Drugs of the Future 2001, 26(12): 1199-1220

CCC: 0377-8282/2001

Information Update

Volume 1-25, Number 12

Estimated developmental phase for this month's updated products:

Preclinical

CP-9634 (anti-HIV, analgesic; Pfizer)

Phase I

Parthenolide (urologic; Cardiff Univ.)
Perifosine (oncolytic; Asta Medica, Zentaris, Nippon Kayaku)
RG-12525 (antidiabetic, PPARγ agonist; Aventis Pharma)

Phase II

Batimastat (matrix metalloproteinase inhibitor; British Biotech, InSite Vision)
Bay-38-4766 (anti-CMV; Bayer)
Edodekin alfa (oncolytic, anti-HCV; Genetics Inst.)
Elsamitrucin (antineoplastic antibiotic; Bristol-Myers Squibb, NeoOncoRx)
Emiglitate (antidiabetic; Mitsubishi-Tokyo Pharm., Bayer)
INN-00835 (antidepressant; Innapharma)
SR-48692 (antipsychotic, neurotensin antagonist; Sanofi-Synthélabo)

Phase III

ADL-82698 (treatment of constipation, treatment of IBS; Lilly, Adolor)
BMS-284756 (quinolone antibacterial; Toyama, Bristol-Myers Squibb)
Deramciclane fumarate (anxiolytic; Egis, Orion Corp., Pharmacia, Japan Tobacco)
Gestodene (hormone replacement therapy, prevention of osteoporosis; Schering AG)
Ilomastat (treatment of corneal wounds, antiasthmatic; Ligand, Sankyo, Arriva Pharm.)
Roflumilast (antiallergy/antiasthmatic, treatment of COPD; Byk Gulden)
Rubitecan (oncolytic; Stehlin Found. Cancer Res., SuperGen, Abbott)

Preregistered

FK-463 (antifungal; Fujisawa; Merck & Co.)

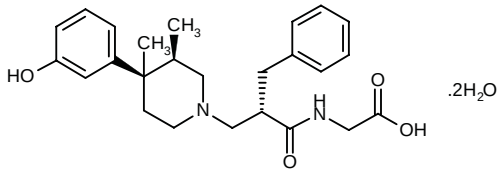
Launched/Year

Drospirenone (contraceptive, hormone replacement therapy; Schering AG)/2000
Fasudil hydrochloride (antiischemic, antianginal; Asahi Kasei, Schering AG)/1995
Lercanidipine hydrochloride (antihypertensive; Recordati, Pierre Fabre, Zambon, Forest)/1997
Maxacalcitol (antipsoriatic, treatment of thyroid disease; Chugai, Maruho)/2000
Mirtazapine (antidepressant; Organon, Solvay)/1994
Risperidone (antipsychotic; Janssen, Organon, Alkermes)/1993
Rofecoxib (antiarthritic, COX-2 inhibitor; Merck & Co.)/1999
Tenofovir disoproxil fumarate (anti-HIV; Gilead)/2001
Tiagabine hydrochloride (antiepileptic; Novo Nordisk, Sanofi-Synthélabo, Cephalon)/1996

ADL-82698
LY-246736 Dihydrate

Treatment of Constipation
Treatment of IBS

EN: 207549



$C_{25}H_{32}N_2O_4.2H_2O$ **Lilly; Adolor**

The effects of ADL-8-2698 on postoperative gastrointestinal function and length of hospitalization were evaluated in a randomized trial in 79 patients undergoing major abdominal surgery (partial colectomy, total abdominal hysterectomy) who received ADL-8-2698 as capsules of 1 mg or 6 mg or placebo capsules, in addition to opioids for postoperative pain relief. The higher dose of ADL-8-2698 was associated with significantly more rapid recovery of GI function compared to placebo, with a median time to the first passage of flatus of 49 h *versus* 70 h on placebo and a median time to first bowel movement of 70 h *versus* 111 h on placebo. The time to hospital dischage was also significantly shorter on ADL-8-2698 6 mg: 68 h *versus* 91 h on placebo. A beneficial effect on nausea and vomiting was also seen for the higher dose of ADL-8-1698. The effects of the lower dose of the opioid antagonist were less pronounced and not significantly different from placebo. The analgesic effect of systemic opioids was not affected, as evidenced by similar pain scores and daily opioid consumption in the three groups (1).

