeprazole (20 mg) when taken once in the morning and causes a significantly greater reduction in 24-h intragastric activity. After 8 days treatment with rabeprazole, plasma gastrin concentrations were higher indicating greater inhibition of acid secretion by this compound (8).

Eisai has filed an NDA with the U.S. Food and Drug Administration for rabeprazole sodium (Aciphex®) for the treatment and maintenance of gastroesophageal reflux disease and treatment of duodenal and gastric ulcers and of pathological hypersecretory conditions, including Zollinger-Ellison syndrome (9).

Rabeprazole sodium received marketing authorization from the U.K. Medicines Control Agency for use in the treatment of gastroesophageal reflux disease and duodenal and gastric ulcers. Eisai will now pursue European marketing authorizations under the mutual recognition procedure using the U.K. as the reference member state (10).

During the third quarter of 1998, European Union regulatory authorities granted approval to market rabeprazole sodium in all member countries of the E.U. Janssen-Cilag and Eisai have since introduced the drug in the U.K. under the trade name Pariet®, supplied as tablets, 10 and 20 mg (11).

1. Fujisaki, H., Oketani, K., Nagakawa, J., Takenaka, O., Yamanishi, Y. *Effects of rabeprazole, a gastric proton pump inhibitor, on biliary and hepatic lysosomal enzymes in rats*. Jpn J Pharmacol 1998, 76(3): 279.

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8. Williams, M., Sercombe, J., Pounder, R.E. *Comparison of the effects of rabeprazole and omeprazole on 24-hour intragastric acidity and plasma gastrin concentration in healthy subjects*. 62nd Annu Sci Meet Amer Coll Gastroenterol (Nov 3-5, Chicago) 1997, Abst P371.

9. *Eisai files NDA for Aciphex, novel treatment for GERD and ulcers*. Prous Science Daily Essentials April 3, 1998.

10. *First European clearance for Eisai's Pariet*. Prous Science Daily Essentials June 11, 1998.

11. *E.U. approval granted for rabeprazole: Product launched in U.K.*. Prous Science Daily Essentials Oct 16, 1998.

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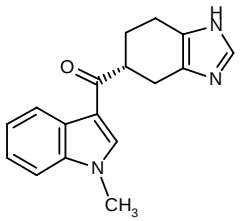
Ramosetron Hydrochloride
Nasea OD™
Nasea®

Antiemetic
Treatment of IBS
5-HT$_3$ Antagonist

EN: 164547



.HCl

$C_{17}H_{17}N_3O.HCl$ **Yamanouchi**

Nasea® OD, an orally disintegrating tablet formulation of ramosetron hydrochloride, has been launched for the first time in Japan. This novel formulation, which is designed to be taken without water, was developed based on the company's WOWTAB® technology (1).

1. *Yamanouchi introduces novel formulation of antiemetic drug*. Prous Science Daily Essentials Oct 20, 1998.

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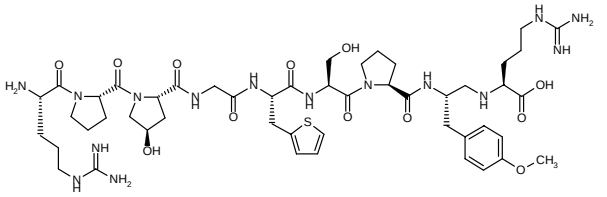
RMP-7

Absorption Promoter
Oncolytic

EN: 216365



$C_{49}H_{75}N_{15}O_{12}S$ **Alkermes; Alza**

Eighteen pediatric patients with refractory brain tumors participated in a phase I trial of intravenous RMP-7 and carboplatin. Overall, combination treatment was safe and well-tolerated with doses of RMP-7 up to 600 ng/kg ideal body weight. Of 14 evaluable patients, 2 had partial response and 4 stable disease. Based on these results, the recommended dose of RMP-7 for phase II studies in children is 600 ng/kg ideal body weight (1).

