Drugs of the Future 2001, 26(4): 395-427

CCC: 0377-8282/2001

Information Update

Volume 1-25, Number 4

Estimated developmental phase for this month's updated products:

Phase I

Curcumin (chemopreventive; Central Drug Res. Inst.)
E-1010 (carbapenem; Eisai)
E-5842 (antipsychotic, σ-receptor antagonist; Esteve)
Indirubin (oncolytic; Chin. Acad. Sci., Inst. Materia Medica)
TZT-1027 (oncolytic, microtubule inhibitor; Teikoku Hormone)

Phase II

Examorelin (growth hormone secretagogue; Europeptides, Mediolanum)
FK-888 (antimigraine; Fujisawa)
Lifibrol (hypolipidemic; Klinge, Merckle)
T-588 (cognition enhancer; Toyama)

Phase III

Anidulafungin (antifungal; Lilly, Versicor)
BMS-232632 (anti-HIV, HIV protease inhibitor; Bristol-Myers Squibb)
Repinotan hydrochloride (5-HT_{1A} agonist, neuronal injury inhibitor; Bayer)
S-4661 (carbapenem; Shionogi)
Tiazofurin (oncolytic; ICN)
Ziracin™ (everninomicin antibiotic; Schering/Plough)

Registered/Year

Perflenapent emulsion (ultrasound contrast agent; Sonus)/1998

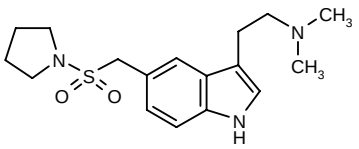
Launched/Year

Almotriptan (antimigraine; Almirall Prodesfarma, Lundbeck, Bayer, Pharmacia)/2000
Amprenavir (anti-HIV, HIV protease inhibitor; Vertex, GlaxoSmithKline, Kissei)/1999
Budesonide (antiallergy/antiasthmatic, treatment of IBD; AstraZeneca, Orion Corp.)/1981
Butorphanol tartrate (opioid analgesic; Bristol-Myers Squibb, Nastech)/1979
Capecitabine (oncolytic; Roche)/1998
Desloratadine (treatment of allergic rhinitis, treatment of urticaria; Sepracor, Schering-Plough)/2001
Dosmalfate (cytoprotectant; FAES)/2000
Exemestane (oncolytic; Pharmacia)/1999
Famciclovir (antiviral; GlaxoSmithKline, Novartis, Solvay)/1994
Ganirelix acetate (treatment of female infertility, GnRH antagonist; Roche, Organon)/2000
Lamivudine (anti-HBV, anti-HIB; BioChem Pharma, GlaxoSmithKline, Ajinomoto)/1995
Letrozole (oncolytic, aromatase inhibitor; Novartis, Chugai)/1996
Mycophenolate mofetil (immunosuppressant; Roche)/1995
Nelfinavir mesilate (anti-HIV, HIV protease inhibitor; Agouron, Roche, Japan Tobacco, Welfide)/1997
Pergolide mesylate (antiparkinsonian; Lilly, Athena Neurosciences, Draxis Health)/1989
Pramipexole hydrochloride (antiparkinsonian; Boehringer Ingelheim, Pharmacia)/1997
Sertraline (antidepressant, 5-HT reuptake inhibitor; Pfizer)/1990
Topiramate (antiepileptic, antimigraine, treatment of neurogenic pain; Janssen, Kyowa Hakko)/1995
Valrubicin (oncolytic; Anthra, Paladin, Celltech Medeva, Pharmaci)/1999
Virulizin(R) (oncolytic; Lorus Therapeutics, Faulding)/1997

Almotriptan
PNU-180638
LAS-31416
Axert®
Almogran®

Antimigraine

EN: 208489



$C_{17}H_{25}N_3O_2S$

Almirall Prodesfarma; Lundbeck; Bayer; Pharmacia

The activity of almotriptan was characterized in several animal models. Almotriptan increased carotid vascular resistance following i.v. or intraduodenal administration to anesthetized cats (ED_{100} = 11 μg/kg i.v.; ED_{50} = 339 μg/kg i.v.) or dogs (116 μg/kg i.v.). Further results from studies in cats showed that almotriptan selectively increased resistance of the carotid arteriovenous anastomoses with no effects on brain irrigation. Studies in guinea pigs revealed that the agent (0.3-3 mg/kg i.v.) inhibited electrical stimulation (trigeminal ganglion)-induced meningeal extravasation (1).

The activity of almotriptan was characterized in several models. The agent displayed low (nM) affinity for 5-HT_{1B} and 5-HT_{1D} receptors in humans and several species. Affinity of other types of 5-HT receptors was even less. For example, affinity for 5-HT_7 and 5-HT_{1A} receptors was about 40 and 60 times less, respectively, than the affinity observed for 5-$HT_{1B/1D}$ receptors. No affinity was observed for several non-5-HT receptors examined (adenosine A_1 and A_{2A}, angiotensin AT_1 and AT_2, histamine H_1 and H_2, dopamine D_1 and D_2, endothelin ET_A and ET_B, CGRP, muscarinic M_1, M_2 and M_3 and tachykinin NK_1, NK_2 and NK_3) at doses up to 100 μM. *In vitro* studies using HeLa cells transfected with human 5-HT_{1B} or 5-HT_{1D} receptors showed that almotriptan inhibited forskolin-stimulated cAMP accumulation with the same activity as that observed for serotonin. Almotriptan also dose-dependently induced contractions in isolated dog saphenous veins with an EC_{50} value of 394 nM. Similarly, infusion of the agent into porcine meningeal vasculature resulted in vasoconstriction. However, pig renal and rabbit renal and mesenteric arteries showed low responses to the agent at doses up to 100 μM (2).

A randomized, double-blind, placebo-controlled, single-dose study in 1013 patients showed the efficacy and safety of almotriptan (6.25 or 12.5 mg) in treating multiple migraine attacks. Results from the 722 evaluable patients indicated that the number of attacks relieved (*i.e.*, severe or moderate pain reduced to mild or no pain) was significantly higher at 2 h postdosing with almotriptan as compared to placebo (60 and 70% for the respective almotriptan doses *vs.* 38% for placebo). In addition, consistent intrapatient responses were obtained for at least 2 out of 3 attacks (64 and 75% *vs.* 36% in placebo). The agent was well tolerated with no significant difference in the incidence of adverse events observed between treated and placebo groups. The 12.5 mg dose was concluded to be the recommended dose (3).

Results from a 1-year open study conducted in 806 adults suffering from migraines with or without aura showed the efficacy and long-term safety of single-dose almotriptan (12.5 mg p.o.) as a treatment for moderate to severe migraine pain from consecutive migraine episodes. Treatment was well tolerated. At 2 h postdosing, 81% of the attacks were relieved and 56% of the subjects were pain-free. Approximately 50% of the patients developed at least 1 adverse event and 71% of all adverse events reported were not related to almotriptan. Eighty-seven percent of the adverse events experienced were mild or moderate and the most common were back pain (7.23%), bronchitis (5.76%) and influenza-like symptoms (5.62%) (4).

Almirall Prodesfarma has reported that almotriptan (Almogran®) is expected to be launched soon in Germany by commercialization partner Bayer pursuant to an agreement signed between the companies in February. This launch will be the fifth market for the drug following commercialization in Spain, the U.K., Finland and Denmark. In the near future, additional introductions are expected in Ireland, Norway and Sweden. Lundbeck holds commercialization rights to the product in Scandinavia and the U.K. On January 22, 2001, the EMEA approved Almogran® under the E.U.'s mutual recognition procedure and an NDA is undergoing review by the FDA in the U.S., where it will be marketed by licensee Pharmacia as Axert® (5, 6).

1. Gras, J., Bou, J., Llenas, J., Fernández, A.G., Palacios, J.M. *Functional profile of almotriptan in animal models predictive of antimigraine activity.* Eur J Pharmacol 2000, 410(1): 43.

2. Bou, J., Doménech, T., Puig, J., Heredia, A., Gras, J., Fernández-Forner, D., Beleta, J., Palacios, J.M. *Pharmacological characterization of almotriptan: An indolic 5-HT receptor agonist for the treatment of migraine.* Eur J Pharmacol 2000, 410(1): 33.

3. Pascual, J. et al. *Consistent efficacy and tolerability of almotriptan in the acute treatment of multiple migraine attacks: Results of a large, randomized, double-blind, placebo-controlled study.* Cephalalgia 2000, 20(6): 588.

4. Cabarrocas, X., Esbri, R., Peris, F., Ferrer, P. *Long-term efficacy and safety of oral almotriptan: Interim analysis of a 1-year open study.* Headache 2001, 41(1): 57.

5. *German launch of antimigraine Almogran imminent.* DailyDrugNews.com (Daily Essentials) March 29, 2001.

6. *Almogran granted wide approval in Europe for migraine.* DailyDrugNews.com (Daily Essentials) July 31, 2000.

Original monograph - Drugs Fut 1999, 24: 367.

Additional References

Boyce, M. et al. *Hemodynamic and electrocardiographic effects of almotriptan in healthy volunteers.* J Cardiovasc Pharmacol 2001, 37(3): 280.

Cabarrocas, X. et al. *Almotriptan: Consistency of response in the treatment of multiple migraine attacks.* Cephalalgia 2000, 20(4): Abst 99.

Cabarrocas, X. et al. *Tolerability and safety profile of almotriptan in the treatment of multiple migraine attacks: Results of a long-term study.* Cephalalgia 2000, 20(4): Abst 133.

Cabarrocas, X. et al. *Pharmacokinetics of oral almotriptan during and outside a migraine attack.* Cephalalgia 2000, 20(4): Abst 378.

Fleishaker, J.C. et al. *Effect of ketoconazole on the clearance of the antimigraine compound, almotriptan, in humans.* Clin Pharmacol Ther 2001, 69(2): Abst PI-96.

Fleishaker, J.C. et al. *Evaluation of the potential pharmacokinetic interaction between almotriptan and fluoxetine in healthy volunteers.* J Clin Pharmacol 2001, 41(2): 217.

Fleishaker, J.C. et al. *Pharmacokinetic interaction between verapamil and almotriptan in healthy volunteers.* Clin Pharmacol Ther 2000, 67(5): 498.

Gomez-Marcilla, B. et al. *A 6-month-open-label study of orally administered almotriptan in migraine patients.* Neurology 2000, 54(7, Suppl.3): Abst P04.010.

Martínez, E. et al. *Efficacy and safety of almotriptan in the treatment of migraine: A meta-analysis.* Cephalalgia 2000, 20(4): Abst 108.

Rabasseda, X. *Almotriptan in the treatment of migraine.* Drugs Today 2001, 37(1): 5.

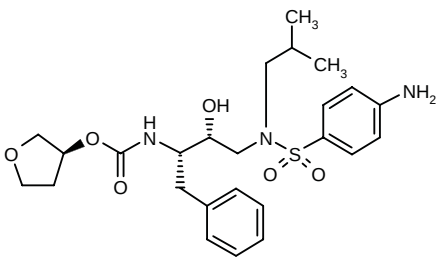
Sisson, T.A. et al. *Lack of interaction between propranolol and almotriptan in healthy volunteers.* Neurology 2000, 54(7, Suppl.3): Abst P04.009.

Spierings, E.L.H. et al. *Oral almotriptan versus oral sumatriptan in a double-blind, randomized, parallel-group study of quality of life and health economics in migraine patients.* Neurology 2000, 54(7, Suppl.3): Abst P04.002.

Amprenavir
Agenerase®
Prozei®

Anti-HIV
HIV Protease Inhibitor

EN: 205414



$C_{25}H_{35}N_3O_6S$ **Vertex; GlaxoSmithKline; Kissei**

Glaxo Wellcome has announced important changes to the labeling of Agenerase® (amprenavir) Oral Solution, a protease inhibitor indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents in patients four years of age and older. The changes in labeling reflect potential safety concerns associated with the large amount of the excipient propylene glycol contained in the oral solution. Propylene glycol is metabolized by the alcohol and aldehyde dehydrogenase enzyme pathway, but this pathway does not attain full adult activity until 12-30 months of age. In addition, certain patient subgroups may have more difficulty in metabolizing and eliminating propylene glycol. No reports of death or serious injury have been attributed to the propylene glycol in Agenerase®, but potential safety concerns have prompted a revision of the prescribing information for this product. Full details on the new labeling information can be found on the FDA's Web Site (1).

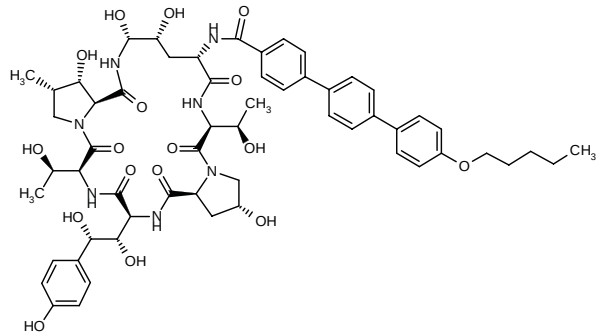
1. *Important labeling changes reported for Agenerase.* DailyDrugNews.com (Daily Essentials) May 18, 2000.

Original monograph - Drugs Fut 1996, 21: 347.

Anidulafungin
LY-303366
V-echinocandin

Antifungal

EN: 194685



$C_{58}H_{73}N_7O_{17}$ **Lilly; Versicor**

A study has reported that DBA/2 mice infected with pulmonary aspergillosis and pretreated with cortisone acetate suffered lethal toxicity following treatment with LY-303366 (12.5-50 mg/kg/day i.p.). Ninety percent of uninfected pretreated DBA/2 mice given 50 mg/kg LY-303366 died as compared to no deaths observed in nonpretreated, uninfected mice treated with LY-303366. Further analysis of glucocorticoid pretreatment in uninfected DBA/2 mice treated with LY-303366 (25 mg/kg/day i.p.) showed that hydrocortisone (1 or 2 times the equivalent cortisone dose), triamcinolone (1 or 5 times the cortisone dose) and cortisone (5 mg) all resulted in lethal toxicity; dexamethasone pretreatment did not increase lethality. In uninfected CD-1 mice treated with LY-303366 (25 mg/kg/day i.p.), only pretreatment with triamcinolone (5 times the cortisone dose) resulted in lethality with 3/5 mice dying 10 days after LY-303366 treatment. The

explanation for why DBA/2 mice are more sensitive is not known (1).

V-echinocandin has been examined for its efficacy and safety in experimental fluconazole-resistant oropharyngeal and esophageal candidiasis in immunosuppressed rabbits in comparison to amphotericin B and fluconazole. The rabbits received V-echinocandin at doses of 1, 2.5 or 5 mg/kg/day i.v., fluconazole 2 mg/kg/day i.v. or amphotericin B 0.3 mg/kg/day i.v. Significant, dose-dependent clearance of *Candida albicans* from tongue, oropharynx, esophagus, stomach and duodenum was seen on V-echinocandin, and it was more effective than the reference antifungal agents. This was consistent with the concentration-dependent fungicidal activity of V-echinocandin seen *in vitro*. Concentrations of V-echinocandin in esophageal tissue, saliva and plasma were proportional to dose, and in contrast to amphotericin B and fluconazole, concentrations equivalent to or exceeding the MIC values for *C. albicans* isolates were detected in both esophageal tissue and saliva. In terms of safety, no effects were seen on serum creatinine, serum potassium, transaminases or bilirubin. V-echinocandin and related compounds thus appear to represent a major advance in the treatment of esophageal candidiasis, a common opportunistic infection in immunocompromised patients such as those positive for HIV, and further clinical evaluation is recommended (2).

Promising results from a phase II trial of the novel antifungal compound V-echinocandin have been presented. The echinocandins, in development for the treatment of serious, life-threatening systemic infections, are the first new class of antifungal agents in several decades and act as fungicidal drugs rather than just inhibiting fungal cell growth. In the randomized, open-label phase II trial, 36 patients with esophageal candidiasis were given V-echinocandin i.v. as a 50-mg loading dose followed by 25 mg/day, or a 70-mg loading dose followed by 35 mg/day, for a maximum of 14-21 days. Of the 29 evaluable patients, clinical improvement according to endoscopic findings was obtained in 81% on the 50/25 mg regimen and in 85% on the 70/35 mg regimen. No drug-related adverse events were reported (3).

A double-blind, placebo-controlled trial was performed in healthy volunteers to determine optimal and maximum tolerated doses of V-echinocandin. One group received a loading dose of 100 mg on day 1 followed by 70 mg/day over 10 days, and the other group received a loading dose of 140 mg and maintenance doses of 100 mg/day. The 100/70 mg regimen was well tolerated. The higher dose regimen was considered to be the maximum tolerated dose, with 2 cases of grade 2 toxicity consisting of nausea, headache and epigastric pain (4).

Versicor has initiated a phase III trial to study the efficacy, safety and tolerability of V-echinocandin (anidulafungin) for the treatment of esophageal candidiasis. A total of approximately 450 patients in the U.S. and South Africa will be treated with a single daily intravenous infusion of V-echinocandin for up to 21 days. At the end of treatment, patients will be assessed by endoscopy. In the first arm, patients will be treated with V-echinocandin alone, and in the second arm, patients will be treated with fluconazole alone. A favorable response will be defined as either complete resolution (complete response) or a marked reduction in fungal lesions (partial response), measured by endoscopy. Stable, nonprogressive disease will be considered an unfavorable response (5).

1. Clemons, K.V., Sobel, R.A., Stevens, D.A. *Toxicity of LY303366, an echinocandin antifungal, in mice pretreated with glucocorticoids.* Antimicrob Agents Chemother 2000, 44(2): 378.

2. Petraitis, V., Petraitiene, R., Groll, A.H., Sein, T., Schaufele, R.L., Lyman, C.A., Francesconi, A., Bacher, J., Piscitelli, S.C., Walsh, T.J. *Dosage-dependent antifungal efficacy of V-echinocandin (LY303366) against experimental fluconazole-resistant oropharyngeal and esophageal candidiasis.* Antimicrob Agents Chemother 2001, 45(2): 471.

3. Brown, G.L., White, R.J., Turik, M. *Phase II, randomized, open label study of two intravenous dosing regimens of V-echinocandian in the treatment of esophageal candidiasis.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst J-1106.

4. Brown, G.L., White, R.J., Taubel, J. *Phase I dose optimization study for V-echinocandin.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst J-1105.

5. *Versicor begins phase III trial with V-echinocandin for treatment of esophageal candidiasis.* DailyDrugNews.com (Daily Essentials) March 23, 2001.

Original monograph - Drugs Fut 1994, 19: 338.

Additional References

Ernst, E.J. et al. *Postantifungal effects of echinocandin, azole, and polyene antifungal agents against Candida albicans and Cryptococcus neoformans.* Antimicrob Agents Chemother 2000, 44(4): 1108.

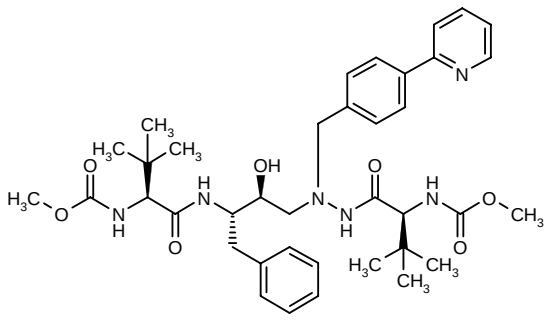
Rex, J.H. *Candins.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst 1123.

Stevens, D.A. *Drug interaction studies of a glucan synthase inhibitor (LY 303366) and a chitin synthase inhibitor (nikkomycin Z) for inhibition and killing of fungal pathogens.* Antimicrob Agents Chemother 2000, 44(9): 2547.

BMS-232632
CGP-73547

Anti-HIV
HIV Protease Inhibitor

EN: 257722



$C_{38}H_{52}N_6O_7$

Bristol-Myers Squibb

The *in vitro* activity of BMS-232632 was examined against 58 clinical HIV-1 isolates resistant to currently used protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir or saquinavir). The resistance profile of BMS-232632 was unique as compared to the other protease inhibitors. Sensitivity to BMS-232632 was generally maintained in those isolates resistant to 1 or 2 other protease inhibitors. However, those isolates highly resistant to more than 3 protease inhibitors and carrying a significant number of amino acid substitutions showed a decrease in sensitivity to BMS-232632. No mutational pattern could be related to BMS-2326932 resistance (1).

In vitro studies of BMS-232632 have shown that the drug has generally greater potency than the 5 currently approved HIV-1 protease inhibitors against a variety of HIV-1 strains, with EC_{50} and EC_{90} values of 2.6-5.3 nM and 9-15 nM, respectively. The drug was found to be highly selective for HIV-1 protease and did not exhibit cytotoxicity at concentrations needed for anti-HIV activity. In 2-drug combination studies in HIV-infected peripheral blood mononuclear cells, the addition of BMS-232632 to each of 9 other antiretrovirals resulted in additive to moderately synergistic antiviral effects. At the highest concentrations used for antiviral evaluation, none of the 2-drug combinations resulted in antagonistic antiviral activity or enhanced cytotoxic effects (2).

The resistance profile of BMS-232632 was reported following *in vitro* passage of the agent with HIV-1 RF. Resistant variants were selected more slowly with BMS-232632 as compared to nelfinavir and ritonavir. A N88S substitution in the viral protease was seen in 2 of 3 BMS-232632 resistant strains and an I184V change was noted in the third strain; other mutations were seen at the protease cleavage sites. BMS-232632-resistant strains continued to be sensitive to saquinavir and displayed different levels of cross-resistance with nelfinavir, indinavir, ritonavir and amprenavir (0.1- to 71-fold decrease in sensitivity). Those strains resistant to nelfinavir, saquinavir and amprenavir remained sensitive to BMS-232632. However, the strains resistant to indinavir and ritonavir showed 6- to 9-fold changes in BMS-232632 sensitivity (3).