ADL-8-2698 has successfully completed phase II evaluation for two indications: the management of both opioid-induced bowel dysfunction and postoperative ileus. ADL-8-2698 has been developed to treat or prevent the gastrointestinal adverse effects of opioid analgesics, such as morphine and codeine without interfering with the beneficial analgesic effects of the opioid narcotics. A double-blind, placebo-controlled trial evaluated ADL-8-2698 in 20 patients with chronic opioid-induced constipation. Patients were randomly assigned to receive placebo, 0.5 mg or 1 mg of ADL-8-2698 for 21 consecutive days. Both groups taking ADL-8-2698 had dose-dependent improvement compared to placebo in the frequency and quality of bowel movements. In addition, the drug effect was sustained throughout the trial. In general, adverse effects reported were not significantly different between the placebo and drug groups, although a somewhat higher incidence of diarrhea was reported in the high-dose group early in the trial. Results from two additional phase II trials of ADL-8-2698 for the management of postoperative ileus have also been reported. These results have been combined with results from a previous phase II trial in order to analyze the overall dose-response to confirm doses for a phase III trial which began in March 2001. In the phase III trial, doses of 6 mg and 12 mg are being administered twice daily. The combined phase II results indicate that each of the twice-daily doses (3, 6 and 12 mg) resulted in statistically significant improvement in the primary clinical efficacy endpoint. The first of the two recently completed phase II trials was a multicenter, double-blind, placebo-controlled trial involving 65 patients undergoing abdominal surgery who were randomized to receive placebo or 12 mg of ADL-8-2698 twice daily. The median times for the recovery of gastrointestinal function and time to discharge from the hospital were improved by 9 and 5 h, respectively, and reached statistical significance. There were no drug-related safety concerns and ADL-8-2698 did not reduce the beneficial analgesic effects of systemic opioid narcotics administered to patients. The second trial was a multicenter, double-blind, placebo-controlled trial involving 132 patients who were randomized to receive placebo or ADL-8-2698 (3, 6 or 12 mg) twice daily. No serious adverse effects were reported and patients did not experience loss of analgesic effect. The median time for the recovery of gastrointestinal function improved by 16 h and reached statistical significance in the 12-mg dose group. The time to discharge from the hospital did not reach statistical significance (2).

Patient enrollment has begun in a double-blind, placebo-controlled, multicenter phase III trial of ADL-8-2698 for the treatment of opioid bowel dysfunction in patients taking opioid narcotics for chronic pain. In the U.S. phase III trial, a total of approximately 160 patients aged 18 years of age and older will receive either ADL-8-2698 or placebo once daily for 21 days (3).

1. Taguchi, A., Sharma, N., Saleem, R.M., Sessler, D.I., Carpenter, R.L., Seedsadr, M., Kurz, A. *Selective postoperative inhibition of gastrointestinal opioid receptors.* New Engl J Med 2001, 345(13): 935.

2. *Adolor's opioid narcotic antagonist completes phase II trials for two indications.* DailyDrugNews.com (Daily Essentials) July 2, 2001.

3. *Adolor's ADL-8-2698 enters phase III for second indication.* DailyDrugNews.com (Daily Essentials) July 11, 2001.

Original monograph - Drugs Fut 1994, 19: 1078.