Intraarterial delivery of carboplatin (600 mg) with RMP-7 (300 ng/kg) in 50 patients with malignant glioma was found to be safe and well tolerated. One complete response, 4 partial responses and 25 cases of stable disease were observed. Median survival was 47 weeks for all subjects, while 6- and 12-month survivals were estimated to be 67 and 39%, respectively, for all subjects (2).

Alkermes' drug delivery technology, RMP-7™, is designed to improve the passage into the brain of pharmaceutical compounds by transiently increasing the permeability of the blood-brain barrier. The company has completed four phase II trials of RMP-7™ and carboplatin administered intravenously in patients whose brain tumor had recurred following surgery, radiotherapy and, in certain cases, chemotherapy, and has decided to proceed with phase III trials (3).

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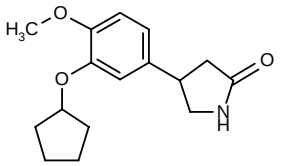
Rolipram
ZK-62711
ME-3167

Antidepressant
Treatment of IBD

EN: 107859



$C_{16}H_{21}NO_3$ **Schering AG; Meiji Seika**

Rolipram was studied in murine models of ongoing and established colitis. The drug was injected i.p. at a dose of 2 x 5 mg/kg/day. In ongoing colitis, rolipram reduced the clinical colitis score, as evaluated by weight loss, stool consistency and bleeding, as well as the histological score. The degree of inflammation was also reduced by rolipram as evaluated by colon length. In the established colitis model, rolipram-treated mice recovered more rapidly and showed reduced colonic inflammation (1).

Four-vessel occlusion for 20 min resulted in global cerebral ischemia in male Wistar rats. Six hours post-ischemia onset, rolipram (0.3 or 3.0 mg/kg i.p.) was administered for 7 days once daily. Four weeks later, neuronal density was measured. Untreated ischemic animals had 12 ± 6 intact neurons while those given rolipram at 0.3 mg or 3.0 mg/kg had 90 ± 23 or 22 ± 4, respectively. The expression of TNF-α and IL-1β in the CA1 sector had decreased. Thus, the decrease of ischemic neuronal damage produced by rolipram appears to be due to its capacity to reduce the synthesis of the cytokines TNF-α and IL-1β (2).

Inhibition of phosphodiesterase IV by rolipram and Ro-20-1724 produced a depression of neuronal transmission within the enteric nervous system as studied in a two-compartment bath containing the oral and the anal end of a segment of guinea pig ileum, respectively. The effect was possibly due to the release of noradrenaline acting at α_2-adrenoreceptors on enteric neurons. Phosphodiesterase I, III and V did not produce this effect (3).

PDEIII and PDEIV were reported to be two dominant classes of PDEs expressed in HL60 cells. The effects of PDE inhibitors on apoptosis in HL60 cells was studied. The nonspecific inhibitor IBMX and PDEIII specific inhibitors (milrinone and trequinsin) did not promote apoptosis which may result by increasing intracellular cAMP; moreover, both agents inhibited apoptosis induced by paclitaxel or thapsigargin. PDEIV specific inhibitors (rolipram and Ro-20-1724) promoted apoptosis within 5 h which is not likely due to increased cAMP level. These results suggested that rolipram and Ro-20-1724 promoted apoptosis in HL60 cells through cAMP-independent mechanism (4).

Rolipram *in vitro* reduced the numbers of myelin basic protein (MBP)-reactive IFN-γ and TNF-α mRNA expressing blood mononuclear cells (MNC) in multiple sclerosis patients. Blood MNC were cultured in the presence of MBP or acetylcholine receptor and with or without rolipram. *In situ* hybridization determined the number of blood MNC that expressed IFN-γ, TNF-α, LT, TGF-β, IL-4, IL-10 and mRNA. Rolipram decreased the numbers of MBP-reactive IFN-γ- and TNF-α mRNA-expressing blood MNC in multiple sclerosis and (for reference) of AChR-reactive IFN-γ-, TNF-α-, and LT mRNA-positive cells in myasthenia gravis. Th2 cell-related expression of IL-4, IL-10 and TGF-β was not affected. Thus, rolipram has a role in the treatment of diseases such as multiple sclerosis (5).