BMS-232632 appears to have potential as the first protease inhibitor that can be used as once-daily monotherapy, according to preclinical activity and pharmacokinetic data. Its resistance profile has now been examined and compared to other protease inhibitors. Over 60 HIV-1 clinical isolates with various resistance profiles and genotypic patterns were tested for sensitivity to BMS-232632, amprenavir, indinavir, nelfinavir, ritonavir and saquinavir. BMS-232632 exhibited a resistance profile different from that of all the other protease inhibitors and loss of sensitivity to this inhibitor was correlated with high-level crossresistance to 3 or more protease inhibitors and the presence of several mutations (4).

An open-label trial conducted in 15 healthy subjects showed that concomitant ketoconazole (200 mg once daily on days 7-13) had no clinically significant effects on the pharmacokinetics of BMS-232632 (400 mg once daily on days 1-13). C_{max}, t_{max}, AUC_{τ} and $t_{1/2}$ values for BMS-232632 alone and in combination with ketoconazole (respectively) were: 5225.9 and 5145.8 ng/ml, 2.5 and 2.3 h, 28225.2 and 31054.5 ng·h/ml and 8 and 8.9 h (5).

The interaction between BMS-232632 and ritonavir was evaluated in healthy volunteers. In this open-label study, subjects were given BMS-232632 at doses of 200 or 400 mg once daily for 6 days followed by the addition of ritonavir 100 or 200 mg once daily starting on day 7. The results showed that coadministration of the two drugs led to increased exposure to BMS-232632, in the absence of serious adverse events or laboratory abnormalities (6).

A study conducted in 53 healthy subjects given BMS-232632 examined the effect of the uridine diphosphate-glucuronosyl transferase (UDP-GT) 1A1 genotype on bilirubin elevations. Those subjects with at least 1 allele 7 (*i.e.*, 6/7 or 7/7), which indicates decreased enzyme activity, had a significantly greater increase in bilirubin levels as compared to subjects with a normal genotype (6/6) (7).

A randomized, comparator (nelfinavir) trial conducted in 29 protease inhibitor-naive HIV positive patients examined the efficacy and pharmacokinetics of BMS-232632 (200, 400 and 500 mg once daily) as a monotherapy for 2 weeks followed by combination therapy with 2 other nucleosides. The AUC_{∞} values on day 1 for the 3 dose groups were 3627 ± 3423, 7980 ± 8785 and 4454 ± 4347 ng·h/ml, respectively, and the AUC_{τ} values on day 29 were 7862 ± 12543, 14187 ± 6478 and 16802 ± 11706 ng·h/ml, respectively. C_{max} and $t_{1/2}$ values on day 29 were 1488 ± 2493, 2542 ± 1188 and 3310 ± 2105 ng/ml, respectively, and 4.87 ± 1.33, 6.10 ± 1.84 and 5.81 ± 2.61 h, respectively. Although no significant differences were noted between dose groups, a significant change in HIV RNA between baseline and day 15 and 29 of 1.342 and 1.85 log copies, respectively, was observed (8).

An ongoing, 2-stage phase II multicenter, randomized trial in 300 antiretroviral therapy-naive HIV-infected subjects (HIV RNA ≥ 2000 copies/ml) is comparing the safety and efficacy of BMS-232632 (200, 400 and 500 mg once daily) with nelfinavir (750 mg t.i.d.) as monotherapies (for 2 weeks) and in combination with ddI and d4T for 24 weeks. After 12 weeks, this first stage (stage I) was followed by randomization of subjects into a second, 48-week stage (stage II) of the trial to further examine the safety and efficacy of the treatments. To date, 92 subjects have completed 24 weeks of stage I with results showing BMS-232632 to be safe and well tolerated alone and in combination. A decrease in RNA HIV of about 1.5 $\log_{10}$ copies/ml was observed with monotherapy. The percentage of patients in the 200, 400 and 500 mg BMS-232632 dose groups and the nelfinavir group with HIV RNA levels of < 400 copies/ml were 52, 52, 65 and 67% and the percentage with levels of < 50 copies/ml were 33, 20, 35 and 38%, respectively. The most common adverse events for the BMS-232632 and nelfinavir groups were diarrhea (29 *vs.* 75%, respectively), mild infection and nausea (24 *vs.* 15%). Dose-dependent grade 1-2 elevated levels of

unconjugated bilirubin were more often seen in patients given BMS-232632 (62%) (9).

BMS-232632 has demonstrated excellent antiviral activity and the potential for once-daily dosing according to results from a phase II trial in antiretroviral-naive HIV-infected patients. This randomized trial involved a 2-week comparison of three different doses of BMS-232632 and nelfinavir (750 mg t.i.d.) as monotherapy, followed by their combination with didanosine and stavudine. In all treatment groups, a significant proportion of patients with HIV RNA below 400 copies/ml and 50 copies/ml was seen at 12 and 24 weeks; of those treated with a dose of BMS-232632 of 400 mg once daily, 70% had < 400 copies/ml and 31% had < 50 copies/ml at 12 weeks. All treatment groups also showed increases in CD4+ cell counts. BMS-232632 was well tolerated as both monotherapy and in combination with other antiretroviral agents, the most frequent adverse events or laboratory abnormalities consisting of diarrhea, infection, nausea and asymptomatic hyperbilirubinemia. In contrast to nelfinavir, BMS-232632 treatment was not associated with significant increases in cholesterol, LDL cholesterol or triglyceride levels. Once-daily BMS-232632 appears to be safe and effective in combination regimens (10).

1. Colonno, R.J. et al. *Efficacy of BMS-232632 against a panel of HIV-1 clinical isolates resistant to currently used protease inhibitors.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst I-2114.

2. Robinson, B.S., Riccardi, K.A., Gong, Y.-F. et al. *BMS-232632, a highly potent human immunodeficiency virus protease inhibitor that can be used in combination with other available antiretroviral agents.* Antimicrob Agents Chemother 2000, 44(8): 2093.

3. Gong, Y.-F., Robinson, B.S., Rose, R.E., Deminie, C., Spicer, T.P., Stock, D., Colonno, R.J., Lin, P.-F. *In vitro resistance profile of the human immunodeficiency virus type 1 protease inhibitor BMS-232632.* Antimicrob Agents Chemother 2000, 44(9): 2319.

4. Colonno, R.J., Hertogs, K., Larder, B.A., Limoli, K., Heilek-Snyder, G., Parkin, N. *BMS-232632 sensitivity of a panel of HIV-1 clinical isolates resistant to one or more approved protease inhibitors.* Antivir Ther 2000, 5(Suppl. 3): Abst 8.

5. O'Mara, E.M., Randall, D., Mummaneni, V., Uderman, H., Knox, L., Schuster, A., Geraldes, M., Raymond, R. *Steady-state pharmacokinetic interaction study between BMS-232632 and ketoconazole in healthy subjects.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst I-1646.

6. O'Mara, E. et al. *Steady-state pharmacokinetic interaction study between BMS-232632 and ritonavir in healthy subjects.* 8th Conf Retroviruses Opportunistic Infect (Feb 4-8, Chicago) 2001, Abst 740.

7. O'Mara, E.M. et al. *Assessment of the effect of uridine diphosphate-glucuronosyl transferase (UDP-GT) 1A1 genotype on indirect bilirubin elevations in healthy subjects dosed with BMS-232632.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst L-13.

8. O'Mara, E. et al. *A preliminary pharmacokinetic and pharmacodynamic evaluation of the HIV protease inhibitor BMS-232632 in a protease inhibitor-naive HIV+ population.* AIDS 2000, 14(Suppl. 4): Abst P9.

9. Piliero, P.J. et al. *BMS-232632 - Clinical trial AI424-007: Safety, efficacy of a once-daily protease inhibitor at 24 weeks.* AIDS 2000, 14(Suppl. 4): Abst PL6.6.

10. Squires, K., Gatell, J., Piliero, P., Sanne, I., Wood, R., Schnittman, S.M. *AI424-007: 48-Week safety and efficacy results from a phase II study of a once-daily HIV-1 protease inhibitor (PI), BMS-232632.* 8th Conf Retroviruses Opportunistic Infect (Feb 4-8, Chicago) 2001, Abst 15.

Original monograph - Drugs Fut 1999, 24: 375.

Additional References

Drusano, G.L. et al. *Hollow-fiber unit evaluation of a new human immunodeficiency virus type 1 protease inhibitor, BMS-232632, for determination of the linked pharmacodynamic variable.* J Infect Dis 2001, 183(7): 1126.

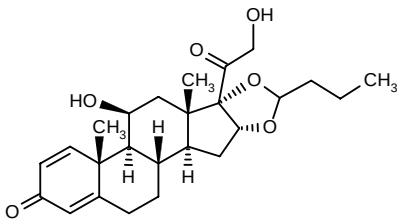
O'Mara, E.M. et al. *Relationship between uridine diphosphate-glucuronosyl transferase (UDP-GT) 1A1 genotype and total bilirubin elevations in healthy subjects receiving BMS-232632 and saquinavir.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst I-1645.

Sanne, I. et al. *Safety and antiviral efficacy of a once-daily HIV-1 protease inhibitor BMS-232632: 24 Week results from a phase II clinical trial.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst I-691.

Budesonide
Pulmicort Respules®
Entocort®

Antiallergy/Antiasthmatic
Treatment of IBD

EN: 091057



$C_{25}H_{34}O_6$ **AstraZeneca; Orion Corp.**

The FDA has approved AstraZeneca's Pulmicort Respules™ (budesonide inhalation suspension) for the treatment of asthma in children aged 1-8 years. Pulmicort Respules™ is the first inhaled corticosteroid to be approved for use in children under 4 years of age. Approval of Pulmicort Respules™ was based on 3 randomized, double-blind, 12-week U.S. studies of the product in nearly 950 children 1-8 years of age with mild to moderate persistant asthma. The product reduced the need for bronchodilators and improved the control of nighttime and daytime asthma symptoms. Improvement in asthma control can occur as early as 2 weeks after initiating therapy, although maximum benefit is not generally reached until 4-6 weeks after starting treatment. Pulmicort Respules™ is not indicated for the relief of acute bronchospasm or other acute episodes of asthma,

and children using the product should avoid exposure to chicken pox or measles (1).

An NDA for the budesonide Easyhaler for use in the prevention of the symptoms of asthmatic inflammation is currently under review in Germany (2).

The FDA has granted priority review status for AstraZeneca's Entocort® (budesonide modified-release capsules) NDA for the treatment of mild to moderate active Crohn's disease. The application was submitted to the FDA on January 24, 2001 (3).

1. *Pulmicort Respules approved in U.S. for children aged 1 to 8 years.* DailyDrugNews.com (Daily Essentials) Aug 9, 2000.

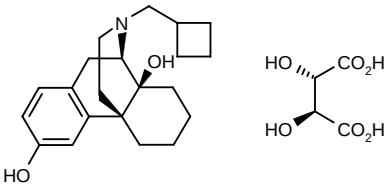
2. *Orion product update reported.* DailyDrugNews.com (Daily Essentials) March 21, 2001.

3. *FDA grants priority review status for Entocort modified-release capsules.* DailyDrugNews.com (Daily Essentials) April 2, 2001.

Original monograph - Drugs Fut 1980, 5: 179.

Butorphanol Tartrate *Opioid Analgesic*
Stadol NS®

EN: 091356



$C_{21}H_{29}NO_2.C_4H_6O_6$ **Bristol-Myers Squibb; Nastech**

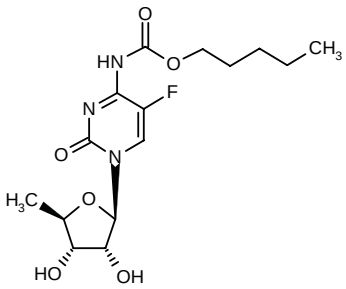
Nastech has announced the results of pilot phase I studies of an intranasal formulation that improves the nasal absorption of butorphanol tartrate, the active ingredient in Stadol NS®. The new formulation is primarily targeted to provide relief from acute migraine pain faster than Stadol NS®, and possibly reduce its side effects. Nastech plans to initiate and complete pilot phase II clinical efficacy studies of the new formulation this year. Stadol NS®, licensed by Nastech to Bristol-Myers Squibb, is the only FDA-approved opioid nasal product indicated for moderate to severe pain, including acute migraine. Nastech has filed patent applications to protect its proprietary position and is seeking a licensing partner to jointly develop and market the improved product (1).

1. *Nastech reports pilot phase I trial results for new formulation of butorphanol.* DailyDrugNews.com (Daily Essentials).

Original monograph - Drugs Fut 1977, 2: 231.

Capecitabine *Oncolytic*
Xeloda®

EN: 211639



$C_{15}H_{22}FN_3O_6$ **Roche**

The efficacy and tolerability of oral capecitabine was shown in a study in 19 pretreated patients (taxanes and/or anthracyclines; median treatments = 3) with metastatic breast cancer. No grade 3 or 4 hematological toxicities were observed. All 19 patients developed grade 1 palmar-plantar-erythrodysesthesia (PPE), of whom 16 developed grade 2 or 3 PPE. One case of severe grade 3 diarrhea was seen. The maximum toxicity was seen during the second treatment course and required dose reductions and increased treatment interval. Partial responses and stable disease were seen in 26 and 32% of the patients, respectively. Median times to progression for all patients and for those showing a partial responses were 16 and 28 weeks, respectively (1).

A marketing application for capecitabine (Xeloda®) was filed by Nippon Roche in mid-January 2001 (2).

The European Commission has granted marketing authorization for capecitabine tablets (Xeloda®) for the treatment of metastatic colorectal cancer. The approval was based on the results of phase III clinical trials involving more than 1200 patients worldwide. The multicenter trials compared the safety and efficacy of oral capecitabine with 5-fluorouracil and leucovorin (5-FU/LV) as first-line treatment for metastatic colorectal cancer. Results from the study demonstrate that capecitabine was associated with a significantly superior tumor response rate compared to the Mayo Clinic regimen (intravenous bolus 5-FU/LV; 26% *vs.* 17%). Data also demonstrated that capecitabine had substantial safety advantages compared to i.v. bolus 5-FU/LV. In addition to the E.U., Xeloda® is available in New Zealand and was recently approved in Canada, Australia and Switzerland, among other countries, for metastatic colorectal cancer (3, 4).

Roche has submitted a supplemental New Drug Application (sNDA) to the FDA for capecitabine in combination with docetaxel. The new combination is indicated for the treatment of women with locally and/or metastatic breast cancer in whom prior anthracycline chemotherapy has failed. The capecitabine/docetaxel combination is the first combination chemotherapy to show significantly

superior survival compared to docetaxel alone. The sNDA is supported by phase III trial results of capecitabine in combination with docetaxel compared to docetaxel alone. Patients receiving the drug combination experienced a 25% reduction in the risk of death when compared to women treated with docetaxel alone. In addition, women in the combination group demonstrated superior improvements in both time to progression (6 months *vs.* 4 months) and tumor response rates (42% *vs.* 30%). The study, conducted in the U.S., Australia, Europe, Asia and Latin America, involved 511 women with metastatic breast cancer previously treated with anthracycline therapy (5).

Roche has submitted an application to the European authorities for the use of capecitabine (Xeloda®) in combination with docetaxel. The application was supported by results from a major clinical trial in Europe, the U.S., Canada, Australia, Asia and Latin America involving women with advanced breast cancer previously treated with anthracycline. Roche has also submitted an application for capecitabine monotherapy for metastatic breast cancer in the E.U. At present, the drug is approved as monotherapy for metastatic breast cancer in more than 53 countries worldwide (6).

1. Robner, D., Lück, H.-J., Scholz, U., Canzler, U., Böhmer, G., Langer-Nitsche, C., Hollwitz, B., Kühnle, H. *Capecitabine in pretreated patients (pts) with metastatic breast cancer (MBC).* 10th Int Congr Anti-Cancer Treat (Jan 31-Feb 3, Paris) 2000, Abst P030.

2. *Roche highlights recent achievements in Japan.* DailyDrugNews.com (Daily Essentials) Jan 24, 2001.

3. *Xeloda approved in New Zealand as treatment for colorectal cancer.* DailyDrugNews.com (Daily Essentials) June 16, 2000.

4. *First oral chemotherapy for treatment of metastatic colorectal cancer approved in Europe.* DailyDrugNews.com (Daily Essentials) Feb 12, 2001.

5. *Roche seeks FDA approval for Xeloda/Taxotere combination for the treatment of breast cancer.* DailyDrugNews.com (Daily Essentials) March 9, 2001.

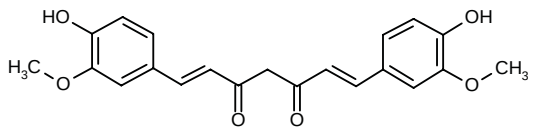
6. *Roche files for E.U. approval of Xeloda/Taxotere combination for treatment of breast cancer.* DailyDrugNews.com (Daily Essentials) April 11, 2001.

Original monograph - Drugs Fut 1996, 21: 358.

Curcumin

Chemopreventive

EN: 119974



$C_{21}H_{20}O_6$ **Central Drug Res. Inst. (IN)**

An *in vitro* study showed the antitumor effects of curcumin and resveratrol against human stage IV neuroblastoma cell lines (NUB-7 and LAN-5). Treatment with either agent (up to 100 μM for 48 h) resulted in apoptotic changes including dose-dependent cell rounding, detachment and fragmentation. Cell viability was also dose-dependently decreased with treatments and this effect was more marked when cells were treated (25 μM) for 4 days (reductions of 85 and 81% in NUB-7 and 93 and 90% in LAN-5 cells for curcumin and resveratrol, respectively). Doses of 50 μM also significantly reduced cell number and viability. Curcumin and resveratrol were found to block cells in the G_2/M and S phases, respectively. Treatment with either agent for 48 h also resulted in translocation of p53 to the nucleus, a process that is impaired in neuroblastoma cells. Results indicate that the cytotoxicity induced by the agents is mediated by a p53-dependent mechanism (1).

An *in vitro* study using human breast cell lines (HBL100, T47D and MDA468) showed that both EGCG (5-10 μM) and curcumin (5-10 μM) inhibited cell growth. EGCG dose-dependently inhibited ornithine decarboxylase activity in HBL100 cells with maximum effects observed at a concentration of 50 μM. Curcumin (40 μM) pretreatment inhibited epidermal growth factor (EGF) receptor phosphorylation by 70% in MDA468 and HBL100 cells and ERK phosphorylation in HBL100 and T47D cells by about 75%; 80 μM curcumin inhibited ERK phosphorylation in MDA468 cells. Pretreatment with EGCG (up to 50 μM) had no effects on these pathways. Curcumin pretreatment also dose-dependently inhibited (60-85%) c-jun terminal kinase (JNK) but had no effects on p38. In contrast, these kinases were inhibited by EGCG when the agent was added directly to the assay and not administered as a pretreatment (2).

An *in vitro* study using colon tumor cells showed that curcumin inhibited growth (IC_{50} = about 5 μM) and IκB kinase activity (IC_{50} = about 5 μM) and downregulated cyclin D1. COX-2 levels were not affected by curcumin treatment. The inhibitory effects on cell growth were determined to be partly due to induction of cell death via chromatin condensation and micronucleation; no DNA laddering was observed (3).

A study examining the spectral and photophysical properties of curcumin and curcuminoids showed that the agents are markedly affected by solvent, water and pH. As the concentration of water increased or when solvent pH was decreased from neutral to acidic (< pH 1.5) or increased from neutral to basic (> than pH 8), the fluorescent intensity of curcumin and dimethylated curcumin decreased (4).

The metabolism and bioavailability of single-dose curcumin administered i.v. (10 and 40 mg/kg) and p.o. (0.5 and 2.5 g/kg) were examined in a study using rats. Curcumin could not be detected in plasma 30 min post i.v. dosing and only trace amounts were found following oral dosing. Metabolites identified in plasma following i.v. dosing were tetrahydrocurcumin (THC), hexahydrocurcumin (HHC), hexahydrocurcuminol (HHCO), curcumin sul-

phate and curcumin glucuronide; in contrast, only the conjugates of curcumin were detected in plasma after oral dosing. *In vitro* studies using rat and human hepatocytes showed that curcumin (100 μM for 1-2 h) was metabolized to THC, HHC and HHCO with only small amounts of the sulphate and glucuronide conjugates seen. Results indicate that the systemic bioavailability of the agent is poor and that the metabolites of the agent may be involved in its pharmacological activity (5).

A study examined the metabolism and disposition of curcumin in rats, isolated human and rat hepatocytes and cellular fractions of human intestine. Administration of the agent i.v. (40 mg/kg) resulted in rapid metabolism of the agent to THC, HHC, HHCO, curcumin sulphate and curcumin glucuronide. Following intragastric administration (500 mg/kg), curcumin was detected in colonic scrapings (1.7 ± 0.9 nmol/g), liver (0.05 ± 0.01 nmol/kg) and plasma (0.03 ± 0.01 nmol/ml) and curcumin sulphate and glucuronide were found in plasma. Following oral administration of the agent in the diet (200-400 mg/kg), only curcumin was detected in plasma but at levels much less than those observed following intragastric administration. Curcumin was metabolized to THC, HHC and HHCO in rat and human hepatocytes; curcumin glucuronide and sulphate were minor metabolites and curcumin sulphate was detected in human gut cytosol (6).

A study in rats did not show any inhibitory effects of oral lycopene (45 ppm) or curcumin (500 ppm) on PhIP (100 mg/kg twice/week for 10 weeks)-induced prostatic cancer (7).

A study using neonatal rats showed that curcumin (10 mg/kg i.p. starting 48 h after birth) inhibited AOM (15 mg/kg s.c. once every 2 weeks starting 7 weeks from birth)-induced precancerous colonic lesions in adult animals (8).

Results from a study in rats showed that curcumin (200 mg/kg p.o.) prevented adriamycin-induced kidney injury. Treatment with the agent protected against adriamycin-induced proteinuria, albuminuria, hypoalbuminemia and hyperlipidemia. In addition, adriamycin-induced increases in urinary excretion of *N*-acetyl-β-D-glucosaminidase, fibronectin, glycosaminoglycan and plasma cholesterol were prevented. The glomerular filtration rate of curcumin-treated rats was increased, indicating restoration of renal function, and treatment also resulted in suppression of oxidative stress and kidney microsomal and mitochondrial lipid peroxidation and enhancement of kidney glutathione content and glutathione peroxidase activity (9).