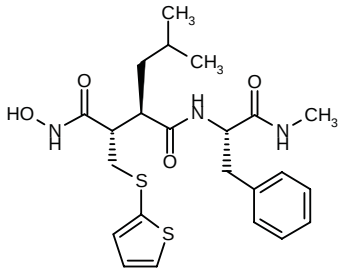
Additional Reference

Liu, S.S. et al. *ADL 8-2698, a trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine, prevents gastrointestinal effects of intravenous morphine without affecting analgesia.* Clin Pharmacol Ther 2001, 69(1): 66.

Batimastat

Matrix Metalloproteinase Inhibitor

EN: 193260



$C_{23}H_{31}N_3O_4S_2$ **British Biotech; InSite Vision**

Evidence implicating the involvement of matrix metalloproteinases (MMPs) in the disintegration of the vasculature following cerebral ischemia led investigators to examine the effects of pharmacological inhibition of MMPs with the relatively nonspecific inhibitor batimastat in a rabbit model of tPA-induced hemorrhage after thromboembolic stroke. This series of experiments involved the administration of batimastat (30 mg/kg s.c.) or vehicle at 5 min after occlusion of the middle cerebral artery and of batimastat or vehicle in combination with tPA (3.3 mg/kg i.v.) at 60 min after embolization. Control rabbits showed a 24% incidence of hemorrhage following embolic stroke compared to an 18% incidence on batimastat and a 77% incidence on tPA. Combination of batimastat and tPA was associated with a significant reduction in the incidence of hemorrhage compared to animals treated with tPA alone(41% *vs*. 77%). The clot lysis rate was not significantly different in tPA (49%) and batimastat + tPA groups (35%), whereas both groups showed significantly greater thrombolysis compared to vehicle-treated animals (5%). A trend for a reduction in the infarct rate was seen in the batimastat + tPA-treated animals (65% *vs.* 94% in the tPA group), but, on the other hand, this group also showed a trend for larger areas of ischemic damage compared to the tPA group. This study suggests that pretreatment with an MMP inhibitor may improve the safety of tPA in the management of acute stroke, preventing intracerebral hemorrhage, although further studies are necessary (1).

Batimastat was shown to have dose-dependent beneficial effects on inflammatory alterations in rats with trinitrobenzenesulfonic acid (TNB)-induced colitis. Rats were administered either TNB alone, or TNB plus intraperitoneal batimastat at doses of 5, 10 or 20 mg/kg. A separate group of control rats received intracolonic saline. Batimastat was administered 30 min prior to induction of colitis and twice daily for 7 days, at which time the animals were sacrificed and colon segments were removed for histological assessment of inflammation and myeloperoxidase (MPO) activity. Inflammation scores for control rats and rats treated with TNB alone were 0.9 and 12.4, respectively, as compared to scores of 10.1, 8.3 and 5.0 in rats treated with batimastat doses of 5, 10 and 20 mg/kg, respectively. Respective scores for MPO activity in the 5 groups were 0.235, 0.715, 0.474, 0.287 and 0.256 U/mg. The results further support the role of MMP in intestinal inflammation and suggest that MMP inhibition may be a novel therapeutic strategy in the treatment of inflammatory bowel disease (2).

1. Lapchak, P.A. et al. *Metalloproteinase inhibition reduces thrombolytic (tissue plasminogen activator)-induced hemorrhage after thromboembolic stroke.* Stroke 2000, 31(12): 3034.

2. Di Sebastiano, P., Di Mola, F.F., Artese, L., Rossi, C., Mascetta, G., Pernthaler, H., Innocenti, P. *Beneficial effects of batimastat (BB-94), a matrix metalloproteinase inhibitor, in rat experimental colitis.* Digestion 2001, 63(4): 234.

Original monograph - Drugs Fut 1996, 21: 1215.

Additional References

Balcom, J.H. IV et al. *Perioperative matrix metalloproteinase inhibition therapy does not impair wound of anastomotic healing.* Dig Dis Week (May 20-23, Atlanta) 2001, Abst 2049.

Colombo, S. et al. *An eye drop form of an extracellular proteinase inhibitor prevents retinal neovascularization in an animal model.* Invest Ophthalmol Visual Sci 2000, 41(4): Abst 3398.