Oral administration of rolipram 10 mg/kg in adrenalectomized mice significantly reduced ovalbumin-induced eosinophilia in bronchoalveolar lavage and the airway hyperresponsiveness to metacholine, suggesting that adrenal-derived factors are involved in the inhibitory actions of rolipram in the pathogenesis of pulmonary eosinophilia and airway hyperresponsiveness (6).

Pentoxifylline and rolipram have been revealed as potent inhibitors of IL-12 and IFN-γ production *in vitro*. *In vivo* efficacy was demonstrated whereby both agents inhibited IL-12 production by the peritoneal mononuclear cells of superantigen-treated mice. In addition, both drugs effectively prevented insulitis and diabetes in NOD mice (7).

Rolipram was compared to methylprednisolone for the treatment of experimental TNBS-induced colitis in rats. Animals were treated from day 7 after TNBS administration at doses of 10 mg/kg p.o. for rolipram and 5 mg/kg i.m. for methylprednisolone. Eicosanoid release was significantly lower in rolipram- and steroid-treated rats as compared to placebo-treated animals, and myeloperoxidase activity was also significantly lower in these animals than in controls. Rolipram significantly reduced colonic lesion scores and tissue collagen content as compared to both steroid and no treatment. TNF-α levels in colonic tissue were significantly reduced by both active treatments, whereas TGF1β was only reduced by rolipram. The results from the study indicate that rolipram is able to improve the course of chronic colitis and is more effective than steroids in preventing collagen deposition (8).

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S-16020-2

Oncolytic Alkaloid
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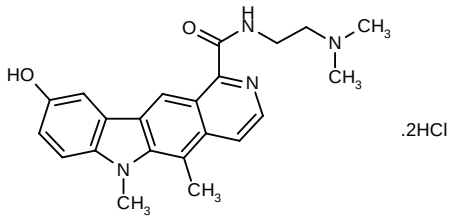
EN: 210038



$C_{22}H_{24}N_4O_2.2HCl$ **Servier**

The accumulation of S-16020-2 was investigated in P-glycoprotein (Pgp)-overexpressing cells. The compound was effectively transported by Pgp overexpressed by KB-A1 cells with efficiency being near that of adriamycin. Similar results were observed with the P388/VCR-20 cell line. The starting rate of uptake and the accumulation of S-16020-2 were significantly higher than those of adriamycin in the studied cell lines. The cytotoxic potency of S-16020-2 on tumor cells overexpressing Pgp was probably due to its quick rate of uptake that bypasses Pgp and causes high cellular accumulation (1).

DNA topoisomerase II most likely serves as the cellular target in the cytotoxicity mechanism of S-16020-2. An interaction study of S-16020-2 and DNA demonstrated that it binds by intercalation between adjacent DNA base pairs causing a 10-degree unwinding of the double helix. Its DNA affinity was equivalent to that of 2-methyl-9-hydroxy-ellipticinium (NMHE). The catalytic cycle of DNA topoisomerase I was not interfered with by S-16020-2 although it did induce DNA topoisomerase II-mediated DNA cleavage by an ATP-dependent mechanism. Both S-16020-2 and NMHE show similar interactions with DNA topoisomerase II *in vitro* as well as the same DNA sequence specificity and biphasic dose-effect response; neither constrained the rate of DNA religation. However, S-16020-2 stimulated topoisomerase II-mediated DNA strand breaks at concentrations 500-fold lower than NMHE (2).

The potent antitumor activity observed during preclinical testing of S-16020-2 in a panel of human renal cancer xenografts implanted subcutaneously in nude mice indicated that phase II testing is warranted (3).

The effect of incubation time and concentration on the activity of S-16020 was tested on 7 human tumor cell lines (mouth, ovary and kidney) with 2 cell lines resistant to topoisomerase II inhibitors. Doxorubicin was used as a reference agent. Findings indicate time-schedule independence in all tested cell lines. IC_{50} and $IC_{50\text{-}1h}/IC_{50\text{-}24h}$ ratio values distribution had somewhat different profiles depending on the tested cell line (4).