A study using rats (7 weeks old) with *N*-nitroso-*N*-methylurea (50 mg/kg via the tail vein)-induced mammary tumors fed a diet containing 20% casein (C) or soy protein isolate (S) with or without curcumin showed that when curcumin was added to the diets, body weight gain was significantly reduced (40.1 ± 6 g for C and 49.2 ± 4.2 g for S) at 23 weeks of age as compared to rats fed the C (62 ± 2.7 g) and S (61.6 ± 4.4 g) diets without curcumin. No differences in food intake, tumor incidence or tumor multiplicity were observed between treatment groups (10).

A pharmacokinetic study in rats examined the effects of curcumin (2% dissolved in corn oil p.o. for 14 days) on some biomarkers associated with cancer chemoprevention (such as glutathione S-transferase [GST] and malondialdehyde-deoxyguanosine DNA adducts [M1G]) in colon epithelial scrapings, liver tissue and peripheral blood leukocytes. The unchanged compound was found in colon epithelium at concentrations 100-fold higher than those observed in liver tissue; curcumin could not be detected in plasma. Glucuronide and sulphate conjugates were detected only in colon epithelium. Higher levels of GST (860 ± 73 *vs.* 634 ± 66 nmol/min/mg protein) and significantly lower levels of M1G (43 ± 9 *vs.* 62 ± 6 adducts/10^8 bases) were observed in curcumin-treated rats as compared to controls. M1G was detected in liver tissue and leukocytes of control but not curcumin-treated animals. It was concluded that sufficient levels of curcumin were achieved in colon epithelium and liver to favorably change biomarker levels despite the low bioavailability of the agent (11).

1. Liontas, A., Yeger, H. *Curcumin and resveratrol exhibit antitumor effects in human neuroblastoma.* Proc Amer Assoc Cancer Res 2001, 42: Abst 1128.

2. Squires, M., Howells, L., Hudson, E.A., Dickens, M., Prigent, S.A., Manson, M.M. *Inhibition of cell signalling may contribute to the chemopreventive activity of curcumin and epigallocatechin-3 gallate.* Proc Amer Assoc Cancer Res 2000, 41: Abst 5374.

3. Plummer, S., Wakelin, D., Bouer, M., Shepherd, P., Howells, L., Gescher, A., Chow, S., Manson, M. *Inhibition of growth of colon tumour cells by curcumin correlates with inhibition of the IkappaB kinase and down regulation of cyclin D1.* Br J Cancer 2000, 83(Suppl. 1): Abst 4.10.

4. Bong, P.-H. *Spectral and photophysical behaviors of curcumin and curcuminoids.* Bull Korean Chem Soc 2000, 21(1): 81.

5. Ireson, C.R. et al. *Metabolism and bioavailability of the chemopreventive agent curcumin in rats.* Br J Cancer 2000, 83(Suppl. 1): Abst P211.

6. Ireson, R., Verschoyle, R.D., Orr, S. et al. *Disposition of the chemopreventive agent curcumin in rats and in human liver and gut cells.* Proc Amer Assoc Cancer Res 2001, 42: Abst 115.

7. Kato, K. et al. *Chemoprevention of PhIP-induced rat prostate carcinogenesis by lycopene and curcumin.* Jpn J Cancer Res 2000, 91(Suppl.): Abst 3900.

8. Kobayashi, H. et al. *Inhibition of AOM carcinogenesis in the colon by neonatal injection of curcumin.* Jpn J Cancer Res 2000, 91(Suppl.): Abst 2915.

9. Venkatesan, N., Punithavathi, D., Arumugam, V. *Curcumin prevents adriamycin nephrotoxicity in rats.* Br J Pharmacol 2000, 129(2): 231.

10. Vital, R., Imrhan, V., Radcliffe, J.D., Grossie, B., Czajka-Narins, D. *Curcumin has no effect on NMU-induced mammary tumors but reduces weight gain in rats.* FASEB J 2000, 14(4): Abst 498.12.

11. Sharma, R.A. et al. *Preclinical pharmacokinetic study of dietary curcumin and its effects on biomarkers of cancer chemoprevention.* Clin Cancer Res 2000, 6(Suppl.): Abst 103.

Original monograph - Drugs Fut 1987, 12: 331.

Additional References

Cheng, X. et al. *Curcumin cytotoxicity on cultured bladder cancer cells is not dependent on cyclooxygenase expression.* Proc Amer Assoc Cancer Res 2001, 42: Abst 2365.

Chuang, S.E. et al. *Curcumin-containing diet inhibits diethylnitrosamine-induced murine hepatocarcinogenesis.* Carcinogenesis 2000, 21(2): 331.

Chun, K.-S. et al. *Curcumin down-regulates phorbol ester-induced cyclooxygenase-2 and inducible nitric oxide synthase in mouse kin by blocking activation of p38 and NF-kappaB.* Proc Amer Assoc Cancer Res 2001, 42: Abst 3083.

Dorai, T. et al. *Therapeutic potential of curcumin in human prostate cancer - I. curcumin induces apoptosis in both androgen-dependent and androgen-independent prostate cancer cells.* Prostate Cancer Prostatic Dis 2000, 3(2): 84.

Gimenez-Conti, I.B. et al. *Chemopreventive effects of curcumin, green tea and fenretinide (4-HPR on BalphaP-induced hamster cheek pouch carcinogenesis.* Proc Amer Assoc Cancer Res 2001, 42: Abst 112.

Ireson, C. et al. *Characterization of metabolites of the chemopreventive agent curcumin in human and rat hepatocytes and in the rat in vivo, and evaluation of their ability to inhibit phorbol ester-induced prostaglandin E_2 production.* Cancer Res 2001, 61(3): 1058.

Jean, M. et al. *The effect of curcumin on pancreatic cancer.* Proc Amer Assoc Cancer Res 2001, 42: Abst 3537.

Kim, J.-H. et al. *Curcumin and structurally related diarylheptanoids suppress phorbol ester-induced COX-2 expression and NF-kappaB activation in mouse skin and MCF10A cells.* Proc Amer Assoc Cancer Res 2000, 41: Abst 3162.

Lal, B. et al. *Role of curcumin in idiopathic inflammatory orbital pseudotumours.* Phytother Res 2000, 14(6): 443.

Limtrakul, P. et al. *Effect of curcumin on level and distribution of TPA-induced PKC-epsilon in human keratinocytes.* FASEB J 2000, 14(8): Abst 1312.

Limtrakul, P. et al. *Effects of curcumin on P-glycoprotein expression in carcinoma of cervix cells (KB-carcinoma cell line) induced by vinblastine.* Proc Amer Assoc Cancer Res 2001, 42: Abst 4359.

Logan-Smith, M.J. et al. *Curcumin: A novel inhibitor of the calcium pump SERCA.* FASEB J 2000, 14(8): Abst 1503.

Masuda, T. et al. *A novel radical terminated compound produced in the antioxidation process of curcumin against oxidation of a fatty acid ester.* Tetrahedron Lett 2000, 41(13): 2157.

Orr, S. et al. *Curcumin metabolism and cytochrome P450 activity in human hepatocytes.* Proc Amer Assoc Cancer Res 2000, 41: Abst 2626.

Parveen, I., Threadgill, M.D. *Labelled compounds of interest as antitumour agents - VII. [^{2}H]- and [^{14}C]-curcumin.* J Label Compd Radiopharm 2000, 43(9): 883.

Piwocka, K. et al. *The involvement of glutathione, Bcl-2 protein and acidic nuclease in mitochondria-independent apoptosis-like pathway induced by curcumin.* Mitochondrial Dysfunct Pathogenesis (Jan 15-20, Santa Fe) 2000, Abst 233.

Plummer, S.M. et al. *Curcuminoids inhibit cyclooxygenase-mediated prostaglandin E_2 production and COX-2 expression in human blood.* Proc Amer Assoc Cancer Res 2001, 42: Abst 93.

Ramachandran, C. et al. *Inhibition of hTERT expression and telomerase activity by curcumin.* Proc Amer Assoc Cancer Res 2001, 42: Abst 3085.

Rao, C.V. et al. *Modulation of inducible nitric oxide synthase and cyclooxygenase activities by curcumin during different stages of experimental colon carcinogenesis.* Proc Amer Assoc Cancer Res 2001, 42: Abst 3084.

Ross, L. et al. *On the antioxidant mechanism of curcumin: Classical methods are needed to determine antioxidant mechanism and activity.* Org Lett 2000, 2(18): 2841.

Sacks, P.G. et al. *Curcumin perturbs mitosis in oral epithelial cells.* Proc Amer Assoc Cancer Res 2001, 42: Abst 114.

Santibanez, J.F. et al. *Genistein and curcumin block TGF-beta1-induced u-PA expression and migratory and invasive phenotype in mouse epidermal keratinocytes.* Nutr Cancer 2000, 37(1): 49.

Sharma, R.A. et al. *Effect of curcumin on basal and induced malondialdehyde-DNA adduct levels in F344 rats.* Proc Amer Assoc Cancer Res 2000, 41: Abst 2619.

Shashed, A.R. et al. *Quercetin and curcumin up-regulate antioxidant gene-expression in rat kidney after ureteral obstruction or ischemia-reperfusion injury.* Transplant 2000 (May 13-17, Chicago) 2000, Abst 345.

Shih-Chieh, J. et al. *Curcumin enhances immunosuppressive effectiveness of cyclosporine in an in vivo model of rat cardiac allografts.* Transplant 2000 (May 13-17, Chicago) 2000, Abst 322.

Xu, J.H. et al. *Curcumin inducing apoptosis and inhibiting expression of p210ber-abl protein in human chronic myelogenous leukemia K562 cells.* FASEB J 2000, 14(8): Abst 1169.

Xu, M.-J. et al. *A method for determination of curcumin in biological specimens by RP-HPLC.* Proc Amer Assoc Cancer Res 2001, 42: Abst 113.

Desloratadine
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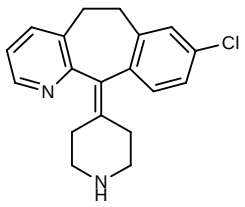
Neoclarityn®
Clarinex®

Treatment of Allergic Rhinitis
Treatment of Urticaria

EN: 109908



$C_{19}H_{19}ClN_2$ **Sepracor; Schering-Plough**

Schering Corporation has claimed methods for the treatment of noninfective sinusitis and otitis media by administering antihistamines with reduced anticholinergic activity in the absence of antibiotics. Preferred compounds are loratadine and its metabolite desloratadine (1).

Scientists have described the use of antiallergic drugs for the treatment of mental and vascular disorders, particularly depression, alcoholism, weight control, sexual dysfunction, panic and obsessive/compulsive disorder, migraine, stroke, orthostatic hypotension, gastrointestinal stasis, nausea, dizziness and jet lag. Preferably useful are nonsedating or low-sedating antihistamines such as loratadine or its metabolite desloratadine. It is believed that they exert their effects by interacting with the 5-HT_7 receptor as demonstrated in a binding assay where desloratadine gave a K_i value of 204 nM for displacement of [^{3}H]-LSD (2).

Results from an *in vitro* study using Caco-2 monolayers to examine the mechanism of action of desloratadine indicated that the agent may act as a P-glycoprotein (P-GP) substrate. The bidirectional absorptive ($Papp_{abs}$) and secretory permeability ($Papp_{sec}$) coefficients and efflux ratios (ER) for concentrations of 1, 10 and 100 μM (respectively) were: $Papp_{abs}$: 21.4 ± 6.35, 27 ± 8.74 and 46.58 ± 2.99 E-6 cm/s; $Papp_{sec}$: 65.58 ± 2.62, 67.2 ±4.65 and 48.25 ± 5.2 E-6 cm/s; and ER: 3.06, 3.14 and 1.04, respectively. Since ER values were > 1 with all concentrations and efflux permeation was concentration-dependent and saturable, it was concluded that an efflux mechanism involving P-GP plays a role in desloratadine transport (3).

A recent report has summarized the preclinical efficacy of desloratadine as a novel histamine H_1 receptor antagonist. The agent was 25-50 times more potent than terfenadine, fexofenadine, cetirizine, loratadine, ebastine and mizolastine in binding to the human H_1 receptor expressed in CHO cells. The rank order for inhibiting histamine-induced calcium flux from CHO cells was desloratadine (pA_2 = 0.4 nM), mizolastine, terfenadine, cetirizine, ebastine, loratadine and fexofenadine. Desloratadine was 10-fold more potent than loratadine in suppressing histamine-induced increases in nasal microvascular permeability in a guinea pig nasal challenge model. The antiallergic properties of desloratadine were also discussed. The agent (0.1 μM) inhibited production of IL-4 and IL-13 *in vitro* from ionomycin- or anti-IgE-stimulated human basophils; expression of IL-4 mRNA was also inhibited with treatment. Desloratadine (5 mg/kg) decreased acute bronchospasm and airway resistance in allergic cynomolgus monkeys. Antigen-induced cough was inhibited (ED_{50} = 0.3 mg/kg) in guinea pigs allergic to inhaled albumin. The safety of the agent was also mentioned with studies showing that doses up to 300 mg/kg produced no behavioral, neurologic or autonomic effects in mice. Studies in rats, guinea pigs and monkeys showed that high doses of desloratadine did not affect heart rate, blood pressure or ECGs; the agent (10 μM) had no effect on cardiac K^+ HERG channels. Results in guinea pigs showed that desloratadine does not interfere with subsequent [^{3}H]-pyrilamine binding to brain H_1 receptors, suggesting that the agent would not have sedative effects (4).

The pharmacokinetics of desloratadine have been summarized. The agent can be administered once daily due to its $t_{1/2}$ of 21-24 h. No dose adjustments were required in patients with renal or hepatic failure and when administered with food or grapefruit juice. The pharmacokinetics of the agent were not altered by race or sex. The C_{max} and AUC of desloratadine were slightly increased when given in combination with the cytochrome P450 inhibitors, ketoconazole and erythromycin, although no significant accumulation of the agent was observed. High dosing (45 mg/day for 10 days) resulted in elevated plasma desloratadine levels but was not accompanied by any significant adverse events including no effects on the corrected QT interval even when administered in combination with ketoconazole or erythromycin (5).

A randomized, open-label, single-dose, 2-way crossover study in 18 healthy volunteers showed that the oral bioavailability of desloratadine (7.5 h after a 10-h fast or a high fat, high caloric meal) was unaffected by food intake. The mean AUC_{0-t} and C_{max} were 77.5 ± 71.5 ng·h/ml and 3.30 ± 1.20 ng/ml, respectively, after fasting, and 73.8 ± 59.4 ng·h/ml and 3.53 ± 1.17 ng/ml after food intake. The relative bioavailability (fasted/fed) for AUC_{0-t} and C_{max} were 99.6 and 108.1%, respectively. Headache was the most common averse event (6).

A recent report has described the efficacy and safety of desloratadine as a treatment for chronic idiopathic urticaria. The new data indicate that the agent may be superior to available therapies in improving symptoms (7).

Treatment with once-daily desloratadine was shown to significantly improve seasonal allergic rhinitis (SAR) and asthma symptoms and reduce daily use of β_2 agonists in patients with concurrent SAR and asthma. Pulmonary function was maintained with use (8).

The efficacy of once-daily desloratadine as a decongestant was demonstrated in patients with SAR. Treatment not only improved symptoms of SAR but also improved patient ratings of nasal congestion (9).

A multicenter, randomized, double-blind, placebo-controlled trial in 190 patients with chronic idiopathic urticaria (CIU) examined the safety and efficacy of desloratadine (5 mg once daily for 6 weeks). Treatment was safe and well tolerated. The agent had a rapid onset of action with significant effects observed after only 1 dose. A sustained effect was observed over the study period. The agent was significantly superior to placebo in reducing pruritus, the number of hives, the size of the largest hive and the total symptom score (10).

Results from a multicenter, randomized, double-blind, placebo-controlled trial conducted in 190 patients with CIU showed that treatment with desloratadine (5 mg once daily for 6 weeks) was safe and well tolerated; adverse events were similar to those for placebo. Significant improvements in sleep and reductions in interference with daily activities as compared to placebo were observed after only 1 dose and were maintained for up to 6 weeks (11).

Results from a multicenter, randomized, double-blind, placebo-controlled trial conducted in 190 patients with CIU showed that treatment with desloratadine (5 mg once daily for 6 weeks) was safe and well tolerated and

improved CIU symptoms. Treatment significantly reduced pruritus, the overall condition of CIU and resulted in a better response according to patient and investigator scores. No tachyphylaxis was observed with treatment (12).

The safety of desloratadine (up to 4 times the recommended daily dose of 5 mg) was determined according to pooled data from several placebo-controlled phase II/III trials conducted in a total of 2346 evaluable patients. The incidence of adverse events was similar in both desloratadine and placebo groups. The most common adverse event was headache (4 and 5% in desloratadine and placebo groups, respectively) and no cardiovascular events or effects on CNS, hepatic or renal functions were observed with treatment. Desloratadine alone or in combination with ketoconazole or erythromycin had no effect on ECGs even when administered at 9 times the recommended dose. Results indicate that the agent is not a substrate for P-glycoprotein. Results from these studies also showed the efficacy of desloratadine as a treatment for improving signs and symptoms of CIU, allergic rhinitis and other allergic inflammatory disorders (13).

Two randomized, double-blind, placebo-controlled, parallel-group studies in patients with a 2-year history of seasonal allergic rhinitis showed the efficacy of desloratadine (5 or 7.5 mg p.o. for 14 days) in relieving symptoms. Total (nasal + nonnasal) symptom severity scores were significantly improved with both doses as compared to placebo. Nasal, nonnasal and individual symptom severity scores were also improved in joint patient/physician evaluations. Headache was the only adverse event occurring in both placebo (14-22%) and desloratadine-treated groups (16-24%). No adverse CNS or cardiac events were observed (14).

Two multicenter, double-blind, randomized, parallel-group, placebo-controlled trials have examined the efficacy and tolerability of once-daily desloratadine (5 mg) during the spring and fall allergy seasons in patients with seasonal allergic rhinitis at least 12 years of age. The spring study enrolled 172 and 174 patients, respectively, in the desloratadine and placebo groups, and the fall study 164 patients in each group, who were treated for 14 days. The primary efficacy variable in both studies was the change from baseline in the average reflective am/pm total symptom score (TSS), a sum of individual nasal and nonnasal symptom scores. This treatment regimen of desloratadine was associated with significant improvement in TSS compared to placebo in both studies as early as the second day and sustained over the 2-week treatment period; the average reduction on desloratadine in the spring study was 28% *versus* 12.5% on placebo, and average reductions in the fall were 30% *versus* 22%. Adverse events were mild to moderate and similar in both groups, the most frequent being headache. Neither group showed clinically significant sedation or ECG changes from baseline. These data support the use of this once-daily regimen of desloratadine for the treatment of seasonal allergic rhinitis in adolescents and adults (15).

Schering-Plough has submitted a variation to its original marketing application for desloratadine tablets to the EMEA seeking approval to market the drug as a treatment for CIU in adults and adolescents aged 12 and older. The company also submitted to the EMEA an abridged application seeking clearance to market desloratadine in a syrup formulation for the treatment of SAR and CIU in patients as young as age 2. On January 15, 2001, the European Commission approved desloratadine 5 mg tablets as a once daily, nonsedating treatment of SAR in adults and children aged 12 and older. Desloratadine will be marketed in the E.U. as Aerius® and NeoClarityn®. The product will be launched upon receiving pricing and/or reimbursement approvals, where necessary, from individual E.U. countries (16).

Sepracor recently reported that Schering-Plough has submitted an NDA to the FDA seeking to broaden the allergy indication for desloratadine (Clarinex®, 5-mg tablets). The proposed indication of allergic rhinitis would encompass both SAR and perennial allergic rhinitis (PAR). The allergic rhinitis NDA is based on 8 randomized, placebo-controlled studies evaluating 4700 patients with either SAR or PAR. Clarinex® has already received an approvable letter for the treatment of SAR. A separate marketing application for Clarinex® is currently pending with the FDA for the treatment of CIU. Schering-Plough has also submitted separate marketing applications to the FDA for Clarinex® RediTabs®, a rapidly disintegrating formulation, Clarinex® Syrup for use in patients as young as 2 years of age, and Clarinex-D® 12 Hour, a fixed combination of Clarinex® and a decongestant (17).

1. Harris, A.G. et al. (Schering Corp.). *Antihistamines for treating non-infective sinusitis or otitis media.* WO 0015226.

2. Binder, G. et al. (Schering Corp.). *Methods for the treatment of mental disorders.* WO 0113905.

3. Hwang, K.K., Correll, M., Offord, S.J. *Evaluation of desloratadine as a P-glycoprotein substrate using CaCo-2 cells: Possible mechanism and potential site of drug-drug interaction.* J Clin Pharmacol 2000, 40(9): Abst 64.

4. Kreutner, W., Hey, J.A., Anthes, J.C., Barnett, A. *Preclinical efficacy and antiallergic profile of desloratadine, A potent next-generation histamine H_1-receptor antagonist with additional antiallergic properties.* 59th Annu Meet Am Acad Dermatol (March 2-7, Washington DC) 2001, Abst P452.

5. Henz, B.M. *The pharmacologic profile of desloratadine: A review.* Allergy 2001, 56(Suppl. 65): 7.

6. Gupta, S., Padhi, D., Banfield, C., Marbury, T., Affrime, M.B., Marco, A., Cayen, M.N. *The oral bioavailability of desloratadine is unaffected by food.* Allergy 2000, 55(Suppl. 63): Abst 959.

7. Ring, J., Hein, R., Gauger, A. *Desloratadine in the treatment of chronic idiopathic urticaria.* Allergy 2001, 56(Suppl. 65): 28.

8. Baena Cagnani, C.E. *Desloratadine activity in concurrent seasonal allergic rhinitis and asthma.* Allergy 2001, 56(Suppl. 65): 21.

9. Bachert, C. *Decongestant efficacy of desloratadine in patients with seasonal allergic rhinitis.* Allergy 2001, 56(Suppl. 65): 14.