Herzog, M.E. et al. *Inhibition of matrix metalloproteinase activity reduces prostate tumor cell proliferation, osteoclast recruitment, and bone degradation in human bone.* J Urol 2001, 165(5, Suppl.): Abst 219.

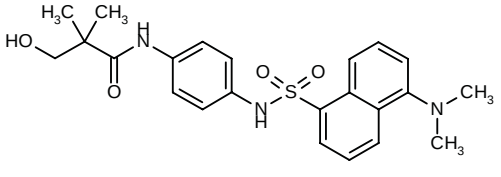
Lee, J. et al. *A matrix metalloproteinase inhibitor, batimastat, retards the development of osteolytic bone metastases by MDA-MB-231 human breast cancer cells in Balb C nu/nu mice.* Eur J Cancer 2001, 37(1): 106.

Van Beusekom, H.M.M. et al. *Matrix metalloproteinase inhibitor batimastat does not affect the degree of intimal thickening nor vascular wound healing in atherosclerotic stented porcine femoral arteries.* Eur Heart J 2001, 22(Suppl.): Abst 2513.

Bay-38-4766
Tomeglovir

Anti-CMV

EN: 279333



$C_{23}H_{27}N_3O_4S$ **Bayer**

Bay-38-4766 (10 mg/kg b.w. p.o.) demonstrated antiviral activity similar to that of ganciclovir in immunodeficient mice in which human cytomegalovirus-infected human cells were implanted (1).

Tomeglovir is the proposed international nonproprietary name for Bay-38-4766 (2).

1. Weber, O., Bender, W., Eckenberg, P. et al. *Inhibition of murine cytomegalovirus and human cytomegalovirus by a novel non-nucleosidic compound in vivo.* Antivir Res 2001, 49(3): 179.

2. *Proposed international nonproprietary names (Prop. INN): List 84.* WHO Drug Inf 2000, 14(4): 272.

Original monograph - Drugs Fut 1999, 24: 1297.

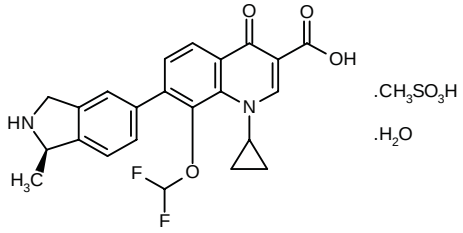
Additional Reference

McSharry, J.J. et al. *Susceptibilities of human cytomegalovirus clinical isolates to Bay 38-4766, Bay 43-9695, and ganciclovir.* Antimicrob Agents Chemother 2001, 45(10): 2925.

BMS-284756
T-3811ME

Quinolone Antibacterial

EN: 254897



$C_{23}H_{20}F_2N_2O_4.CH_4O_3S.H_2O$

Toyama;
Bristol-Myers Squibb

The antimicrobial spectrum of the desfluoroquinolone BMS-284756 against a range of bacterial isolates was studied. Its activity was tested against 300 staphylococcal isolates and 102 enterococcal isolates. Excellent activity was seen against oxacillin-susceptible staphylococci, all strains being inhibited at 0.5 μg/ml, while strains resistant to oxacillin required a concentration of 1 μg/ml. BMS-284756 inhibited 47% of *Enterococcus faecalis*, 68% of *Enterococcus* spp. and only 4% of *Enterococcus faecium* at 1 μg/ml, but all vancomycin-resistant enterococci were inhibited at 2 μg/ml (1).

BMS-284756 exhibited excellent activity against viridans group and hemolytic streptococci with MIC_{50} and MIC_{90} values of 0.06 and 0.12 μg/ml, respectively. Similar activity was seen against 328 *Streptococcus pneumoniae*, including penicillin-resistant isolates, with respective MIC_{50} and MIC_{90} values of 0.06 and 0.12 μg/ml. It was 16-fold more potent than levofloxacin against streptococci and levofloxacin-resistant strains remained susceptible with MICs of 0.5-4 μg/ml (2).