The antitumor activity of S-16020-2 was evaluated in a phase I trial in 28 patients with breast, head and neck, gastrointestinal or other tumors. In addition to skin toxicity, which was controlled with methylprednisolone, the side effects produced by S-16020-2 (30-150 mg/m^2 by 1-h i.v. infusion every 3 weeks) were mild and manageable and included nausea and vomiting, headache, diarrhea and pain at the tumor site. Severe acne at the highest dose was the dose-limiting adverse effect. One partial response and 5 cases of symptomatic improvement were obtained in this patient group (5).

In a phase I clinical trial, 21 patients were given a 1-h i.v. infusion of S-16020 every 3 weeks to define its maximum tolerated dose (MTD) and pharmacokinetics (PK). No renal, hepatic, immune reactions or alopecia were registered. Pre- and postmedication with methyl prednisolone relieved acute maculopapular, hidradenitis-related skin rash. The MTD was 150 mg/m^2 with acne lesions being the DLT (6).

The pharmacokinetics and metabolism of S-16020 were determined in advanced stage cancer patients. One hour infusions were administered on a 3-weekly schedule with doses ranging from 30-150 mg/m^2. Plasma levels of S-16020 generally declined biphasically with a terminal half-life of 4 h. High plasma clearance, mainly metabolic, decreased with dose suggesting non-linear pharmacokinetics. Blood levels were generally higher than plasma. The volume of distribution was large. Metabolic analysis showed quantifiable *N*-demethylated S-16018 in plasma and urine. The methylated S-16016 was occasionally

noted in urine. S-16020, according to mass spectral analysis, was metabolically cleared by direct glucoronidation and sulphation at the hydroxyl group, along with *N*-oxidation, *O*-methylation, cyclic hydroxylation and formation of the *N*-demethylation product (7).

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Sabcomeline Hydrochloride

SB-202026A *Cognition Enhancer*

Memric® *Muscarinic M_1 Agonist*

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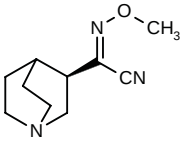

.HCl

$C_{10}H_{15}N_3O.ClH$ **SmithKline Beecham**

A new synthesis of sabcomeline hydrochloride has been described: The hydrolysis of quinuclidine-3-carboxylic acid ethyl ester (I) with refluxing aqueous HCl gives the corresponding acid (II), which by reaction with thionyl chloride in refluxing dichloromethane yields the expected acyl chloride (III). The reaction of (III) with *O*-methylhydroxylamine in chloroform/pyridine affords *N*-methoxyquinuclidine-3-carboxamide (IV), which by reaction with triphenylphosphine/CCl_4 in refluxing acetonirile is converted into the imidoyl chloride (V). The reaction of (V) with NaCN in hot DMSO gives 2-(methoxyimino)-2-(3-quinuclidinyl)acetonitrile (VI) as a mixture of the (*E*)- and (*Z*)-isomers that is resolved by column chromatography yielding the (*Z*)-isomer (VII). Finally, this compound (VII) is submitted to optical resolution with (*R*)-(–)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate [(*R*)-(–)-BNHP] (1). Scheme 4.

A profile study of SB-202026, conducted on rodents, marmosets and humans, predicted cognition-enhancing activity at doses below those resulting in adverse events. SB-202026 displaced [^{3}H]-oxotremorine-M from muscarinic receptors in the rat brain and showed low affinity for cholinergic nicotinic receptors and other neuroreceptors. In cloned human muscarinic receptors, SB-202026 exhibited equal affinity in displacing [^{3}H]-quinuclidinyl benzilate from all muscarinic receptor subtypes. At low concentrations in functional models *in vivo*, SB-202026 effected maximal depolarization of the rat superior cervical ganglion (M_1)-mediated effect) but caused a lower maximal effect than oxotremorine-M on M_2-mediated release of ACh and carbachol on M_3-mediated smooth muscle contraction (guinea pig ileum) (2).