10. Hein, R., Gauger, A., Breneman, D., Guerrero, R., Rikken, G., Ring, J. *Rapid onset and durability of response of desloratadine in the treatment of chronic idiopathic urticaria.* 59th Annu Meet Am Acad Dermatol (March 2-7, Washington DC) 2001, Abst P448.

11. Miller, B.H., Patel, P., Bernstein, D., Rikken, G. *Therapy with desloratadine for chronic idiopathic urticaria reduces interferences with sleep and daily activities.* 59th Annu Meet Am Acad Dermatol (March 2-7, Washington DC) 2001, Abst P449.

12. Monroe, E.W., Raimer, S., Bronsky, E., Rikken, G. *Efficacy and safety of desloratadine in the treatment of chronic idiopathic urticaria.* 59th Annu Meet Am Acad Dermatol (March 2-7, Washington DC) 2001, Abst P450.

13. Banfield, C., Affrime, M., Lorber, R. *Desloratadine, a novel H_1-receptor antagonist, has a placebo-like safety profile.* 59th Annu Meet Am Acad Dermatol (March 2-7, Washington DC) 2001, Abst P451.

14. Salmun, L.M., Lorber, R.R., Danzing, M.R., Staudinger, H. *Desloratadine is safe and effective treatment for relief of seasonal allergic rhinitis.* Allergy 2000, 55(Suppl. 63): Abst 960.

15. Meltzer, E.O., Prenner, B.M., Nayak, A. *Efficacy and tolerability of once-daily 5 mg desloratadine, an H-1-receptor antagonist, in patients with seasonal allergic rhinitis - Assessment during the spring and fall allergy seasons.* Clin Drug Invest 2001, 21(1): 25.

16. *Schering-Plough submits two new applications for desloratadine in the E.U.* DailyDrugNews.com (Daily Essentials) Jan 22, 2001.

17. *Schering-Plough seeks FDA approval of broader Clarinex indication; first launches in E.U.* DailyDrugNews.com (Daily Essentials) April 18, 2001.

Original monograph - Drugs Fut 2000, 25: 339.

Additional References

Affrime, M.B. et al. *Lack of electrocardiographic effects when desloratadine and ketoconazole are coadministered.* Allergy 2000, 55(Suppl. 63): Abst 992.

Banfield, C. et al. *Race and gender do not affect the multiple-dose pharmacokinetics and safety of desloratadine.* Allergy 2000, 55(Suppl. 63): Abst 991.

Bonini, S. *Desloratadine: A new approach in the treatment of allergy as a systemic disease - pharmacology and clinical overview - Introduction.* Allergy 2001, 56(Suppl. 65): 5.

Glue, P. et al. *Lack of electrocardiographic interaction between desloratadine and erythromycin.* Allergy 2000, 55(Suppl. 63): Abst 989.

Herron, J.M. et al. *Desloratadine demonstrates dose proportionality/linear pharmacokinetics in healthy adults.* Allergy 2000, 55(Suppl. 63): Abst 955.

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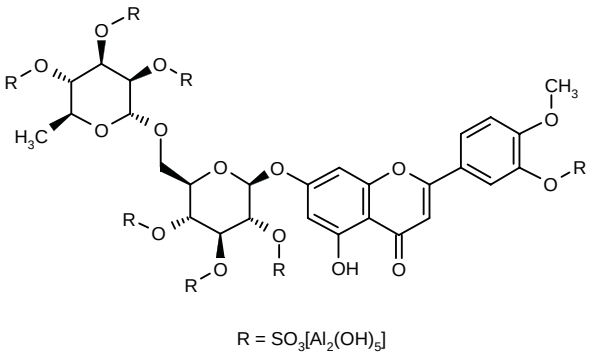
F-3616M
Diotul®

EN: 162108



R = $SO_3[Al_2(OH)_5]$

$C_{28}H_{60}O_{36}Al_{14}O_{71}S_7$ **FAES**

Dosmalfate (Diotul®), discovered and developed by Faes, was launched in Spain in May 2000. In patients diagnosed with rheumatic disease receiving NSAID therapy, dosmalfate has been shown to prevent gastroduodenal lesions. The drug creates a barrier effect that prevents the formation of lesions caused by gastric acid and pepsin. Dosmalfate also activates the secretion of cytoprotective prostaglandin E_2 in gastric juices. In addition, the results of various studies undertaken with dosmalfate confirm that the product's efficacy is comparable to that of misoprostol, while it shows much better tolerance (1).

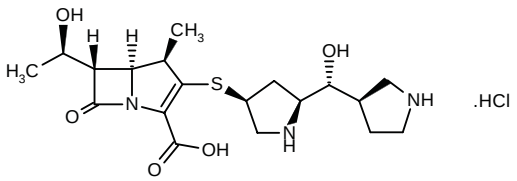
1. *Dosmalfate launched in Spain for prophylaxis of gastric lesions and ulcers.* DailyDrugNews.com (Daily Essentials) June 1, 2000.

Original monograph - Drugs Fut 1999, 24: 381.

E-1010 *Carbapenem*

ER-35786

EN: 226620



$C_{19}H_{29}N_3O_5S.HCl$ **Eisai**

The *in vitro* activity of E-1010 against 647 bacterial isolates was compared to activities of imipenem and meropenem using disk diffusion tests. The MIC_{90} values obtained for the respective agents were (μg/ml): 0.06-4, 0.25-4 and 0.03-0.25 against enteric bacilli; 1, 2 and

4 against imipenem-susceptible *Pseudomonas aeruginosa*; 8, 64 and 32 against imipenem-resistant *P. aeruginosa*; 0.06-0.25, 0.016-0.06 and 0.12-1 against methicillin-susceptible *Staphylococcus* spp.; 1-8, 1-128 and 8-64 against methicillin-resistant *Staphylococcus* spp.; 0.008-0.25, ≤ 0.004-0.25 and 0.008-0.25 against penicillin-sensitive *Streptococcus* spp.; 0.5-1, 0.25-0.5 and 0.5-1 against penicillin-intermediate and -resistant *Streptococcus pneumoniae*; 8-128, 2->128 and 16->128 against *Enterococcus* spp.; and 0.5-1, 1, 0.06-0.12 against *Haemophilus* spp. (1).

The *in vitro* bactericidal activity of E-1010 was compared to imipenem against imipenem-susceptible and -resistant strains of *P. aeruginosa*. E-1010 (0.5 g) maintained a > 99.9% reduction in inoculum (99.9% killing = RII) of the susceptible strain for 5 h; a maximum decrease of 3.5 logs was observed 5 h postdosing. In contrast, imipenem (0.5 g) only reduced inoculum by 2.5 logs and did not achieve RII. E-1010 (0.5 g) decreased the resistant strain by 2.5 logs after 8 h while imipenem (1 g) decreased inoculum by 2.2 logs after 4 h. Multiple doses of E-1010 (0.5 g x 3) and imipenem (0.5 g x 4) both produced RII against the susceptible strain for 12 h; 3 doses of 0.5 g imipenem achieved RII for only 3 h. E-1010 (0.5 g x 3) also resulted in RII of the resistant strain for 3 h while imipenem (1 g x 3) did not (2).

A phase I, double-blind, placebo-controlled, ascending, single-dose pharmacokinetics trial in 40 healthy male volunteers showed the tolerability of E-1010 (50, 100, 250, 500 and 1000 mg i.v. over 30 min). C_{max} and AUC values appeared to be dose-proportional. C_{max}, AUC and $t_{1/2}$ values for the 250, 500 and 1000 mg doses were 19.7 ± 3.3, 30.9 ± 3.5 and 66 ± 12 μg/ml, 37 ± 5.4, 61.5 ± 6.4 and 130.4 ± 17.8 μg·h/ml and 1.7 ± 0.2, 1.7 ± 0.1 and 1.8 ± 0.1 h, respectively. The cumulative urinary excretion rate was 60.4-69.7% by 24 h postdosing (3).

Eisai has indicated that it is planning the worldwide development of E-1010 (ER-35786). In the U.S., phase I trials have been completed and phase II studies are scheduled to commence next year. The company is also studying licensing opportunities for the carbapenem in Japan (4).

1. Traczewski, M.M., Barry, A.L., Brown, S.D., Fuchs, P.C. *Comparative in vitro activity of E1010, imipenem, and metropenem and interpretive criteria for E1010 disk diffusion tests.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst E-389.

2. Toyosawa, T., Inoue, M. *Comparative bactericidal activity of E1010 (ER-35786), a new carbapenem, and imipenem (IPM) against Pseudomonas aeruginosa, in an in vitro pharmacodynamic model.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst A-497.

3. Hirasawa, T., Okereke, C., Wheeler, J., Lynn, M., Hasegawa, J. *Pharmacokinetics (PK), safety and tolerability of E1010,a new parenteral long half-life carbapenem, in healthy male volunteers.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst A-492.

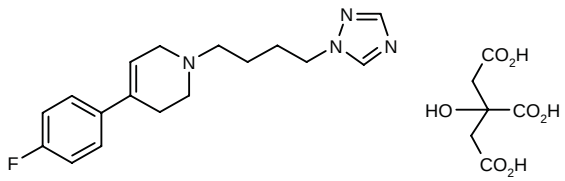
4. *Development plans for carbapenem E-1010 revealed by Eisai.* DailyDrugNews.com (Daily Essentials) Dec 20, 2000.

Original monograph - Drugs Fut 1996, 21: 361.

E-5842

Antipsychotic
σ-Receptor Antagonist

EN: 256549



$C_{17}H_{21}FN_4.C_6H_8O_7$ **Esteve**

Results from a study in rats showed that chronic administration of E-5842 (for 21 days; animals killed 24 h after the last dose) upregulated fibroblast growth factor-2 (FGF-2) mRNA in the prefrontal cortex and striatum and downregulated FGF-2 mRNA in the hypothalamus. Acute administration (single dose; animals killed 6 h postdosing) resulted in transient dose-dependent upregulation of FGF-2 mRNA in the prefrontal cortex, striatum, hypothalamus and hippocampus which disappeared 24 h postdosing (1).

E-5842 exhibits activity in models of positive symptoms of schizophrenia without inducing catalepsy. Preliminary indications of anxiolytic activity led scientists at the University of Manchester to study E-5842 in the elevated plus-maze and the Vogel conflict test in rats. At the low doses of 0.6 and 0.3 mg/kg i.p., E-5842 displayed anxiolytic-like activity in the former test, but efficacy in the Vogel test was seen only at a dose of 6.1 mg/kg i.p. These findings suggest a $sigma_1$-mediated effect and no significant benzodiazepine-like effect, consistent with its weak anticonvulsant activity and lack of benzodiazepine receptor binding. The investigators also conclude that its anxiolytic-like actions may contribute to its atypical antipsychotic profile in animals (2).

A study examined the mechanism of action of acute and chronic administration of EB-5842 (20 mg/kg i.p. for up to 21 days). Results from analysis of phospholipase C and Gα(q/11) protein activity in cortical brain slices and isolated synaptic membranes suggest that phosphoinositide turnover may be involved in the mechanism of action of E-5842 following chronic administration (3).

E-584 was examined in healthy volunteers for effects on cognition. Following single doses of 10-75 mg, E-5842 was associated with some impairment of cognitive function compared to placebo, as assessed on the Cognitive Drug Research assessment battery. However, in a separate study in 24 volunteers given multiple doses of 10 or 20 mg/day for 7 days, or placebo, no significant impairment of cognition was seen and significant improvement was even detected on some measures. It is concluded that neuroleptic agents such as E-5842 that do not impair

cognitive function should be particularly valuable as treatments for schizophrenia (4).

A placebo-controlled trial examined the effects of E-5842 on cognitive function following single (10, 25, 50 or 75 mg) and multiple dosing (10 or 20 mg/day for 7 days) in 36 and 24 healthy volunteers, respectively. Cognitive function was evaluated at 1, 2.5, 4 and 6 h on days 1, 2, 4 and 7. While single dosing with 25 and 50 mg resulted in several impairments in speed detections on the Digit Vigilance task, multiple dosing produced only a few significant cognitive impairments and a number of cognitive enhancements. Multiple dosing with 10 mg resulted in an improvement in the sensitivity index measure of Numeric Working Memory at most time points as compared to placebo. Results suggest that multiple dosing may be effective as a treatment for schizophrenia (5).

1. Ovalle, S., Zamanillo, D. Andreu, F., Farre, A.J., Guitart, X. *Fibroblast growth factor-2 is selectively modulated in the rat brain by E-5842, a preferential σ-1 receptor ligand and putative atypical antipsychotic.* Eur J Neurosci 2001, 13(5): 909.

2. Codony, X., Fisas, A., Ruiz, M.T., Guitart, X., Farré, A.J. *Anxiolytic-like effects of E-5842, a selective σ_1 ligand with antipsychotic profile.* Behav Pharmacol 2000, 11(3-4): 334.

3. Pérez, M.P., Romero, G., Carceller, A., Guitart, X., Farré, A. *Regulation of phospholipase C activity in rat brain by the preferential σ-1 receptor ligand and putative atypical antipsychotic E-5842.* Methods Find Exp Clin Pharmacol 2000, 22(6): Abst CO-34.

4. Taubel, J., Arezina, R., Ward, T., Wesnes, K.A. *A comparison of the effects on cognitive function of E-5842 administered as a single or multiple dose.* Int J Neuropsychopharmacol 2000, 3(Suppl. 1): Abst P.18.38.

5. Taubel, J. et al. *A comparison of the effects on cognitive function of E-5842 administered as a single or multiple dose.* Eur Neuropsychopharmacol 2000, 10(Suppl. 3): Abst P.2.031.

Original monograph - Drugs Fut 1999, 24: 386.

Additional Reference

Guitart, X. et al. *Regulation of gene expression response to chronic treatment with E-5842, a sigma-1 receptor to ligand and potential atypical antipsychotic.* Soc Neurosci Abst 2000, 26(Part 1): Abst 97.20.

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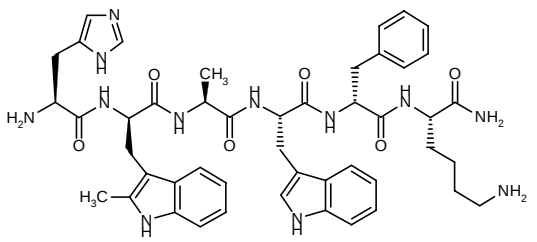

$C_{47}H_{58}N_{12}O_6$ **Europeptides; Mediolanum**

Examorelin has been shown to bind with high affinity to sites in animal and human hearts and to protect rats from ischemia-induced myocardial damage. The compound exhibits high-affinity binding in H9c2 cells, an undifferentiated cell line derived from fetal cardiomyocytes, and inhibits doxorubicin-induced cell death. Inhibition of doxorubicin-induced cell death was also seen in adult guinea pig differentiated cardiomyocytes exposed to micromolar concentrations of examorelin. Pretreatment with the hexapeptide also prevented apoptosis induced by Fas stimulation in these cardiomyocytes. It is concluded that the ability of examorelin to inhibit cardiomyocyte cell death may at least partially account for its cardioprotective effects (1).

A study showed that examorelin (80 μg/kg s.c.) administered to rats *in vivo* for 3 or 7 days provided protection against calcium depletion-induced ventricular dysfunction *in vitro*. The agent time-dependently prevented the increase in resting tension observed in isolated hearts following perfusion with calcium-depleted medium. Protective effects were more marked after 7-day treatment *in vivo* where recovery of left ventricular developed pressure was 2-fold higher and creatine kinase release was significantly decreased by 40% as compared to untreated controls. Plasma and heart IGF-1 levels were similar in both control and treated rats, indicating that stimulation of the GH/IGF axis is not responsible for the protective effects of the agent. Administration of GH (400 μg/kg s.c.) for 7 days *in vivo* did not protect isolated hearts against calcium depletion and 60-min perfusion of untreated animal hearts with examorelin (8 μg/ml) did not protect against the ventricular hypercontractility observed following reperfusion with calcium (2).

The endocrine and cardiovascular effects of examorelin were examined during general anesthesia in 6 patients with coronary artery disease undergoing bypass surgery. Acute administration of examorelin (2.0 μg/kg i.v.) during general anesthesia induced by remifentanil, cisatracurium and propofol resulted in a significant increase in left ventricular ejection fraction, similar to previous studies in conscious adults, but no significant effect was seen on cortisol, prolactin or GH levels. Thus, general anesthesia abolishes the endocrine but not the cardiovascular effects of the hexapeptide. Moreover, based on previous findings showing that cisatracurium and propofol anesthesia is associated with normal GH secretion, this effect appears to be due to the mu-opioid agonist remifentanil (3).

A placebo-controlled study conducted in 7 young (20-30 years old), healthy males showed that multiple dosing with hexarelin (50 μg i.v. at 10, 11 and 12 p.m. and 1 a.m.) stimulated nocturnal GH, cortisol and ACTH release. No changes in leptin levels were observed between subjects treated with the agent or placebo. Analysis of sleep EEGs showed that administration of the agent also significantly decreased sleep stage 4 during the first half of the night (25.7 ± 19.2 *vs.* 17.8 ± 14.8 min) (4).

A study in 6 young (26-32 years) female volunteers examined the effects of glucagon (0.017 mg/kg i.m.) and examorelin (2 µg/kg i.v.) alone and in combination on somatotroph and corticotroph secretion. Glucagon administration alone significantly increased GH (11.6 ± 3.4 *vs.* 3.3 ± 0.7 µg/l), ACTH (11.6 ± 3.3 *vs.* 4.1 ± 0.3 pmol/l) and cortisol (613.5 ± 65.6 *vs.* 436.9 ± 13.3 nmol/l) levels as compared to baseline. Examorelin also significantly increased these 3 hormones (55.7 ± 19.8 *vs.* 3.7 ± 1.9 µg/l GH; 5.7 ± 1.1 *vs.* 3.4 ± 0.6 pmol/l ACTH; 400.2 ± 31.4 *vs.* 636.4 ± 32.2 nmol/l cortisol). The GH AUC value following examorelin administration was significantly higher (1637.3 ± 494 *vs.* 479.1 ± 115.7 µg/l/120 min) while the AUC values for ACTH (208 ± 41.3 *vs.* 426.3 ± 80.9 pmol/l/120 min) and cortisol (18875.5 ± 1626 *vs.* 28338.5 ± 2430.7 mol/l/120 min) were significantly lower than those obtained after glucagon administration. Combined examorelin and glucagon resulted in a less than additive effect on ACTH (564.02 ± 76.5 pmol/l/120 min) and cortisol (35424.6 ± 5548.1 nmol/l/120 min) secretion and a synergistic effect on GH secretion (3243.8 ± 687.5 µg/l/120 min) (5).

A study conducted in 6 male patients with coronary artery disease (LEVF = 57.2 ± 1.4%) undergoing bypass surgery under general anesthesia (remifentanil, cisatracurium and propofol) showed that acute examorelin administration (2 mg/kg i.v. at time 0) significantly increased LVEF (63.8 ± 1.2 *vs.* 57.1 ± 1.4%) starting 10 min postdosing and lasting up to 90 min. No effects on LVEDV or SVRI were observed and no significant changes in GH levels were seen. A significant reduction in WP was also observed with acute examorelin treatment (9.0 ± 0.5 *vs.* 11 ± 0.7 mmHg) (6).

1. Graziani, A., Cutrupi, S., Filigheddu, N. et al. *Hexarelin, a peptidyl GH secretagogue, inhibits apoptosis in adult cardiomyocytes in vitro.* 82nd Annu Meet Endocr Soc (June 21-24, Toronto) 2000, Abst 1120.

2. Rossoni, G., Locatelli, V., De Genaro Colonna, V., Müller, E.E., Berti, F. *Hexarelin, a growth hormone secretagogue, protects the isolated rat heart from ventricular dysfunction produced by exposure to calcium-free medium.* Pharmacol Res 2000, 42(2): 129.

3. Broglio, F., Guarracino, F., Benso, A., Gottero, C., Gianotti, L., Arvat, E., De Stefani, R., Muccioli, G. *General anesthesia abolishes the endocrine but not the cardiovascular activities of Hexarelin, a GHRP, in humans.* 82nd Annu Meet Endocr Soc (June 21-24, Toronto) 2000, Abst 1975.

4. Held, K., Friebes, R.-M., Murck, H., Uhr, M., Steiger, A. *Hexarelin stimulates nocturnal growth hormone, cortisol and ACTH release and impairs sleep in normal controls.* Int J Neuropsychopharmacol 2000, 3(Suppl. 1): Abst P.01.020.

5. Arvat, E. et al. *Interaction between glucagon and Hexarelin, a peptidyl GH secretagogue, on somatotroph and corticotroph secretion in humans.* Eur J Endocrinol 2000, 143(5): 601.

6. Guarracino, F. et al. *The acute administration of Hexarelin, a synthetic GHRP, increases left ventricular ejection fraction in patients with coronary artery disease during anesthesia for bypass surgery.* Eur Heart J 2000, 21(Suppl.): Abst P572.

Original monograph - Drugs Fut 1996, 21: 366.

Additional Reference

Conley, L. et al. *Hexarelin, alone and in combination with arginine, differentially affects GH release in male and female acromegalics.* 82nd Annu Meet Endocr Soc (June 21-24, Toronto) 2000, Abst 2022.

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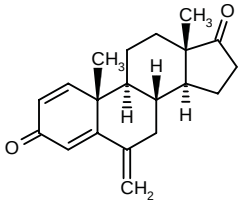
EN: 129640



$C_{20}H_{24}O_2$

Pharmacia

Health Canada has approved exemestane (Aromasin®), which selectively targets and permanently binds to aromatase, for the treatment of postmenopausal women with advanced breast cancer whose tumors no longer respond to tamoxifen. Health Canada based its approval on a European phase III study comparing exemestane with a standard hormonal therapy, megestrol acetate, which showed that exemestane was associated with superior efficacy, delayed tumor growth and significantly increased survival, along with manageable side effects (1).

1. *Pharmacia's Aromasin receives clearance from Health Canada.* DailyDrugNews.com (Daily Essentials) Sept 7, 2000.

Original monograph - Drugs Fut 1992, 17: 278.