BMS-284756 proved highly active against *Moraxella catarrhalis* and *Haemophilus influenzae* (MIC_{90} = 0.03 μg/ml), with equivalent or superior activity to other new quinolones (3).

BMS-284756 demonstrated high activity against 136 ciprofloxacin-susceptible *S. pneumoniae* isolates and 116 ciprofloxacin-nonsusceptible *S. pneumoniae* isolates, with respective MIC_{90} values of 0.03 and 0.12 mg/ml. MIC_{90}s for the other fluoroquinolones tested against ciprofloxacin-nonsusceptible isolates ranged between 0.25-32 mg/ml (4).

Of BMS-284756, levofloxacin and moxifloxacin, BMS-284756 was the most active quinolone against *Chlamydia trachomatis* and *Chlamydia pneumoniae in vitro*, with MICs and MBCs similar to clarithromycin. The MIC_{90} value for 20 isolates of *C. pneumoniae* was 0.015, 0.5, 0.5 and 0.03 μg/ml for BMS-284756, levofloxacin, moxifloxacin and clarithromycin, respectively. The MIC and MBC against *C. trachomatis* for BMS-248756, levofloxacin, moxifloxacin and clarithromycin was 0.015, 0.5, 0.5 and 0.03 μg/ml, respectively. No variation was seen among isolates (5).

Investigators testing the activity of BMS-284756 against over 10,000 bacterial isolates found that the drug was more potent and had a broader spectrum of activity than gatifloxacin, ciprofloxacin and levofloxacin against Gram-positive cocci. BMS-284756 demonstrated less potency, however, against enteric Gram-negative bacilli and *Pseudomonas aeruginosa* bacterial isolates. None of the fluoroquinolones tested were active against *Enterococcus* spp. or *Acinetobacter* spp (6).

Determination of the activities of BMS-284756, levofloxacin and ciprofloxacin against wild-type and mutant strains of *Staphylococcus aureus* revealed that wild-type and GrlA mutant MT5224c(4) strains were susceptible to BMS-284756 and levofloxacin. The results also indicated that BMS-284756 may be the only agent with clinical efficacy against a double mutant such as GrlA/GyrA EN8 (7).

BMS-284756 was tested against over 3500 ciprofloxacin-resistant Gram-positive cocci and was found to have potent activity. At ≤ 4 mg/ml, the drug inhibited 93, 92, 65, 100 and 100% of *S. aureus*, coagulase-negative staphylococci, enterococci, *S. pneumoniae* and other streptococci isolates, respectively. Among the fluoroquinolones, the potency and spectrum of BMS-284756 was most similar to that of trovafloxacin, although it was 2- to 4-fold more potent against ciprofloxacin-resistant *S. pneumoniae* isolates. BMS-284756 also demonstrated potential against some oxacillin-resistant *S. aureus* species and some vancomycin- and fluoroquinolone-resistant streptococci (8).

BMS-284756 was highly active against *Campylobacter jejuni* (38 strains), *Helicobacter pylori* (21 strains) and *Legionella* spp. (66 strains) and most of 197 anaerobic isolates when tested using reference agar dilution and Etest methods (9).

The potential for BMS-284756 to treat community-acquired respiratory tract infections was shown when the drug demonstrated activity similar to levofloxacin, trovafloxacin and gatifloxacin against 257 *S. pneumoniae*, 198 *H. influenzae* and 88 *M. catarrhalis* strains isolated in Latin America. BMS-284756 inhibited all isolates at ≤ 0.12 μg/ml (10).