SmithKline Beecham has put development of sabcomeline hydrochloride on hold pending further decisions. The compound had reached phase III clinical development as a cognition enhancer (3).

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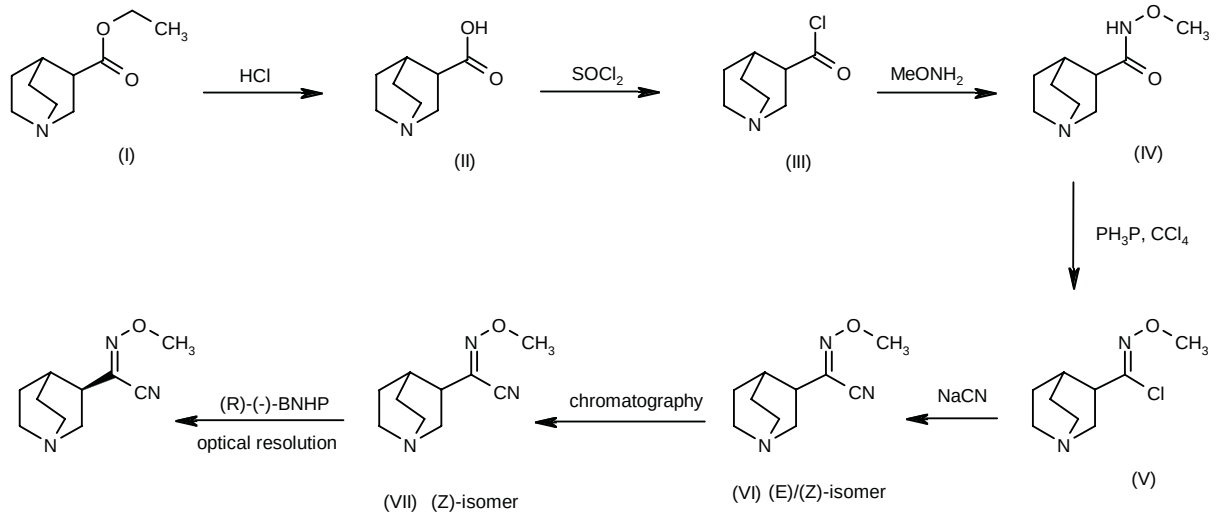
Scheme 4: Synthesis of Sabcomeline



Zaleplon
Sonata®

Sedative/Hypnotic

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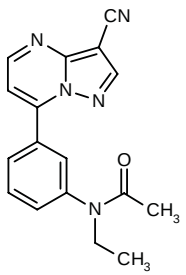

$C_{17}H_{15}N_5O$ **Wyeth-Ayerst**

The effects of zaleplon on melatonin secretion were studied *in vivo* and *in vitro*. Zaleplon stimulated melatonin secretion without stimulating benzodiazepine receptors, as seen *in vitro* in cultured rat pinealocytes (1).

Melatonin concentrations in rabbit plasma increased in a dose-dependent fashion 30 min after administration of zaleplon (1-2 mg/kg i.v.), in contrast to triazolam and zopiclone, neither of which affected plasma melatonin levels. Intracerebroventricular administration of melatonin (100 μg) elicited EEG patterns similar to those produced by i.v. administration of zaleplon (1 mg/kg) in conscious rabbits with chronically implanted electrodes, thus indicating that stimulation of melatonin secretion from the pineal gland may play an important role in the hypnotic activity of zaleplon (2).

Evaluation of the sedative effects of zaleplon and zolpidem, both administered at doses of 10 and 20 mg, showed that both compounds were more efficient than placebo, and that both doses of zolpidem were more effective than zaleplon at either dose (3).

The GABA-A benzodiazepine receptor agonist zaleplon was compared to flurazepam and placebo for next-day sedation following nighttime administration in healthy volunteers. Ninety-three healthy noninsomniac volunteers 18-45 years of age received 10 or 20 mg of zaleplon, 30 mg flurazepam or placebo. Whereas next-day sedation after both doses of zaleplon was not significantly different from placebo, flurazepam administration was associated with marked next-day sedation compared with both zaleplon and placebo. These results suggest a lack of effect of zaleplon on normal sleep architecture in healthy subjects (4).