Additional References

Dixon, J.M. et al. *Exemestane as neoadjuvant treatment for locally advanced breast cancer: Endocrinologic and clinical endpoints.* 23rd Annu San Antonio Breast Cancer Symp (Dec 6-9, San Antonio) 2000, Abst 170.

Goss, P.E., Strasser, K. *Aromatase inhibitors in the treatment and prevention of breast cancer.* J Clin Oncol 2001, 19(3): 881.

Hillner, B.E., Radice, D. *Cost-effectiveness analysis of exemestane compared with megestrol in patients with advanced breast carcinoma.* Cancer 2001, 91(3): 484.

Kaufmann, M. et al. *Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: Results of a phase III randomized double-blind trial.* J Clin Oncol 2000, 18(7): 1399.

Lonning, P.E. *Clinico-pharmacological aspects of different hormone treatments.* Eur J Cancer 2000, 36(Suppl. 4): S81.

Martinetti, A. et al. *Exemestane in post-menopausal patients failing treatment with non-steroidal structure aromatase inhibitors: Effects on insulin-like growth factor (IGF) components.* Ann Oncol 2000, 11(Suppl. 4): Abst 143P.

Miller, W. *Differential effects of steroidal type I and non-steroidal type II anti-aromatase agents.* 23rd Annu San Antonio Breast Cancer Symp (Dec 6-9, San Antonio) 2000, Abst 273.

Paridaens, R. et al. *Exemestane (Aromasin) is active and well tolerated as first-line hormonal therapy (HT) of metastatic breast cancer (MBC) patients (pts): Results of a randomized phase II trial.* Proc Am Soc Clin Oncol 2000, 19: Abst 316.

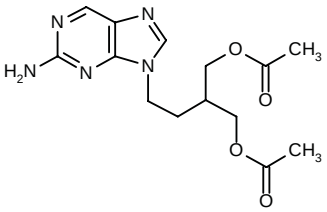
Paridaens, R. et al. *Promising activity and safety of exemestane (E) as first-line hormonal therapy (HT) in metastatic breast cancer (MBC) patients (pts): Final results of an EORTC randomised phase II trial.* 23rd Annu San Antonio Breast Cancer Symp (Dec 6-9, San Antonio) 2000, Abst 167.

Zilembo, N. et al. *Estrogen suppression (ES) and tumor response in breast cancer (BC) patients treated with aromatase inhibitors.* Proc Am Soc Clin Oncol 2000, 19: Abst 399.

Famciclovir
Famvir®

Antiviral

EN: 126242



$C_{14}H_{19}N_5O_4$ **GlaxoSmithKline; Novartis; Solvay**

A new synthetic route to famciclovir has been described: The alkylation of 2,2-dimethyl-1,3-dioxan-5-one (I) with vinylmagnesium bromide (II) in THF gives the 2,2-dimethyl-5-vinyl-1,3-dioxan-5-ol derivative (II), which is treated with methyl chloroformate in the same solvent to yield the mixed carbonate (IV). Condensation of (IV) with 6-chloropurine-2-amine (V) by means of 1,2-bis(diphenylphosphino)ethane (dppe) and tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$] in DMF at 80 ºC for 7.5 h affords a 5:95 mixture of the *N*-7 (VI) and *N*-9 (VII) regioisomers, respectively. Hydrogenation of regioisomer (VII) with H_2 over Pd/C in THF eliminates the 6-chlorine atom and reduces the exocyclic double bond, giving the 2-aminopurine derivative (VIII), which is treated with HCl in methanol to remove the acetonide group, affording diol (IX). Finally, this compound is acylated with acetic anhydride and DMAP/TEA in dichloromethane (1). Scheme 1.

Novartis has acquired famciclovir and penciclovir, divested by SmithKline Beecham in response to antitrust concerns related to the latter's merger with Glaxo Wellcome to form GlaxoSmithKline. The acquisition includes global marketing and production rights in addition to all intellectual property rights and the right to further develop the products. During a transition period, SB will manufacture both products for Novartis until production has been transferred (2).

1. Freer, R., Geen, G.R., Ramsay, T.W., Share, A.C., Slater, G.R., Smith, N.M. *A new route to famciclovir via palladium catalysed allylation.* Tetrahedron 2000, 56(26): 4589.

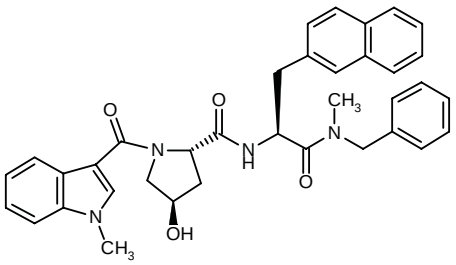
2. *Antiviral drugs acquired by Novartis from SB.* DailyDrugNews.com (Daily Essentials) Jan 2, 2001.

Original monograph - Drugs Fut 1989, 14: 347.

FK-888

Antimigraine

EN: 176252



$C_{36}H_{36}N_4O_4$ **Fujisawa**

In reviewing the company's development projects, Fujisawa has decided to discontinue development of FK-888. Although the company had conducted clinical trials of FK-888 for migraine in Japan and Europe, the compound's efficacy was not sufficient enough in the European trial to advance into phase III clinical trials (1).

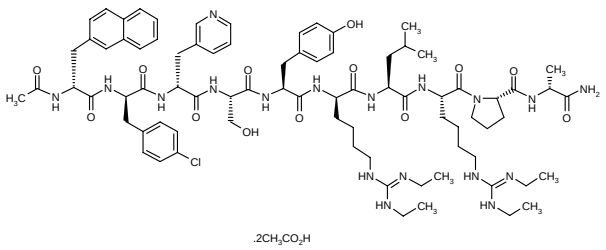
1. *Fujisawa discontinues development of FK-888.* DailyDrugNews.com (Daily Essentials) Sept 29, 2000.

Original monograph - Drugs Fut 1997, 22: 353.

Ganirelix Acetate
Org-37462
RS-26306
Orgalutran®
Antagon®

Treatment of Female Infertility
GnRH Antagonist

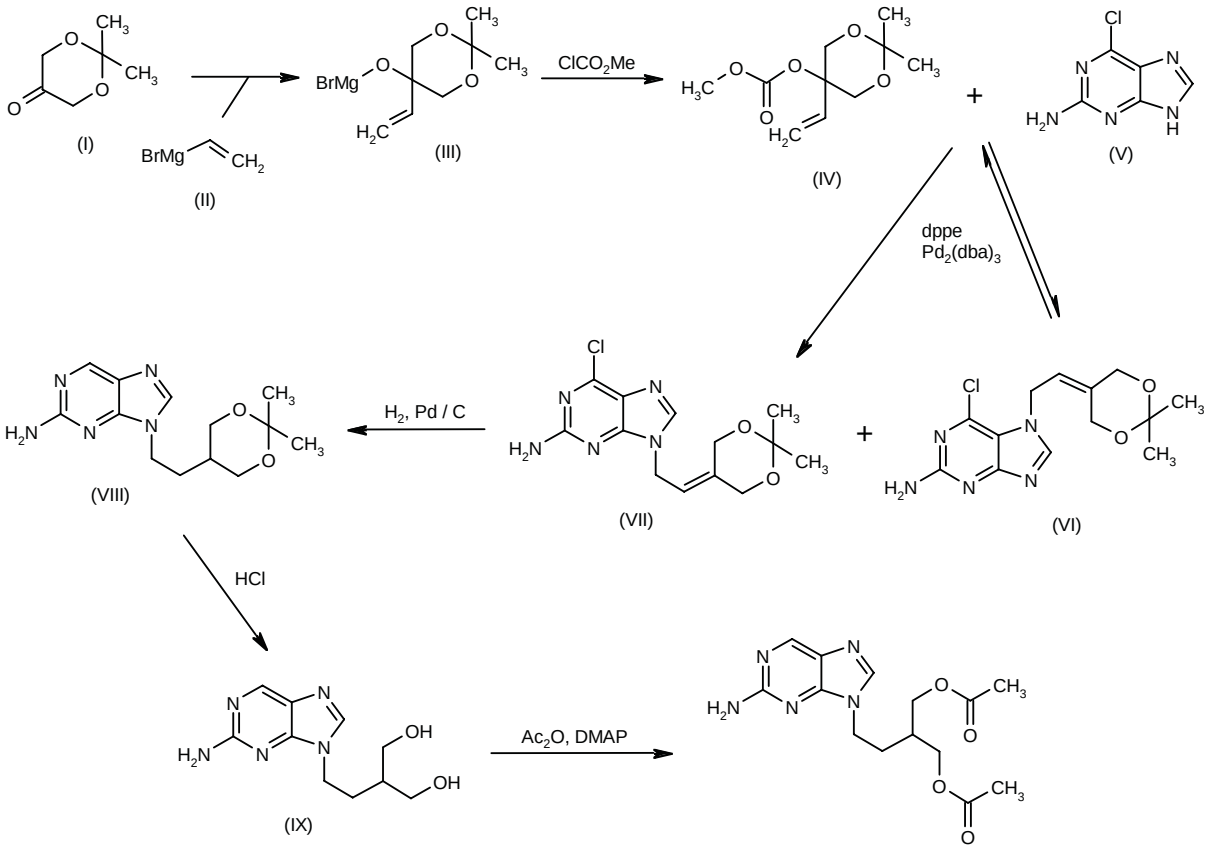
EN: 180634



$C_{80}H_{113}ClN_{18}O_{13}.2C_2H_4O_2$ **Roche; Organon**

The European Medicines Evaluation Agency recently granted marketing approval for ganirelix acetate (Orgalutran®), a new type of fertility drug expected to

Scheme 1: Synthesis of Famciclovir



revolutionize the treatment of infertility by *in vitro* fertilization (IVF). Ganirelix acetate will make a cycle of IVF treatment considerably easier and shorter for both patients and physicians. In a series of studies during the clinical development of ganirelix acetate, Organon demonstrated that the total drug treatment time of IVF was reduced to about 10 days, as opposed to the present drug treatment times in IVF which last from 3 to 4 weeks. 's own reproductive hormones. Most drugs used currently require an additional two to three weeks of treatment to achieve the same effect (1).

According to a company spokesperson, Organon launched ganirelix acetate (Orgalutran®) for the first time in July 2000 in Germany. It is indicated for the inhibition of premature luteinizing hormone surges in women undergoing controlled ovarian hyperstimulation. Ganirelix acetate is already approved for use in the U.S. under the brand name Antagon® and will be available in other countries in Europe shortly (2).

1. *Organon's Orgalutran approved in E.U. for treatment of infertility.* DailyDrugNews.com (Daily Essentials) July 4, 2000.

2. *Organon's fertility treatment now available in Germany.* DailyDrugNews.com (Daily Essentials) July 7, 2000.

Original monograph - Drugs Fut 1999, 24: 393.

Additional References

Borm, G., Mannaerts, B. *Treatment with the gonadotrophin-releasing hormone antagonist ganirelix in women undergoing ovarian stimulation with recombinant follicle stimulating hormone is effective, safe and convenient: Results of a controlled, randomized, multicentre trial.* Hum Reprod 2000, 15(7): 1490.

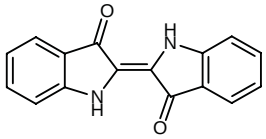
Fluker, M. et al. *Efficacy and safety of ganirelix acetate versus leuprolide acetate in women undergoing controlled ovarian hyperstimulation.* Fertil Steril 2001, 75(1): 38.

Istkovitz-Eldor, J. et al. *Use of a single bolus of GnRH agonist triptorelin to trigger ovulation after GnRH antagonist ganirelix treatment in women undergoing ovarian stimulation for assisted reproduction, with special reference to the prevention of ovarian hyperstimulation syndrome: Preliminary report.* Hum Reprod 2000, 15(9): 1965.

Indirubin

Oncolytic

EN: 090153



$C_{16}H_{10}N_2O_2$ **Chin. Acad. Sci.; Inst. Materia Medica**

Results from an *in vitro* study have shown that indirubins potently inhibited cyclin-dependent kinases (CDKs; IC_{50} = 50-100 nM) and glycogen synthase kinase-3β (GSK-3β; IC_{50} = 5-50 nM). In contrast, the several indoles and bis-indoles examined had no effect on GSK-3β, CDK1/cyclinB or CDK5/p25, indicating that the inhibitory action was unique to indirubins. Crystallographic analysis revealed that indirubins bind to the GSK-3β ATP binding pocket in a manner similar to their binding to CDKs. Indirubin-3'-monoxime was found to inhibit tau phosphate both *in vitro* and *in vivo* at Alzheimer's disease-specific sites, indicating a potential efficacy of the agents in treating neurodegenerative disorders. Additional studies using mouse brain striatum showed that indirubin-3'-monoxime inhibited phosphorylation of DARPP-32 by CDK5 on Thr-75 in a manner similar to dopamine action in the striatum (1).

1. Leclerc, S., Garnier, M., Hoessel, R. et al. *Indirubins inhibit glycogen synthase kinase-3 beta and CDK5/P25, two protein kinases involved in abnormal tau phosphorylation in Alzheimer's disease - A property common to most cycline-dependent kinase inhibitors?* J Biol Chem 2001, 276(1): 251.

Original monograph - Drugs Fut 1984, 9: 266.

Additional References

Eisenbrand, G. et al. *Indirubins, potent inhibitors of cyclin-dependent kinases, inhibit the growth of human xenograft tumors in-vitro and in-vivo.* Clin Cancer Res 2000, 6(Suppl.): Abst 327.

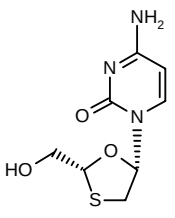
Fiebig, H.H. et al. *Indirubins, novel potent inhibitors of cyclin-dependent kinases, inhibit the growth of human xenograft tumors.* Proc Amer Assoc Cancer Res 2001, 42: Abst 2458.

Kunikata, T. et al. *Indirubin inhibits inflammatory reactions in delayed-type hypersensitivity.* Eur J Pharmacol 2000, 410(1): 93.

Lamivudine
Epivir-HBV®
Heptodin®
Heptovir®
Zefix®
Zeffix®

Anti-HBV
Anti-HIV

EN: 184356



$C_8H_{11}N_3O_3S$

BioChem Pharma; GlaxoSmithKline; Ajinomoto

Therapeutic combinations for the treatment of HBV infections containing lamivudine and abacavir, lamivudine and adefovir and lamivudine and lobucavir, provide synergistic antiviral effects resulting in a reduced toxicity for an equivalent antiviral activity or an increase in drug efficacy (1-3).

Researchers from BioChem Pharma have announced the results obtained from an interim review of a long-term follow-up study of chronic hepatitis B patients treated with lamivudine. The results indicate that 27 of 58 patients (47%) treated with lamivudine achieved hepatitis e antigen seroconversion after 4 years of lamivudine therapy. Seroconversion, a marker of loss of viral replication, is defined in this study as the loss of HBV e antigen and gain of antibody to e antigen. In previous interim evaluations of this long-term study, 17 of 58 (29%) and 23 of 58 (40%) had seroconverted after 2 and 3 years, respectively, of lamivudine therapy. Other data presented showed that in a subset of 26 patients who entered the study with ALT levels more than twice the normal level, the seroconversion rate was 73% after 4 years of therapy. These data suggest that pretreatment serum ALT is associated with increased rates of seroconversion. Patients in the study received 100 mg/day of oral lamivudine. Of the original 58 patients in the study, 44 were still on treatment through 4 years, 5 patients had stopped treatment after 3 years, and 9 additional patients withdrew before the end of 4 years. It was also noted that 39 of 58 (67%) of the patients developed YMDD variant hepatitis B virus, a mutant form that is associated with a diminished treatment response to lamivudine, at some point during treatment. However, 13 of these 39 (33%) achieved HbeAg seroconversion despite having a variant strain of hepatitis B. In 6 of these patients, seroconversion occurred after detection of the YMDD variants. Also, 23 of the 39 patients who were determined to have the YMDD variant virus had normal ALT levels at their last clinic visit. The long-term clinical significance of the YMDD variant is unknown, but these results suggest that the presence of the variant strain may not preclude patients from obtaining therapeutic benefit from lamivudine (4).

Glaxo Wellcome has launched lamivudine tablets (Zefix®) in Japan. The drug is indicated for the improvement in virus markers and hepatic function and histological improvement of liver in chronic hepatitis B associated with evidence of virus replication and abnormal liver function. Clinical trial results have shown that after treatment for 1 year, 64% of patients had negative HBV DNA (below the detection level), 65% of patients had normal ALT (GPT) and 95% had histological improvement. Zefix® provides simple dosing, the dosage for adult patients being 100 mg of lamivudine once daily. Glaxo Wellcome and Ajinomoto will copromote the drug in Japan (5).

1. Brown, N.A. et al. (Glaxo Group Ltd.) *Antiviral combinations comprising lamivudine and abacavir.* WO 0016779.

2. Brown, N.A. et al. (Glaxo Group Ltd.) *Antiviral combinations.* WO 0016755.

3. Brown, N.A. et al. (Glaxo Group Ltd.) *Antiviral combinations.* WO 0016754.

4. *Loss of hepatitis B antigen increases with increasing duration of lamivudine therapy.* DailyDrugNews.com (Daily Essentials) April 13, 2000.

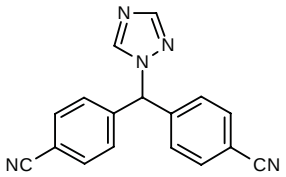
5. *Long-awaited HBV therapy launched in Japan.* DailyDrugNews.com (Daily Essentials) Nov 21, 2000.

Original monograph - Drugs Fut 1993, 18: 319.

Letrozole
Femara®

Oncolytic
Aromatase Inhibitor

EN: 164958



$C_{17}H_{11}N_5$ **Novartis; Chugai**

The utility of aromatase inhibition as a means of inducing ovulation in infertile patients with an inadequate response to clomiphene citrate has been evaluated in a prospective trial. Twelve women with anovulatory polycystic ovary syndrome (PCOS) and 10 with ovulatory infertility, all of whom had failed to ovulate and/or had an endometrial thickness of 0.5 cm or less following clomiphene treatment, were administered a single cycle of the aromatase inhibitor letrozole at an oral dose of 2.5 mg/day on days 3-7 of the menstrual cycle at least 2 months after clomiphene. During letrozole treatment in the PCOS group, ovulation occurred in 9 patients (75%), including 3 of 4 not ovulating in response to clomiphene, and 3 patients became pregnant (25%). In the other group of patients with ovulatory infertility, letrozole induced ovulation in all 10 subjects, a mean of 2.3 mature follicles and a mean endometrial thickness of 0.89 cm on the day of human chorionic gonadotropin (hCG) treatment, and 1 patient became pregnant. In contrast to clomiphene, no adverse effect on the endometrium was seen on letrozole. These preliminary findings indicate that aromatase inhibitors such as letrozole have potential as alternatives to clomiphene, or even as first-line treatment, of anovulatory and ovulatory infertility (1).

The FDA has now approved letrozole tablets (Femara®) for the first-line treatment of postmenopausal women with hormone receptor-positive or hormone receptor-unknown, locally advanced or metastatic breast cancer. The FDA based its decision on a head-to-head, multicenter, double-blind, randomized phase III trial comparing tamoxifen and letrozole in over 900 postmenopausal women with locally advanced (stage IIIB) disease, metastatic breast cancer, or recurrences not amenable to treatment with surgery or radiotherapy. The study showed significant differences favoring letrozole regards delay in disease progression (9.4 months *vs.* 6.0 months), overall tumor response rate (30% *vs.* 20%), clinical benefit (49% *vs.* 38%) and time to treatment failure (9.1 months *vs.* 5.7 months), along with equivalent tolerance (2).

Novartis has received approval under the mutual recognition procedure to market letrozole tablets (Femara®) in 14 European countries as first-line treatment for postmenopausal women with hormone-dependent advanced breast cancer. Individual country marketing authorizations are expected to follow. The agent also received approval from the U.K.'s Medicine Control Agency for the first-line indication, which was under a separate national procedure (3).

1. Mitwally, M.F.M., Casper, R.F. *Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate.* Fertil Steril 2001, 75(2): 305.

2. *FDA approves Femara for first-line treatment of breast cancer.* DailyDrugNews.com (Daily Essentials) Jan 11, 2001.

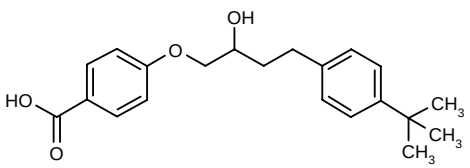
3. *Femara receives E.U. approval as first-line breast cancer therapy.* DailyDrugNews.com (Daily Essentials) Feb 1, 2001.

Original monograph - Drugs Fut 1994, 19: 335.

Lifibrol

Hypolipidemic

EN: 106850



$C_{21}H_{26}O_4$ **Klinge; Merckle**

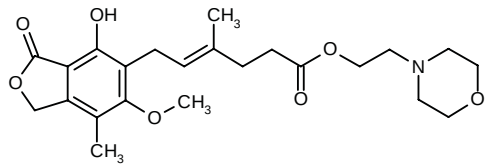
An *in vitro* study examined the effects of lifibrol on cholesterol metabolism in a hepatoma cell line (HepG2). Results suggest that the hypolipidemic action of the agent may be due, in part, to sterol-independent stimulation of the low density lipoprotein (LDL) receptor pathway. The agent decreased sterol formation from [^{14}C]-acetic acid by about 25% and had no effect on sterol formation from [^{14}C]-mevalonic acid. Although HMG-CoA reductase activity was not affected by lifibrol, the agent competitively inhibited HMG-CoA synthase. In addition, cellular binding, uptake and degradation of LDL were dose-dependently enhanced with lifibrol treatment and the amount of LDL receptors detected was increased. Lifibrol and lovastatin were both shown to induce microsomal HMC-CoA reductase activity in the absence of extracellular cholesterol. However, coincubation with LDL suppressed these effects (1).

1. Scharnagl, H. et al. *The effects of lifibrol (K12.148) on the cholesterol metabolism of cultured cells: Evidence for sterol independent stimulation of the LDL receptor pathway.* Atherosclerosis 2000, 153(1): 69.