The antianaerobic activity of BMS-284756 against Gram-positive microorganisms, *Enterobacteriaceae* and other bacteria has been compared to a series of other antimicrobial agents against 357 clinical isolates. Respective MIC_{50} values for BMS-284756, ciprofloxacin, levofloxacin, moxifloxacin, trovafloxacin, amoxicillin/clavulanate, piperacillin/tazobactam, imipenem, clindamycin and metronidazole were 0.5, 2.0, 1.0, 0.5, 0.5, 0.5, 0.25, 0.06, 0.25 and 1.0 μg/ml, and respective MIC_{90} values were 2.0, 16.0, 8.0, 4.0, 2.0, 2.0, 8.0, 1.0, 8.0 and 16.0 μg/ml. BMS-284756 thus exhibited similar potency to trovafloxacin and amoxicillin/clavulanate against anaerobic isolates. Together with its broad-spectrum activity against *Enterobacteriaceae*, these findings indicate potential utility in the empiric therapy of mixed aerobic/anaerobic infections (11).

The killing rates for BMS-284756, trovafloxacin, levofloxacin, beta-lactams and vancomycin have been compared against clinical isolates of *Enterobacteriaceae*, staphylococci, streptococci and enterococci. BMS-284756 was first shown to be highly active against all the bacterial strains tested, with MICs ranging from 0.016-0.25 mg/l. More rapid bactericidal activity was generally seen following exposure to BMS-284756, trovafloxacin and levofloxacin compared to vancomycin and β-lactam antibiotics, although this effect was dependent on the bacterial group. *Enterobacteriaceae* were rapidly killed by the quinolones in under 2 h compared to 6 h or more for the β-lactam antibiotic cefotaxime. Staphylococci were killed somewhat more slowly by BMS-284756, trovafloxacin and levofloxacin (generally 2-4 h), but β-lactams and vancomycin were slower yet (4-24 h). Against most streptococci and *E. faecalis*, a 99.9% decrease in viable count was seen only after 6 h for all antibiotics tested. Overall, the results indicate that quinolones, including BMS-284756, have a superior bactericidal profile compared to vancomycin or beta-lactams (12).

An *in vitro* study examined combinations of BMS-284756 and other antimicrobial agents against multidrug-resistant Gram-positive and Gram-negative pathogens. The results demonstrated that BMS-284756 was not antagonistic in combination with any of the antimicrobials tested (cefepime, aztreonam, amikacin, rifampin, vancomycin) and had synergistic activity in combination with cefepime, aztreonam and amikacin against a number of highly resistant Gram-negative pathogens, including vancomycin-resistant *Stenotrophomonas maltophilia*, *Serratia marcescens*, *Escherichia coli* and *Enterobacter cloacae*. No interaction was seen with rifampin or vancomycin against oxacillin-resistant *S. aureus* or vancomycin-resistant *E. faecium* (13).

The *in vitro* activity of BMS-284756 has been determined against recent fluoroquinolone- and multidrug-resistant pneumococcal isolates. The MIC_{50} and MIC_{90} values against fluoroquinolone-resistant isolates were 0.5 and 1 μg/ml, respectively, and 0.06 μg/ml against the multidrug-resistant strains. The activity of BMS-284756 was superior to several currently available fluoroquinolones (14).

A chinchilla model of experimental otitis media caused by quinolone-susceptible or -resistant *S. pneumoniae* was used to evaluate and compare the activity of BMS-284756 and levofloxacin. Following preliminary pharmacokinetic studies, a dose of BMS-284756 of 17 mg/kg/day and a dose of levofloxacin of 30 mg/kg/day were selected. Both compounds were able to eradicate quinolone-susceptible *S. pneumoniae* in middle ear fluid by day 5, although nasopharyngeal colonization was not completely eradicated. The agents were not effective, however, against the resistant strains of *S. pneumoniae* (15).

The *in vitro* activity of BMS-284756 was compared to ciprofloxacin, levofloxacin, moxifloxacin and gemifloxacin against recent clinical isolates of *S. pneumoniae*, including penicillin/macrolide-resistant, penicillin-resistant and penicillin-susceptible isolates. The MIC values for BMS-284756 were among the lowest of the quinolones tested, with MIC_{90} values of 0.12 mg/l independent of penicillin and/or erythromycin susceptibility. Moreover, it was effective against isolates resistant to ciprofloxacin, with MIC values of 0.5-2 mg/l (16).