A review of 19 clinical pharmacology studies on zaleplon found an excellent consistency among studies demonstrating the absence of significant cognitive impairment at the therapeutic dose and a good parallelism between the duration of effect and the pharmacokinetic parameters (5).

The residual effects on driving ability of zaleplon (10 and 20 mg) were compared to zopiclone (7.5 mg) and placebo when administered after evening and late at night. This crossover study included seven treatments. Although zopiclone severely affected driving, zaleplon did not impair driving if taken up to 5 h prior to driving in healthy subjects (6).

The rapid onset of action and short duration of action of zaleplon indicate that it may be effective when taken on an as-needed basis during nocturnal awakenings rather than at bedtime in anticipation of insomnia. Its potential for residual sedation was therefore evaluated and compared to flurazepam and placebo following administration

during a nocturnal awakening in patients with sleep maintenance insomnia. The trial was performed in 22 healthy sleep maintenance insomniacs who were awakened 3.5 h after lights out and maintained awake for 20 min until the administration of zaleplon 10 mg, flurazepam 30 mg or placebo. In contrast to flurazepam which induced significant residual sedation compared to placebo, zaleplon was not significantly different from placebo on any measure of residual sedation. The drug significantly decreased the latency to persistent sleep compared to placebo following awakening, whereas total sleep time did not differ between zaleplon or placebo. The incidence of side effects (14%) was similar to placebo (17%) and less than flurazepam (31%) (7).

The results from a phase III trial in patients with insomnia comparing zaleplon and zolpidem reported that zaleplon (20 mg) was significantly more effective than zolpidem (10 mg) in decreasing sleep latency (8).

The U.S. FDA has approved Zaleplon (Sonata™) for use as a hypnotic agent for the treatment of insomnia in adults (9, 10).

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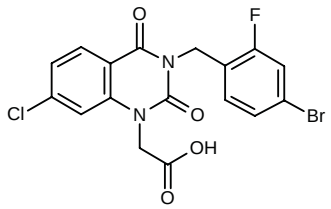
Symptomatic Antidiabetic

EN: 132922



$C_{17}H_{11}BrClFN_2O_4$ **Fujisawa; Warner-Lambert**

The effects of zenarestat on motor nerve conduction velocity (MNCV) and F wave conduction velocity was evaluated in a Zucker fatty rat model of noninsulin-dependent diabetes mellitus. Zenarastat (3.2 or 32 mg/kg/day p.o. for 8 weeks) dose-dependently reduced sciatic nerve sorbitol levels compared to control rats. At the highest dose, it significantly improved the reduction in MNCV and F wave conduction velocity without affecting body weight or plasma glucose levels (1).

The effects of aldose reductase inhibition by FK-366 on the metabolism of myo-inositol were evaluated in cultured bovine pericytes. The drug dose-dependently increased myo-inositol uptake and blocked glucose-induced changes in myo-inositol metabolism, indicating that FK-366 may ameliorate compromised pericyte function associated with diabetes (2).

1. Shimoshige, Y., Ikuma, K., Yamamoto, T., Takakura, S., Kawamura, I., Seki, J., Goto, T. *The effects of zenarestat, an aldose reductase inhibitor, on the nerve conduction velocity in Zucker diabetic fatty rats*. Jpn J Pharmacol 1998, 76(Suppl. 1): Abst O-236.

2. Mizutani, M., Yatoh, S., Asano, M., Yamashita, K., Okuda, Y. *The effect of high glucose and aldose reductase inhibitor (FK366) on myo-inositol uptake in cultured bovine pericyte*. Diabetes 1998, 47(Suppl. 1): Abst 1463.

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Additional Reference

Lee, Y.S. et al. *Molecular modeling studies of the binding modes of aldose reductase inhibitors at the active site of human aldose reductase*. Bioorg Med Chem 1998, 6(10): 1811.