Original monograph - Drugs Fut 1995, 20: 352.

Mycophenolate Mofetil *Immunosuppressant*
CellCept®
Munoloc®

EN: 144096



$C_{23}H_{31}NO_7$ **Roche**

The safety and efficacy of oral mycophenolate mofetil (1 g b.i.d. for 3 weeks followed by 0.5 g b.i.d. for 3 weeks) was shown in a trial involving 11 patients with severe stable plaque psoriasis (PASI = 12-53). Treatment with the agent for 3 weeks resulted in a decrease in PASI of 40-70% in 7 of 11 patients; 1 patient had a decrease in PASI of < 25%. A further although slight improvement in PASI was observed in 6 of the 11 patients following the reduction in dosage. However, 4 of the patients experienced an increase in PASI at the lower dose and another patient withdrew due to possible drug-related muscle pain. No gastrointestinal adverse events were observed in any of the patients. The mean PASI after 6 weeks of treatment was 16.1 (1).

A small randomized trial was conducted to study the safety and efficacy of replacement of ciclosporin or tacrolimus with mycophenolate mofetil in 28 liver transplant patients with renal dysfunction suspected to be due to calcineurin therapy. Ciclosporin or tacrolimus was replaced with mycophenolate mofetil in half of the patients and the other half served as controls. The patients switched to mycophenolate mofetil showed significant decreases in serum creatinine (41.3 μmol/l compared to controls), systolic blood pressure (10.8 mmHg compared to controls), diastolic blood pressure (5.0 mmHg compared to controls) and serum uric acid (83.1 μmol/l compared to controls) at 6 months after entry. Only patients switched to mycophenolate mofetil reported side effects, 8 of 14 reporting diarrhea, nausea, hair loss, vertigo, reduced appetite, pruritus, stomatitis and/or decrease in hemoglobin. Reversible acute rejection episodes arose in 3 patients on mycophenolate mofetil monotherapy, whereas no rejection occurred in the controls. Thus, replacement of calcineurin inhibitors with mycophenolate mofetil is associated with improvement in liver function and also other side effects such as hypertension and hyperuricemia, but on the other hand, mycophenolate mofetil monotherapy may also be associated with a risk of rejection (2).

Roche has received approval from the European Commission for the expanded use of mycophenolate mofetil for the prevention of organ rejection in patients undergoing liver transplantation. The drug is already approved in more than 70 countries for the prevention of organ rejection in patients undergoing kidney and heart transplantation and was approved for the liver transplant indication in the U.S. in August 2000. Regulatory applications for the liver transplant indication are pending in other countries. The decision was based on a double-blind, randomized, 565-patient, multicenter study which evaluated the effect of mycophenolate on acute rejection and survival in liver transplant patients, comparing its use to azathioprine (AZA), both in combination with ciclosporin and corticosteroids. The study showed mycophenolate to be superior to AZA in preventing acute rejection 6 months posttransplant. Rates of death or retransplantation 1 year later were similar in both groups (14.7% and 14.6% for mycophenolate and AZA, respectively) (3).

1. Geilen, C.C., Arnold, M., Orfanos, C.E. *Mycophenolate mofetil as a systemic antipsoriatic agent: Positive experience in 11 patients.* Br J Dermatol 2001, 144(3): 583.

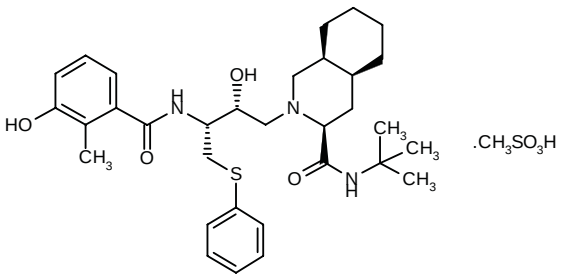
2. Schlitt, H.J., Barkmann, A., Boker, K.H.W. et al. *Replacement of calcineurin inhibitors with mycophenolate mofetil in liver-transplant patients with renal dysfunction: A randomised controlled study.* Lancet 2001, 357(9256): 587.

3. *E.C. approves Roche's CellCept for prevention of liver transplant rejection.* DailyDrugNews.com (Daily Essentials) Nov 20, 2000.

Original monograph - Drugs Fut 1995, 20: 356.

Nelfinavir Mesilate *Anti-HIV*
Viracept® *HIV Protease Inhibitor*

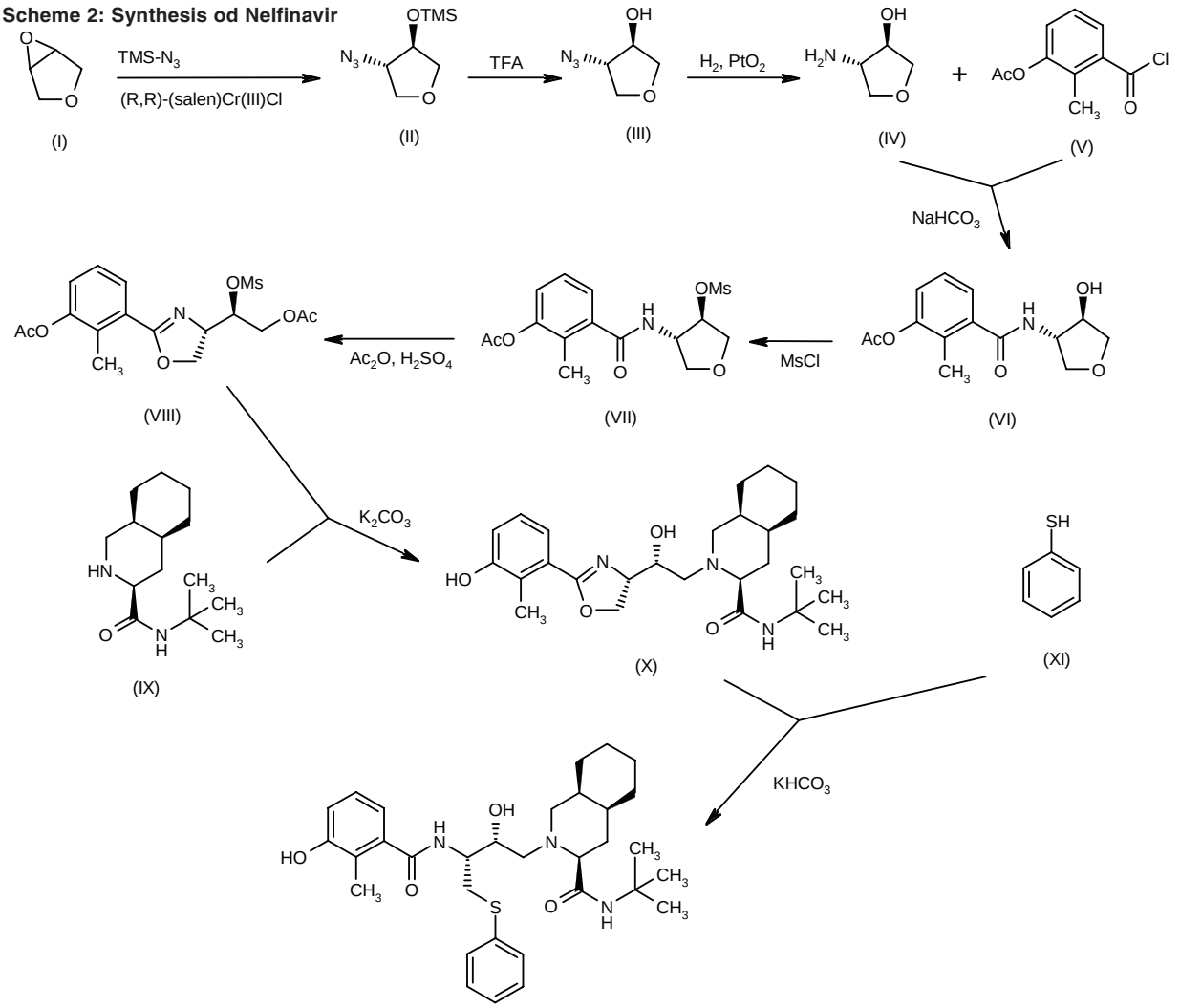
EN: 211732



$C_{32}H_{45}N_3O_4S.CH_4O_3S$ **Agouron; Roche; Japan Tobacco; Welfide**

A new concise synthesis of nelfinavir has been reported: The asymmetric desymmetrization of the *meso*-epoxide (I) by means of azidotrimethylsilane and a chiral

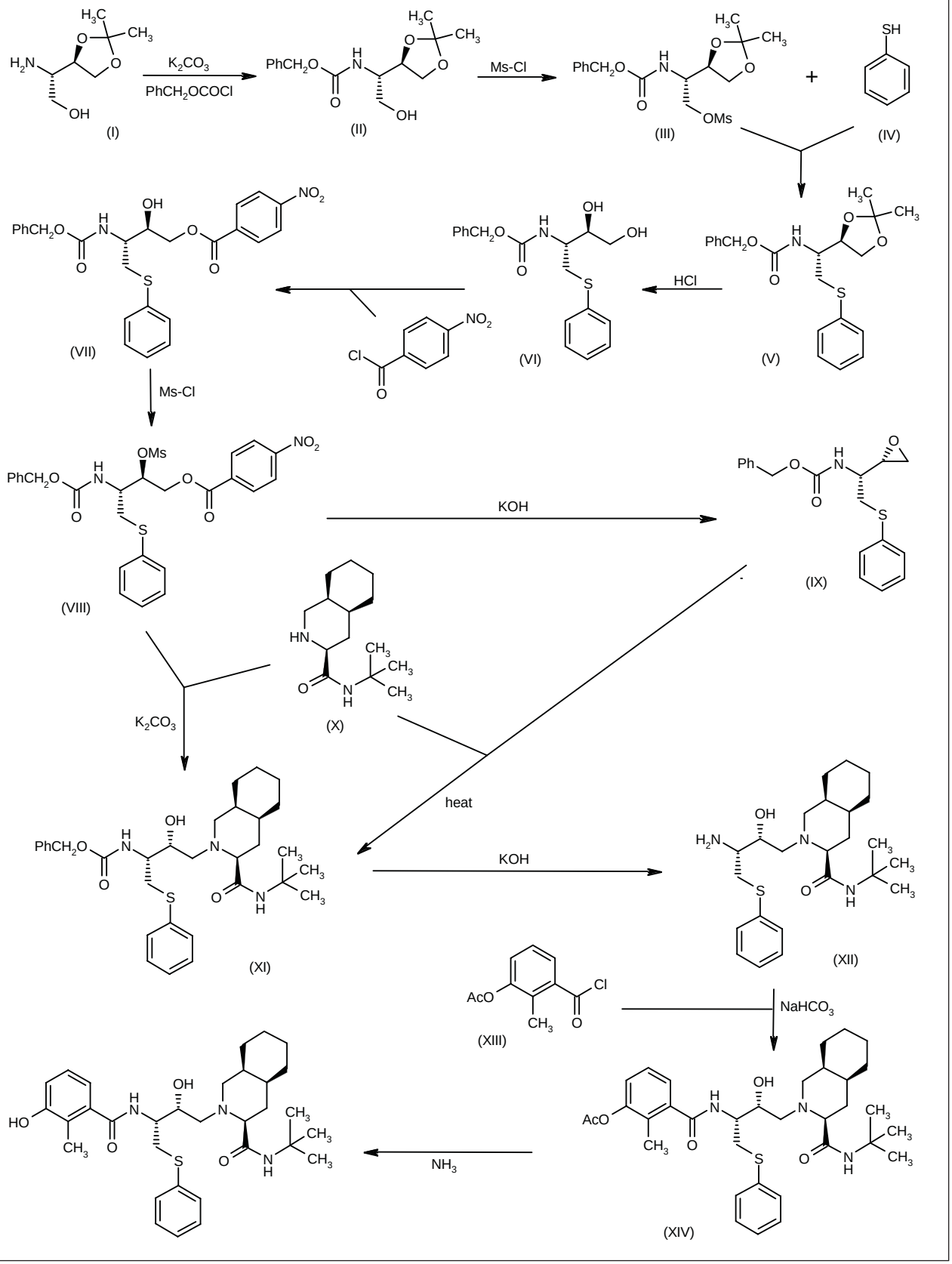
Scheme 2: Synthesis od Nelfinavir



(*R*,*R*)-(salen)chromium(III) complex as catalyst gives the chiral 3-(trimethylsilyloxy)-4-azidotetrahydrofuran (II), which is deprotected with TFA in methanol to yield the chiral 4-azidotetrahydrofuran-3-ol (III). Hydrogenation of (III) with H_2 over PtO_2 affords the chiral 4-aminotetrahydrofuran-3-ol (IV), which is condensed with 3-acetoxy-2-methylbenzoyl chloride (V) by means of $NaHCO_3$ in dichloromethane to provide amide (VI). The mesylation of the OH group of (VI) with MsCl gives mesylate (VII), which is isomerized with Ac_2O and H_2SO_4 to yield oxazoline (VIII). Condensation of compound (VIII) with the perhydroisoquinoline-3-carboxamide derivative (IX) by means of K_2CO_3 in methanol affords the oxazoline-adduct (X). Finally, the oxazoline-ring opening of compound (X) is performed with thiophenol (XI) and $KHCO_3$ (1). Scheme 2.

A new synthesis of nelfinavir has been described: The protection of the amino group of the dioxolane derivative (I) with benzyl chloroformate and K_2CO_3 in toluene gives the carbamate (II), which is mesylated with MsCl and triethylamine in toluene to yield the mesylate (III). Reaction of compound (III) with thiophenol (IV) by means of tetrabutylammonium bromide and NaOH in toluene/water affords the thioether (V), which is treated with HCl in methanol/water to provide diol (VI). Protection of the primary OH group of (VI) with *p*-nitrobenzoyl chloride and 2-picoline yields the *p*-nitrobenzoate (VII), which is mesylated as before to afford the protected compound (VIII). The reaction of (VIII) with KOH in dioxane gives epoxide (IX), which is condensed with *N*-*tert*-butylperhydroisoquinoline-3-carboxamide (X) in refluxing methanol to yield the addition product (XI). This compound (XI) can also be obtained by direct condensation of compound (VIII) with isoquinoline (X) by means of K_2CO_3 in methanol/water. Removal of the benzyloxycarbonyl group of (XI) with KOH in hot isopropanol affords compound (XII), which is condensed with 3-acetoxy-2-methylbenzoyl chloride (XIII) by means of $NaHCO_3$ in ethyl acetate to give

Scheme 3: Synthesis of Nelfinavir



the corresponding amide (XIV). Finally, this compound is deacetylated with ammonia in methanol (2). Scheme 3.

1. Zook, S.E., Busse, J.K., Borer, B.C. *A concise synthesis of the HIV-protease inhibitor nelfinavir via an unusual tetrahydrofuran rearrangement.* Tetrahedron Lett 2000, 41(36): 7017.

2. Inaba, T., Yamada, Y., Abe, H., Sagawa, S., Cho, H. *(1S)-1-[(4R)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-hydroxyethylammonium benzoate, a versatile building block for chiral 2-aminoalkanols: Concise synthesis and application to nelfinavir, a potent HIV-protease inhibitor.* J Org Chem 2000, 65(6): 1623.

Original monograph - Drugs Fut 1997, 22: 371.

Perflenapent Emulsion
EchoGen®

Ultrasound Contrast Agent

EN: 202607

2% w/v Dodecafluoropentane emulsion stabilized with fluorosurfactant (0.6% w/v) in a 30% solution of sucrose in water

Sonus

Sonus has renegotiated the U.S. marketing rights to its ultrasound contrast agent perflenapent (EchoGen®), with Abbott. As previously announced, Sonus and Abbott had entered into a modified agreement in February 2000 to allow the two companies to discuss alternative methods of marketing, selling and distributing perflenapent in the U.S. market. The companies have since agreed that Abbott will return U.S. marketing rights and materials related to the agent at no cost to Sonus and Abbott will have no further economic responsibilities to Sonus. However, as announced in February 2000, Abbott will continue to have responsibility for the manufacturing of the agent until mid-2002. Perflenapent is approved for marketing in the E.U. and is under review by the FDA for marketing in the U.S (1).

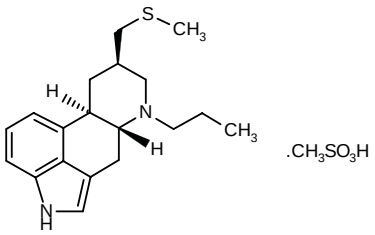
1. *Sonus renegotiates EchoGen marketing rights with Abbott.* DailyDrugNews.com (Daily Essentials) April 14, 2000.

Original monograph - Drugs Fut 1997, 22: 378.

Pergolide Mesylate
Permax®

Antiparkinsonian

EN: 090111



$C_{19}H_{26}N_2S.CH_4O_3S$ **Lilly; Athena Neurosciences; Draxis Health**

Health Canada has approved Draxis Health's pergolide mesilate (Permax®) for use as early therapy without levodopa in the treatment of Parkinson's disease (PD). The drug had previously been indicated solely as an adjunct to levodopa for the treatment of PD, but it has also shown potential when used as monotherapy in early stages of the disease. A new 3-year, double-blind study compared the effects of pergolide monotherapy and levodopa monotherapy. The results of this trial, which involved 294 previously untreated patients, demonstrated that pergolide enhances patient functioning in all stages of PD and that its early use, in place of levodopa, delays the onset of motor fluctuations and dyskinesias (1).

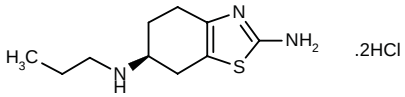
1. *Permax approved in Canada as monotherapy for PD.* DailyDrugNews.com (Daily Essentials) Nov 8, 2000.

Original monograph - Drugs Fut 1981, 6: 231.

Pramipexole Hydrochloride
Mirapex®
Sifrol®
Mirapexin®

Antiparkinsonian

EN: 130601



$C_{10}H_{17}N_3S.2HCl$ **Boehringer Ingelheim; Pharmacia**

A synergistic combination containing an α_2-agonist and a neuropsychopharmaceutical agent was claimed to be useful for the treatment of restless leg syndrome. Useful neuropsychopharmaceutical drugs may be opioids, benzodiazepines, dopamine agonists or a combination of levodopa and a decarboxylase inhibitor. A particularly claimed combination consists of clonidine as α_2-agonist and pramipexole (1, 2).

The Parkinson Study Group initiated the CALM-PD (Comparison of the Agonist pramipexole vs. Levodopa on Motor complications in Parkinson's Disease) trial, comparing pramipexole hydrochloride and levodopa in the early treatment of the disease. The multicenter, parallel-group, double-blind study enrolled 301 early Parkinson's patients who were randomized to pramipexole 0.5 mg 3 times per day with levodopa placebo or carbidopa/levodopa 25/100 mg 3 times per day with pramipexole placebo. Results after 2 years showed that, compared with levodopa, initial pramipexole treatment was associated with significantly less wearing off (24% on pramipexole *vs.* 38% on levodopa), dyskinesias (10% *vs.* 31%) and on-off motor fluctuations (28% *vs.* 51%). Levodopa treatment, however, was associated with more potent antiparkinsonian effects as measured on the Unified Parkinson's Disease Rating Scale. Somnolence and

hallucinations were also more prevalent in the pramipexole group than in the levodopa group. Further studies are needed to assess these side effects and to determine if initial treatment with pramipexole to reduce motor complications is preferable over improvements connected to levodopa therapy (3).

1. Brecht, H.-M. (Boehringer Ingelheim Pharma KG). *Drug therapy of the restless leg syndrome.* WO 0113903, DE 19938823.

2. Brecht, H.-M. (Boehringer Ingelheim Pharma KG). *Combination of active agents, said combination containing clonidine.* WO 0113902.

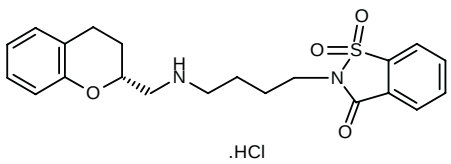
3. *Pramipexole vs levodopa as initial treatment for Parkinson's disease. A randomized controlled trial.* JAMA - J Am Med Assoc 2000, 284(15): 1931.

Original monograph - Drugs Fut 1992, 17: 291.

Repinotan Hydrochloride

5-HT$_{1A}$ Agonist
Neuronal Injury Inhibitor

EN: 224684



.HCl

$C_{21}H_{24}N_2O_4S.HCl$ **Bayer**

The efficacy of repinotan (10 μg/kg/h i.v. 5 min-4 h postinjury) in attenuating neuronal loss and enhancing cognitive performance was demonstrated in an *in vivo* study using rats with controlled cortical impact injury. Neither repinotan nor MK-801 affected motor function although both significantly improved spatial learning and memory. Repinotan decreased neuronal loss in the CA1 (34.2 ± 6.3 *vs.* 97.7 ± 2.6 and 15.9 ± 5.2 in sham and vehicle-treated controls, respectively) and CA3 (47.8 ± 9.7 *vs.* 101.9 ± 4.2 and 43.3 ± 12.3 in sham and vehicle-treated controls, respectively) and significantly decreased cortical tissue loss (20.1 ± 1.5 *vs.* 24.8 ± 1.6 mm^3 in vehicle-treated animals) (1).

The effects of Bay-x-3702 on serotonergic firing and release were examined in anesthetized rats and microdialyzed freely moving rats. The agent (0.25-4 μg/kg i.v.) suppressed the firing of 5-HT neurons in the dorsal raphe nucleus of anesthetized rats and this effect was blocked by the 5-HT$_{1A}$ receptor antagonist, WAY-100635 (5 μg/kg i.v.). Dose-dependent (10-100 μg/kg s.c.) decreases in 5-HT output were observed in the dorsal and median raphe nucleus, dorsal hippocampus and medial prefrontal cortex of freely moving rats. Maximum effects were observed (to about 15% of baseline) in the median raphe nucleus and prefrontal cortex with a dose of 0.1 mg/kg s.c.; a decrease to 45% of baseline was observed in the dorsal raphe nucleus and dorsal hippocampus with this same dose. These effects of the agent (30 μg/kg s.c.) were blocked by WAY-100635 (0.3 mg/kg s.c.). Administration of Bay-x-3702 (1-100 μM) in the dorsal raphe nucleus resulted in a decrease in local output to 25% of baseline. Likewise, administration of the agent (30 μM) in both the dorsal raphe nucleus and prefrontal cortex resulted in decreases in output in these two areas. WAY-100635 (100 μM) coperfusion blocked these effects (2).

Results from *in vitro* and *in vivo* experiments demonstrated that the neuroprotective activity of Bay-x-3702 may involve inhibition of glutamate release. *In vitro* experiments using rat hippocampal slices showed that the agent dose-dependently inhibited evoked glutamate release (IC_{50} = 1 μM); this effect was blocked by WAY-100635 indicating Bay-x-3702 action occurs at the 5-HT$_{1A}$ receptors. Microdialysis studies in rats subjected to permanent middle cerebral artery occlusion showed that the agent (1 or 10 μg/kg i.v. immediately after occlusion) attenuated the increase and total release of cortical extracellular glutamate by about 50% as compared to controls; aspartate levels were not altered by treatment (3).

A study using a rat model of transient forebrain cerebral ischemia demonstrated that Bay-x-3702 (4 μg/kg i.v.) rescued hippocampal and striatal neurons from apoptotic cell death via stimulation of 5-HT$_{1A}$ receptors. Treatment with the agent reduced neuronal damage in the hippocampal CA1 field by 10% and DNA laddering in both the hippocampus and striatum was decreased on day 4 after 10 min of forebrain ischemia. Treatment with WAY-100635 (1 mg/kg) blocked the effects of Bay-x-3702. Higher doses of the agent (12 and 40 μg/kg i.v.) had no effects, possibly due to the pronounced reduction in mean arterial blood pressure occurring during infusion of the agent (4).

In the phase II dose-finding BRAINS study in acute stroke patients, repinotan hydrochloride was characterized as having excellent tolerability and efficacy in improving neurological and functional outcome in patients receiving a dose of 1.25 mg/day over 3 days. Further analysis indicated that patient outcome was correlated both with certain baseline factors including stroke severity and with plasma concentrations in individual patients (5).

1. Kline, A.E., Yu, J., Yan, H.Q., Marion, D.W., Dixon, C.E. *The 5-HT$_{1A}$ agonist, repinotan (BAYx3702), attenuates histopathology and enhances cognitive performance in traumatically brain injured rats.* J Neurotrauma 2000, 17(10): Abst E14.

2. Casanovas, J.M., Berton, O., Celada, P., Artigas, F. *In vivo actions of the selective 5-HT$_{1A}$ receptor agonist BAY x 3702 on serotonergic cell firing and release.* Naunyn-Schmied Arch Pharmacol 2000, 362(3): 248.

3. Mauler, F., Fahrig, T., Horvath, E., Jork, R. *Inhibition of evoked glutamate release by the neuroprotective 5-HT$_{1A}$ receptor agonist BAY x 3702 in vitro and in vivo.* Brain Res 2001, 888(1): 150.

4. Schaper, C. et al. *Stimulation of 5-HT$_{1A}$ receptors reduces apoptosis after transient forebrain ischemia in the rat.* Brain Res 2000, 883(1): 41.

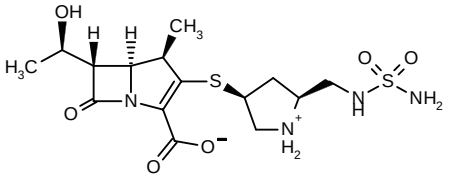
5. Teal, P., Rombout, F., Weber, H., Rodriguez, M., Cyrus, P. *Repinotan: An innovative phase III design in stroke.* Stroke 2000, 31(11): Abst 380.

Original monograph - Drugs Fut 1997, 22: 341.

S-4661
Doripenem

Carbapenem

EN: 194141



$C_{15}H_{24}N_4O_6S_2$ **Shionogi**

The *in vitro* and *in vivo* activity of injectable S-4661 was examined against several gynecological pathogens including *Streptococcus agalactiae*, *Escherichia coli*, *Peptostreptococcus magnus*, *Bacteroides fragilis* and *Prevotella bivia*. The MIC_{50} and MIC_{90} values were 0.25 and 1 mg/l, respectively. The efficacy of the agent was also demonstrated *in vivo* in rats with *E. coli* and *B. fragilis* intrauterine infections. Treated animals showed significantly less intrauterine neutrophil accumulation and a lower number of bacteria as compared to untreated animals (1).

The *in vitro* activity of S-4661 was examined against 202 recent clinical isolates of respiratory pathogens. Activity of the agent was similar or 2 times more potent against Gram-positive bacteria than imipenem, meropenem and biapenem and 8 times more active than ceftazidime. S-4661 was less active than meropenem against Gram-negative bacteria but 2-8 times more active than the other compounds. *Pseudomonas aeruginosa* was the most susceptible to S-4661 (2).

Doripenem is the proposed international nonproprietary name for S-4661 (3).

1. Mikamo, H., Izumi, K., Hua, Y.X., Hayasaki, Y., Sato, Y., Tamaya, T. *In vitro and in vivo antibacterial activities of a new injectable carbapenem, S-4661, against gynaecological pathogens.* J Antimicrob Chemother 2000, 46(3): 471.

2. Watanabe, A., Takahashi, H., Kikuchi, T., Kobayashi, T., Gomi, K., Fujimura, S., Tokue, Y., Nukiwa, T. *Comparative in vitro activity of S-4661, a new parenteral carbapenem, and other antimicrobial agents against respiratory pathogens.* Chemotherapy 2000, 46(3): 184.

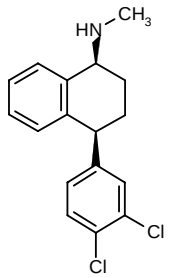
3. *Proposed international nonproprietary names (Prop. INN): List 83.* WHO Drug Inf 2000, 14(2): 112.

Original monograph - Drugs Fut 1995, 20: 367.

Sertraline
Zoloft®

Antidepressant
5-HT Reuptake Inhibitor

EN: 090172

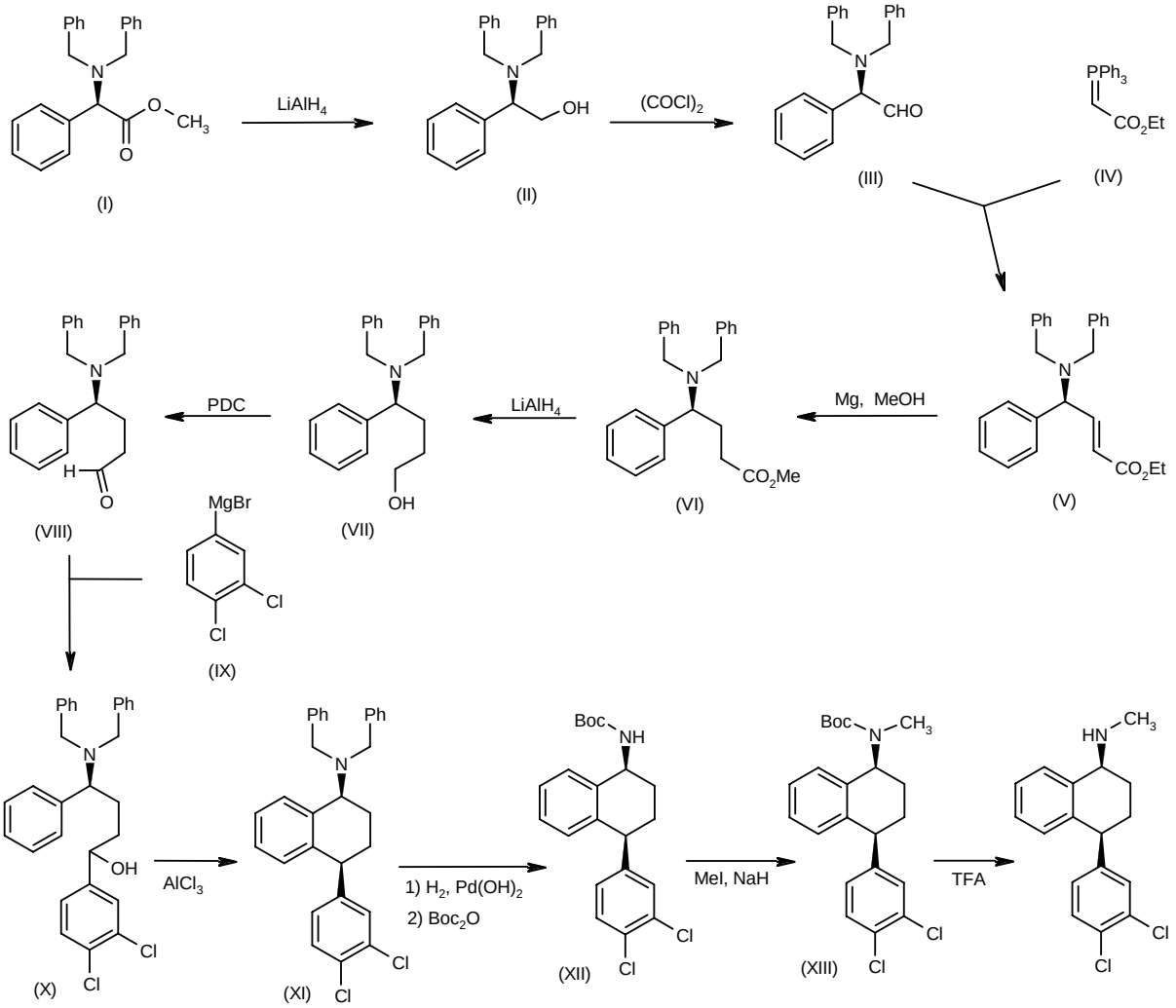


$C_{17}H_{17}Cl_2N$ **Pfizer**

A new total synthesis of sertraline has been described: The reduction of *N,N*-dibenzyl-D-phenylglycine methyl ester (I) with $LiAlH_4$ in THF gives alcohol (II), which is oxidized to aldehyde (III) with oxalyl chloride in dichloromethane. The condensation of (III) with the phosphorane (IV) in benzene yields the unsaturated ester (V), which is reduced with Mg in methanol to afford the saturated methyl ester (VI). Reduction of (VI) with $LiAlH_4$ in THF provides the corresponding butanol derivative (VII), which is oxidized to the aldehyde (VIII) with pyridinium dichromate (PDC) in dichloromethane. The Grignard reaction of (VIII) with 3,4-dichlorophenylmagnesium bromide (IX) in THF affords the secondary alcohol (X), which is cyclized by means of $AlCl_3$ in dichloromethane to yield a mixture of the desired *cis*-isomer (XI) along with some *trans*-isomer separated by column chromatography. Debenzylation of (XI) by H_2 over $Pd(OH)_2$ in methanol, followed by protection with Boc_2O, yields the carbamate (XII), which is methylated with methyl iodide and NaH in THF to afford the protected intermediate (XIII). Finally, compound (XIII) is deprotected with TFA in dichloromethane (1). Scheme 4.

In a 12-week, randomized, double-blind, placebo-controlled clinical trial, sertraline hydrochloride (Zoloft®) demonstrated significant efficacy in the treatment of posttraumatic stress disorder (PTSD). More than half of the patients administered sertraline (50-200 mg/day) responded to treatment as compared to 32% of patients given placebo. The trial included 187 outpatients diagnosed with PTSD, most of whom were women and most of whom had experienced physical or sexual assault. Improvement was measured by changes in Clinician-Administered PTSD Scale Part 2 (CAPS-2) total severity score, Impact of Event Scale (IES) total score, Clinical Global Impression-Severity (CGI-S) and CGI-Improvement ratings. Sertraline therapy improved all measures significantly more than placebo with the exception of the IES total score, which showed a trend toward significance. Sertraline therapy also improved patients' ratings of quality of life. The drug was well tolerated, with insomnia as the most notable adverse effect. Further trials will

Scheme 4: Synthesis of Sertraline



assess the efficacy of sertraline in different groups of PTSD patients and the benefits of long-term treatment. Sertraline was approved in late 1999 by the FDA for the supplementary indication of posttraumatic stress disorder (2).

1. Chandrasekhar, S., Reddy, M.V. *An expedient total synthesis of cis-(+)-sertraline from D-phenylglycine.* Tetrahedron 2000, 56(8): 1111.

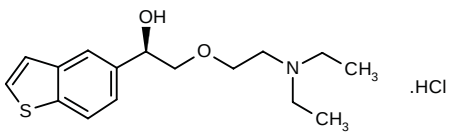
2. Brady, K., Pearlstein, T., Asnis, G.M., Baker, D., Rothbaum, B., Sikes, C.R., Farfel, G.M. *Efficacy and safety of sertraline treatment of posttraumatic stress disorder. A randomized controlled trial.* JAMA - J Am Med Assoc 2000, 283(14): 1837.

Original monograph - Drugs Fut 1984, 9: 277.

T-588

Cognition Enhancer

EN: 197376



$C_{16}H_{23}NO_2S.HCl$ **Toyama**

An *in vitro* study using PC12 cells showed that T-588 stimulated norepinephrine release in a dose-dependent and extracellular calcium-independent manner. Release of [^{3}H]-norepinephrine was observed with concentrations as low as 10 μM. T-588 (30 μM) enhanced the calcium-dependent release of [^{3}H]-norepinephrine induced by

ionomycin (10 μM), ATPγS (300 μM) and forskolin (10 μM). T-588 also dose-dependently increased cytosolic synaptophysin and 25 kDa synaptosome-associated protein immunoreactivity and induced translocation of synaptic vesicle in a calcium-dependent manner (1).

Results from a study using the Wobbler mouse model of motorneuronal disease showed that T-588 (3, 10 and 30 mg/kg/day p.o. for 4 weeks) delayed progression of neuromuscular dysfunction. Treatment resulted in potentiation of grip strength, attenuation of forelimb contracture and an increase in bicep muscle weight. In addition, denervation muscle atrophy was delayed and bicep and cervical cord choline acetyltransferase activity, bicep lactate dehydrogenase activity and cervical cord cAMP levels were increased in treated animals. Oral dosing with the agent resulted in efficient transport into the cerebrum and spinal cord (2).

1. Maekawa, M. et al. *Stimulation of noradrenaline release by T-588, a cognitive enhancer, in PC12 cells.* Jpn J Pharmacol 2000, 82(1): 59.

2. Ikeda, K., Iwasaki, Y., Kinoshita, M., Marubuchi, S., Ono, S. *T-588, a novel neuroprotective agent, delays progression of neuromuscular dysfunction in Wobbler mouse motoneuron disease.* Brain Res 2000, 858(1): 84.

Original monograph - Drugs Fut 1997, 22: 386.

Additional References

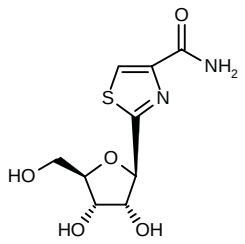
Ono, S., Narita, H. *Development of a novel cognition enhancer, T-588. Its protective effects on cultured cells and neurodegenerative Wobbler mice.* Jpn J Pharmacol 2000, 82(Suppl. 1): Abst S18-4.

Phuagphong, P. et al. *Effect of T-588 on mitochondrial function and cell death of cultured astrocytes.* Jpn J Pharmacol 2001, 85(Suppl. I): Abst P-710.

Takuma, K. et al. *T-588 inhibits astrocyte apoptosis via mitogen-activated protein kinase signal pathway.* Eur J Pharmacol 2000, 399(1): 1.

Tiazofurin *Oncolytic*
Tiazole®

EN: 090553



$C_9H_{12}N_2O_5S$ **ICN**

A new synthesis of tiazofurin has been reported: The cyclization of 5-*O*-benzoyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl-1-carbonitrile (I) with cysteine ethyl ester (II) by means of TEA in dichloromethane gives the thiazoline derivative (III), which is dehydrogenated with MnO_2 in the same solvent to yield the corresponding thiazole derivative (IV). Removal of the isopropylidene protecting group of (IV) with TFA in THF/water affords 2-(5'-*O*-benzoyl-β-D-ribofuranosyl)thiazole-4-carboxylic acid ethyl ester (V), which is finally debenzoylated and amidated by reaction with ammonia in methanol (2). Scheme 5.

ICN has received orphan drug status from the FDA for tiazofurin (Tiazole®) for the treatment of chronic myelogenous leukemia (CML) in accelerated phase or blast crisis. In early clinical studies sponsored by the National Cancer Institute, tiazofurin was found to be active in patients with CML with blast crisis. The drug is currently undergoing phase II/III trials in patients with CML in accelerated phase or blast crisis, ovarian cancer and multiple myeloma (2).

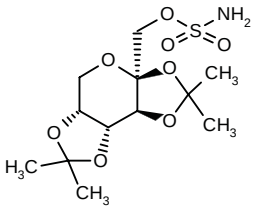
1. Ramasamy, K.S., Bandaru, R., Alverett, D. *A new synthetic methodology for tiazofurin.* J Org Chem 2000, 65(18): 5849.

2. *ICN granted orphan drug status for Tiazole.* DailyDrugNews.com (Daily Essentials) Jan 18, 2001.

Original monograph - Drugs Fut 1985, 10: 304.

Topiramate *Antiepileptic*
Topamax Sprinkle® *Antimigraine*
Topamax® *Treatment of Neurogenic Pain*

EN: 105605



$C_{12}H_{21}NO_8S$ **Janssen; Kyowa Hakko**

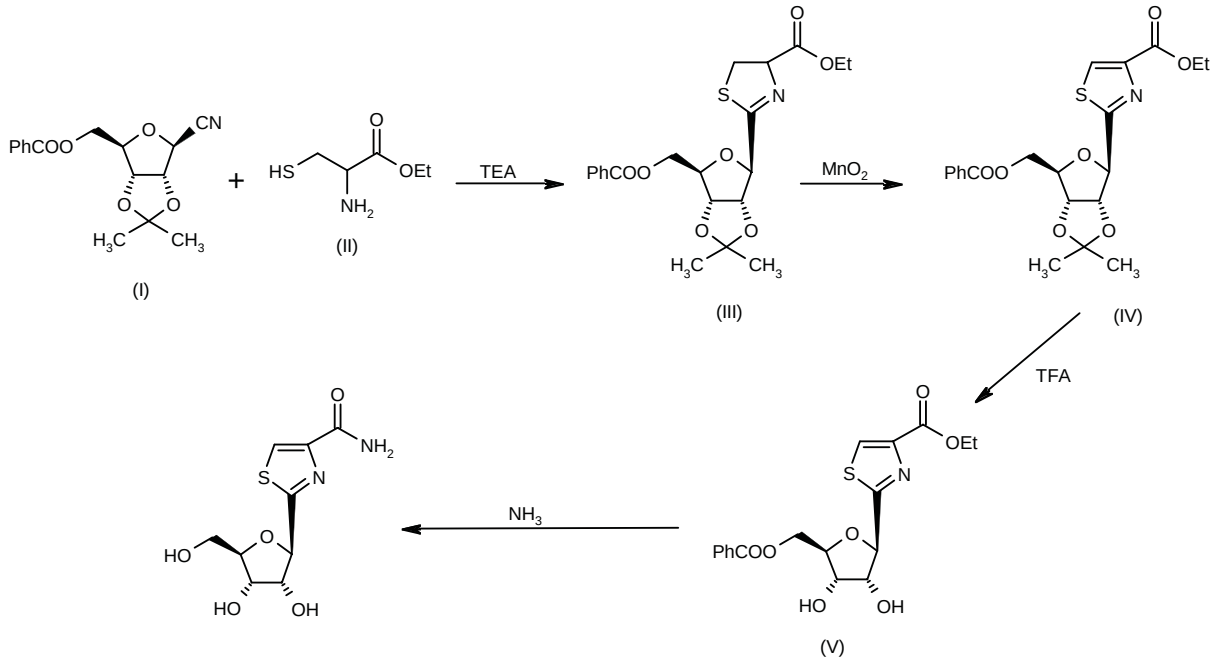
Anticonvulsant agents, such as topiramate, have been found to be useful for the treatment of alcohol dependency, addiction and abuse. Topiramate was found to prevent ethanol withdrawal signs in a rat model of chronic intermittent ethanol ingestion (1).

The use of sulfamates, previously known as anticonvulsants, for the treatment of schizophrenia has been claimed. The preferred compound of the invention is topiramate (2).

The use of anticonvulsants for the treatment of cluster headaches has been claimed. Particularly preferred is topiramate, which demonstrated its efficacy in 5 patients with episodic cluster headaches, producing a rapid improvement in the induction of cluster remission and a reduction in duration of cluster (3).

A method for the treatment of bulimia nervosa comprising the administration of anticonvulsant compounds

Scheme 5: Synthesis of Tiazofurin



has been claimed. Particularly preferred compound for this use is topiramate (4).

The use of anticonvulsant agents, particularly topiramate, for the treatment of transformed migraine has been reported. Four patients with a history of intractable headaches (2 rebound and 2 transformed migraine) reported a decrease in the number of daily headaches following treatment with topiramate (5).

Based on its inhibitory effects against voltage-gated Na^+ and Ca^{2+} channels and its GABAergic and glutamatergic effects, topiramate has been suggested to have potential in the treatment of neuropathic pain and has been evaluated in a double-blind, randomized, placebo-controlled study in 27 patients with diabetes and symptoms of painful diabetic neuropathy of at least 6 months' duration. The patients were randomized (1:2) to receive placebo or topiramate titrated up to 200 mg b.i.d. or the individually maximum tolerated dose over 9 weeks and continued on this dose for 4 more weeks. According to assessment on the Short-Form McGill Pain Questionnaire (SF-MPQ) and the visual analogue scale of the SF-MPQ, patients treated with topiramate had significantly less pain on average than those receiving placebo. However, no significant difference was seen between the groups in Patient Global Impression of Change (PGIC) scores. Side effects most frequently reported on topiramate were asthenia, weight loss and confusion, 5 of 18 topiramate-treated patients and 1 of 9 placebo-treated patients withdrawing due to adverse events. Overall, it was concluded that topiramate may represent a new treatment option for painful diabetic neuropathy and larger trials appear to be indicated (6).

Retrospective analysis of all patients treated with topiramate (from 11/97 to 2/00) identified 20 individuals with neuropathic pain (for 2-5 years) due to diabetes, idiopathy or Guillain-Barre syndrome. These patients failed previous treatments with gabapentin, amitriptyline or carbamazepine. The average topiramate dose received was 260 mg/day with 11 patients administered the agent for 13-27 months. Of these 20 patients, 3, 9 and 5 had complete, excellent and good responses on topiramate, respectively. Objective improvements in small fiber sensory function were seen in 4/12 patients with diabetes. Treatment was well tolerated with the most common adverse events including weight loss (8 cases) and dizziness (2 cases). Of the 6 patients who discontinued, 4 were for adverse events and 1 for lack of response (7).

Retrospective analysis of all patients treated with topiramate (from 11/97 to 2/00) identified 8 individuals with trigeminal neuralgia (for 1-16 years). These patients failed previous treatments with gabapentin, phenytoin, baclofen or carbamazepine. The average topiramate dose received was 175 mg/day and patients were followed for 3-21 months. While 4 patients received topiramate monotherapy, 1, 1 and 2 patients received topiramate with concomitant gabapentin, phenytoin and carbamazepine, respectively. Good to excellent responses were seen in the 4 patients receiving monotherapy and in 2 patients also given carbamazepine. No serious adverse events were seen. One patient experienced dizziness, nausea, disorientation, memory loss and

paresthesias and 1 patient given a dose of 25 mg/day discontinued due to dizziness and nausea (8).

A randomized, double-blind, placebo-controlled, 2-period crossover study in 3 patients with trigeminal neuralgia examined the efficacy of 12 weeks of oral topiramate. Those patients responding were enrolled in a subsequent confirmatory study. In the first part of the study, all 3 patients responded to treatment with a significant reduction in pain of 46% obtained. All patients entered the subsequent confirmatory study although no significant responses were observed. Only a 12% trend for pain reduction was observed. The maximum tolerated topiramate dose was 308 mg. Irritability and diarrhea were the most frequent adverse events reported. It was concluded that a larger study group is required to evaluate the effects of topiramate in trigeminal neuralgia (9).

The FDA has approved a slower initial titration schedule for topiramate (Topamax® Tablets and Sprinkle Capsules). Topiramate is currently indicated as add-on treatment for the majority of seizures affecting epileptic patients. Slower titration has been shown to improve tolerability and may reduce the rate of discontinuation, according to postmarketing data from physicians with clinical experience. The new dosing schedule recommends initiating therapy at 25 mg/day, with weekly increases of 25 mg for the first 4 weeks. Thereafter, the daily dose may be increased by 25-50 mg/day until an effective daily dose is achieved. The time to reach an effective dose may be delayed using the slower titration, but some adult patients may nevertheless begin to experience clinical response at 200 mg/day (10).

1. Gordey, M. et al. (Ortho-McNeil Pharmaceutical, Inc.). *Anticonvulsant derivs. useful in treating alcohol dependency, addiction and abuse.* WO 0023059.

2. Van Kammen, D.P. (Ortho-McNeil Pharmaceutical, Inc.). *Topiramate and related derivs. for treating schizophrenia.* WO 0032183.

3. Carrazana, E., Wheeler, S.D. (Ortho-McNeil Pharmaceutical, Inc.). *Anticonvulsant derivs. useful in treating cluster headaches.* WO 0042996.

4. Hoopes, S.P. (Ortho-McNeil Pharmaceutical, Inc.). *Use of anticonvulsant derivs. for treating bulimia nervosa.* WO 0044374.

5. Potter, D.L. (Ortho-McNeil Pharmaceutical, Inc.). *Anticonvulsant derivs. useful in treating transformed migraine.* WO 0042995.

6. Edwards, K.R., Glantz, M.J., Button, J., Norton, J.A., Whittaker, T., Cross, N. *Efficacy and safety of topiramate in the treatment of painful diabetic neuropathy: A double-blind, placebo-controlled study.* Neurology 2000, 54(7, Suppl. 3): Abst S15.001.

7. Connor, G.S. *Efficacy of the anticonvulsant topiramate in treatment-resistant diabetic or idiopathic neuropathic pain.* 19th Annu Sci Meet Am Pain Soc (Nov 2-5, Atlanta) 2000, Abst 674.

8. Haugh, M.J., Connor, G.S. *Trigeminal neuralgia: Pain relief in patients treated with the anticonvulsant topiramate.* 19th Annu Sci Meet Am Pain Soc (Nov 2-5, Atlanta) 2000, Abst 675.

9. Gilron, I. et al. *Topiramate in trigeminal neuralgia: A randomized, placebo-controlled, multiple crossover trial in three patients.* 19th Annu Sci Meet Am Pain Soc (Nov 2-5, Atlanta) 2000, Abst 857.

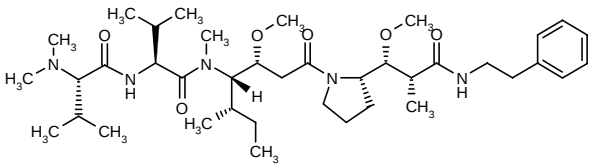
10. *FDA-approved slower Topamax titration schedule improves tolerability.* DailyDrugNews.com (Daily Essentials) May 18, 2000.

Original monograph - Drugs Fut 1989, 14: 342.

TZT-1027
Auristatin PE

Oncolytic
Microtubule Inhibitor

EN: 227146



$C_{39}H_{67}N_5O_6$

Teikoku Hormone

An *in vitro* study using PC14 cells examined the gene expression profile induced by TZT-1027 as compared to vindesine and paclitaxel. TZT-1027 increased expression of the genes encoding for cell cycle and growth regulators and decreased expression of genes encoding for products involved in cell-cell interactions. In contrast, vindesine and paclitaxel increased expression of angiogenesis factors and decreased expression of PAI-1, a gene encoding for a neovascularization inhibitory factor. While these agents decreased the expression of genes encoding MAP kinase (SADkk3, p63-MAPK and p44-MAPK), TZT-1027 increased their expression (1).

The antiangiogenic effects of TZT-1027 have been evaluated. TZT-1027 was much more potent than TNP-470 in the chick chorioallantoic membrane (CAM) assay, producing about 80% inhibition of neovascularization at 0.01 mcg/egg compared to about 40% inhibition at 20 μg/egg for the reference compound. It also potently inhibited tube formation in human umbilical vein endothelial cells, with complete inhibition at concentrations ranging from 0.1 ng/ml to 0.1 μg/ml. In mice bearing advanced colon 26 tumors, administration of TZT-1027 was followed by increases in IL-6 levels in both serum and tumors and an increase in TNF-α levels only in tumors (2).

The results from experimental studies indicated that TZT-1027 initially induces functional impairment of tumor blood vessels, followed by necrosis of both tumor blood vessels and the core of the tumor at later time points (3).

1. Koh, Y. et al. *Gene expression profiling of a novel antimitotic agent TZT-1027 in PC14 cell line in comparison with vindesine and paclitaxel.* Jpn J Cancer Res 2000, 91(Suppl.): Abst 3771.

2. Watanabe, J., Kobayashi, M., Natsume, T., Fujio, N., Endo, Y., Sasaki, T. *Mechanism of anti-vascular effect of TZT-1027.* Jpn J Cancer Res 2000, 91(Suppl.): Abst 1786.

3. Kobayashi, M., Natsume, T., Watanabe, J., Fujio, N., Murakoshi, M., Horiuchi, T., Ogawa, K., Yasumura, K. *Tumor-specific anti-vascular effect of TZT-1027.* Jpn J Cancer Res 2000, 91(Suppl.): Abst 1787.

Original monograph - Drugs Fut 1999, 24: 404.

Additional References

Kobayashi, M. et al. *Antitumor activity of TZT-1027 against cytokinegene-transfected Lewis lung carcinomas inoculated to C57BL/6 mice.* Proc Amer Assoc Cancer Res 2000, 41: Abst 1372.

Natsume, T. et al. *Gene expression profiling of exposure to TZT-1027, a novel microtubule-interfering agent, in non-small cell lung cancer PC-14 cells and astrocytes.* Proc Amer Assoc Cancer Res 2000, 41: Abst 3524.

Niitani, H. et al. *Current status of clinical development in non small cell lung cancer (NSCLC) treated with new agents produced in Japan.* 10th Int Congr Anti-Cancer Treat (Jan 31-Feb 3, Paris) 2000, Abst S3-09.

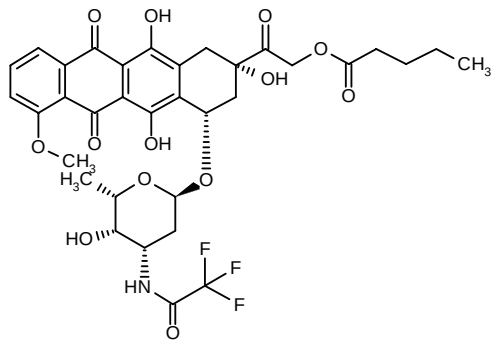
Ogawa, K. et al. *Tumor-specific anti-vascular effect of TZT-1027, an antimicrotuble agent.* Proc Amer Assoc Cancer Res 2001, 42: Abst 2237.

Watanabe, J. et al. *Induction of apoptosis in human cancer cells by TZT-1027, an antimicrotubule agent.* Apoptosis 2000, 5(4): 345.

Valrubicin
Valstar®
Valtaxin®

Oncolytic

EN: 090162



$C_{34}H_{36}F_3NO_{13}$

Anthra; Paladin; Celltech Medeva; Pharmacia

The Canadian Therapeutic Products Programme has granted Paladin a notice of compliance permitting the sale of valrubicin (Valtaxin®) in Canada. Valrubicin is indicated for the intravesical therapy of refractory carcinoma in situ (CIS) of the bladder. Clinical trial results have shown that therapy with the agent allows one-third of patients to retain their bladders for up to 4 years. Valrubicin is also approved in the U.S. as Valstar® for the intravesical treatment of CIS, an indication for which orphan drug status has been granted by the FDA (1).

1. *Valtaxin approved in Canada for CIS of the bladder.* DailyDrugNews.com (Daily Essentials) July 24, 2000.

Original monograph - Drugs Fut 1980, 5: 171.

Virulizin®

Oncolytic

EN: 210243

Lorus Therapeutics; Faulding

Virulizin® activates macrophages and monocytes and potentiates TNF-α release from activated macrophages. Its efficacy appears to be related with natural killer (NK) cell activation. In nude mice, Virulizin® (0.2 ml/day i.p.) significantly inhibited the growth of human pancreatic cancer BxPC-3 and SU.86.86, melanoma A2058 and C8161, and breast adenocarcinoma MDA-MB-231 xenografts, and enhanced activity was seen in combination with gemcitabine against pancreatic cancers, with dacarbazine against melanoma and with paclitaxel against breast adenocarcinoma (1).

Lorus Therapeutics has reported that Virulizin® demonstrated better antitumor activity in mice bearing human breast cancer cells than paclitaxel, one of the standard treatments for breast cancer. Significant tumor growth inhibition was observed in 2 independent trials in a total of 20 mice, including tumor regressions in 9 of these mice, 6 of which experienced complete tumor regressions, following a 4-week treatment with Virulizin®. In another study, when Virulizin® and paclitaxel were combined, antitumor activity was more significant, with tumor regressions in 15 of 20 mice, 8 of which were total regressions (2).

Lorus Therapeutics has completed a meta-analysis of 3 phase I/II studies of Virulizin® which showed that the drug demonstrated clinical activity and was well tolerated by patients. Data from the meta-analysis of 61 patients with advanced pancreatic cancer showed that the number of adverse effects of Virulizin® was low for all 3 studies. The survival rates for patients treated with Virulizin® were also better than for gemcitabine – the standard treatment for pancreatic cancer – in a comparable study. Of the 61 patients, 49 were classified as evaluable, and 87% of these patients had received some form of treatment prior to entering these studies, with 46% receiving gemcitabine, 5-FU or other chemotherapeutic agents and 84% prior surgery. There was no difference in survival between patients who had or had not had prior chemotherapy, but those who did not receive prior surgery had worse prognosis as compared to those who did receive prior surgery. Among the 61 eligible patients treated with Virulizin®, the median survival rate was 4.6 months. The 6-month survival rate was 38% and the 9-month survival rate was 25%. In terms of the 49 evaluable patients, the median survival rate was 5.7 months, with 6-month and 9-month survival rates of 48% and

31%, respectively. In comparison, another study in 63 patients who received gemcitabine as second-line therapy after 5-FU chemotherapy had failed reported a median survival rate of 3.8 months, with a 6-month survival rate of 31% and 9-month survival of 15% (3).

The FDA has granted orphan drug status for Virulizin® for the treatment of pancreatic cancer. The drug, a nontoxic immunotherapy, recruits killer cells, monocytes and macrophages to attack tumor cells. The compound is in development as second-line therapy for advanced pancreatic cancer patients who are refractory or intolerant to conventional first-line therapies. Based on promising findings from a meta-analysis of 3 phase I/II studies for Virulizin® in pancreatic cancer, Lorus is planning a pivotal phase III trial for the drug in North America later this year (4).

1. Young, A., Feng, N.P., Jin, H., Wang, M., Dimitroulakos, J., Zee, B., Ely, G., Wright, J.A. *Virulizin as a novel immunotherapeutic agent for pancreatic cancer and melanomas: Results of preclinical evaluation and clinical trials.* Proc Amer Assoc Cancer Res 2001, 42: Abst 2719.

2. *Lorus Therapeutics' Virulizin shows better antitumor activity than Taxol in preclinical studies.* DailyDrugNews.com (Daily Essentials) Jan 10, 2001.

3. *Lorus Therapeutics reports strong meta-analysis results for Virulizin, prepares for phase III trials.* DailyDrugNews.com (Daily Essentials) June 28, 2000.

4. *Virulizin granted orphan drug status by FDA.* DailyDrugNews.com (Daily Essentials) Feb 20, 2001.

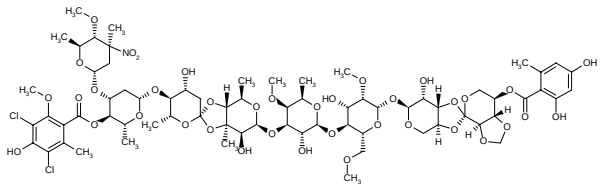
Original monograph - Drugs Fut 2000, 25: 356.

Additional Reference

Liu, C.N. et al. *Virulizin®-2 γ, a novel immunotherapeutic agent, in treatment of human pancreatic cancer xenografts.* Int J Oncol 2000, 16(5): 1015.

Ziracin™ *Everninomicin Antibiotic*
Antibiotic 13-384-1
Sch-27899
Evernimicin

EN: 113569



$C_{70}H_{97}Cl_2NO_{38}$ **Schering-Plough**

Results from an open-label, parallel-group study in 20 healthy male and female subjects grouped according to renal function (creatinine clearance rates [ml/min/1.73 m^2]: normal ≥ 80; mild ≥ 50; moderate > 30-49; severe > 15-29; dialysis ≤ 15) showed that a single dose of Ziracin™ (3 mg/kg) was well tolerated in all subjects and the pharmacokinetics of the agent were not altered by chronic renal insufficiency (1).

Evernimicin is the proposed international nonproprietary name for Ziracin™ (2).

Schering-Plough has announced that the company is voluntarily discontinuing development of Ziracin™. The decision was based on the fact that the antibiotic, which was designed for intravenous use in hospitalized patients with resistant Gram-negative infections, did not demonstrate a favorable enough balance between efficacy and safety in completed phase II and phase III clinical studies. In March 2000, the company suspended enrollment of new patients into these studies pending analysis of interim data. No patients are currently receiving the drug (3).

1. Banfield, C., Krishna, G., Lambrecht, L., Laughlin, M., Affrime, M. *Single dose pharmacokinetics of Ziracin in renal insufficiency.* Rev Esp Quimioter 2000, 13(Suppl. 2): Abst M284.

2. *Proposed international nonproprietary names (Prop. INN): List 82.* WHO Drug Inf 1999, 13(4): 274.

3. *Schering-Plough drops advanced-stage antibiotic upon final analysis of clinical data.* DailyDrugNews.com (Daily Essentials) May 9, 2000.

Original monograph - Drugs Fut 2000, 25: 360.

Additional References

Adrian, P.V. et al. *Evernimicin (SCH27899) inhibits a novel ribosome target site: Analysis of 23S ribosomal DNA mutants.* Antimicrob Agents Chemother 2000, 44(11): 3101.

Adrian, P.V. et al. *Mutations in ribosomal protein L16 conferring reduced susceptibility to evernimicin (SCH27899): Implications for mechanism of action.* Antimicrob Agents Chemother 2000, 44(3): 732.

Appleman, M.D. et al. *In vitro activities of daptomycin (DAP), linezolid (LIN), quinupristin/dalfopristin (SYN), Ziracin(ZIN), and vancomycin (VAN) against 255 unique clinical isolates of oxacillin-resistant Staphylococcus aureus isolated over four years (1996-1999).* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst E-2291.

Banfield, C. et al. *Pharmacokinetics, metabolism, and excretion of ^{14}C-Ziracin (evernimicin) in healthy male volunteers.* Clin Microbiol Infect 2000, 6(Suppl. 1): Abst MoO21.

Banfield, C. et al. *Single dose PK of Ziracin (evernimicin) in renal insuciency.* Clin Microbiol Infect 2000, 6(Suppl. 1): Abst MoO22.

Banfield, C.R. et al. *Effects of gender on the pharmacokinetics of Ziracin (evernimicin).* Rev Esp Quimioter 2000, 13(Suppl. 2): Abst M283.

Belova, L. et al. *A novel site of antibiotic action in the ribosome: Interaction of evernimicin with the large ribosomal subunit.* Proc Natl Acad Sci USA 2001, 98(7): 3726.

Brieland, J.K. et al. *Efficacy of SCH27899 in an animal model of Legionnaires' disease using immunocompromised A/J mice.* Antimicrob Agents Chemother 2000, 44(5): 1333.

Champney, W.S., Tober, C.L. *Evernimicin (SCH27899) inhibits both translation and 50S ribosomal subunit formation in*

Staphylococcus aureus cells. Antimicrob Agents Chemother 2000, 44(6): 1413.

Citron, D.M. et al. *In vitro activities of SCH 27899 (Ziracin, ZIR), quinupristin/dalfopristin (Synercid, SYN), linezolid (LIN), vancomycin (VAN) and other older agents against 255 clinical isolates of oxacillin resistant Staphylococcus aureus isolated over four years.* Clin Microbiol Infect 2000, 6(Suppl. 1): Abst WeP86.

Ganguly, A.K. *Ziracin, a novel oligosaccharide antibiotic.* J Antibiot 2000, 53(10): 1038.

Jones, R.N. et al. *In vitro Gram-positive antimicrobial activity of evernimicin (SCH 27899), a novel oligosaccharide, compared with other antimicrobials: A multicentre international trial.* J Antimicrob Chemother 2001, 47(1): 15.

Jones, R.N. et al. *Antimicrobial activity and spectrum of SCH27899 (Ziracin®) tested against Gram-positive species including recommendations for routine susceptibility testing methods and quality control.* Diagn Microbiol Infect Dis 1999, 34(2): 103.

Krishna, G. et al. *The effect of hepatic and renal impairment on the pharmacokinetics of SCH 27899.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 3461.

Krishna, G. et al. *The effect of gender and age on the pharmacokinetics of SCH 27899.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 2072.

Krishna, G. et al. *The drug interaction of SCH 27899 with an aminoglycoside and P450 probe substrates.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 3462.

Lin, C. et al. *Pharmacokinetics of an everninomicin (SCH 27899) in mice, rats, rabbits, and cynomolgus monkeys following intravenous administration.* Antimicrob Agents Chemother 2000, 44(4): 916.

McNicholas, P.M. et al. *Evernimicin binds exclusively to the 50S ribosomal subunit and inhibits translation in cell-free systems derived from both Gram-positive and Gram-negative bacteria.* Antimicrob Agents Chemother 2000, 44(5): 1121.

McNicholas, P.M. et al. *Update on evernimicin resistance in Gram-positive bacteria.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst C-1133.

Mukwaya, G.M. et al. *Comparative clinical study of Ziracin (evernimicin) and ceftriaxone for acute bacterial pneumonia caused by penicillin-resistant Streptococcus pneumoniae.* Clin Microbiol Infect 2000, 6(Suppl. 1): Abst WeP234.

Mukwaya, G.M. et al. *Comparative study of Ziracin (evernimicin) vs ceftriaxone in bacteriologically proven acute pneumonia caused by Strepytococcus pneumoniae.* Clin Microbiol Infect 2000, 6(Suppl. 1): Abst WeP235.

Pavia, C.S. et al. *Efficacy of an evernimicin (SCH27899) in vitro and in an animal model of Lyme disease.* Antimicrob Agents Chemother 2001, 45(3): 936.

Souli, M. et al. *In vivo activities of evernimicin (SCH 27899) against vancomycin-susceptible and vancomycin-resistant enterococci in experimental endocarditis.* Antimicrob Agents Chemother 2000, 44(10): 2733.

Sugimoto, Y. et al. *Influences of everninomicin, vancomycin and teicoplanin on chemical mediator release from rat peritoneal mast cells.* Jpn J Pharmacol 2000, 83(4): 300.

Tanaka, K. et al. *In vitro activity of an evernimicin derivative, SCH27899, against anaerobic bacteria and Propionibacterium acnes.* J Antimicrob Chemother 2000, 46(3): 465.

Tanba, M. et al. *Study of the tolerability and pharmacokinetics of SCH27899, a novel oligosaccharide antibiotic, following repeated administration in healthy volunteers.* Jpn J Clin Pharmacol Ther 2000, 31(2): 409.

Wang, E. et al. *In vivo activity and pharmacokinetics of Ziracin (SCH27899), a new long-acting everninomicin antibiotic, in a murine model of penicillin-susceptible or penicillin-resistant pneumococcal pneumonia.* Antimicrob Agents Chemother 2000, 44(4): 1010.