BMS-284756 was generally less active *in vitro* than ciprofloxacin, gemifloxacin, levofloxacin and gatifloxacin against nonfermentative Gram-negative bacilli including 129 *P. aeruginosa*, 97 *Stenotrophomonas/Burkholderia* gr. and 43 *Acinetobacter* spp. (17).

More than 2100 isolates associated with skin and soft tissue infections from Europe, North America and Latin America were tested against BMS-284756, ciprofloxacin, gatifloxacin and levofloxacin. BMS-284756 was the most active agent against *S. aureus* and was also active against oxacillin-resistant strains. BMS-284756 was 2-4 times more potent than levofloxacin against coagulase-negative staphylococci and had a greater spectrum and potency against *Enterococcus* spp. Levofloxacin showed greater activity against *Klebsiella* spp. and *Enterobacter* spp. (18).

BMS-284756 was tested against 590 recent clinical isolates of 33 species of Gram-positive and Gram-negative anaerobes and found to be highly active. The agent was generally ≥ 2-fold more active than moxifloxacin and similar to or slightly more active than trovafloxacin (19).

Most of the 1872 isolates of *H. influenzae* and 810 isolates of *M. catarrhalis* tested were highly susceptible to several quinolones tested, including BMS-284756, with MIC_{90} values of 0.016- ≤ 0.03 μg/ml) (20).

Studies in animal models and in humans have indicated that the lack of the 6-position fluorine does not greatly alter the pharmacokinetics or pharmacodynamics of BMS-284756 as compared with other fluoroquinolones.

Multiple oral doses of BMS-284756 (100-1200 mg/day) were well tolerated. Approximate values for the maximum plasma concentration, AUC and elimination half-life for a 400-mg dose were 5 μg/ml, 60 μg·h/ml and 13-17 h, respectively. Both renal and nonrenal pathways are involved in the drug's disposition and absorption is not affected by administration with food. Pharmacodynamic experiments in a murine model suggested that the AUC/MIC ratio is predictive of the drug's antibacterial activity (21).

The safety, tolerability and pharmacokinetics of multiple oral doses of BMS-284756 were assessed in a randomized, double-blind, placebo-controlled study in 40 healthy volunteers. Subjects were divided into 5 sequential dose groups of 100, 200, 400, 800 and 1200 mg. There were no serious adverse events or changes in laboratory parameters or physical examinations. Between 100-400 mg, systemic exposure to the drug increased in a ratio similar to the dose increment. Pharmacokinetic evaluation indicated that the drug can be administered once a day, and that multiple oral doses up to 1200 mg were safe and well tolerated (22).

The safety and efficacy of BMS-284756 have been assessed in a multicenter, open-label trial in 281 adults with acute bacterial maxillary sinusitis, 266 of whom were evaluable for response. At a dose of 400 mg once daily for 10 days, BMS-284756 produced clinical cure in 95.8% and 91.3%, respectively, at days 11-13 and 17-24. Bacteriological eradication rates for *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *Haemophilus parainfluenzae* and *S. aureus* ranged from 86-100%. Only 1 patient reported a serious drug-related adverse event and 7 patients withdrew from the study due to drug-related side effects (23).

Bristol-Myers Squibb plans to complete global regulatory submissions for multiple indications with BMS-284756 in the second half of 2002 (24).

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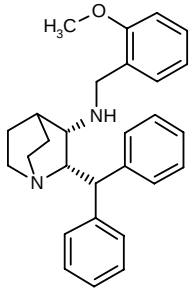
CP-9634

Anti-HIV
Analgesic

EN: 172245



$C_{28}H_{32}N_2O$ **Pfizer**

In an *in vitro* study, CP-96345 inhibited HIV infection in monocyte-derived macrophages (MDMs) isolated from human blood in a concentration-dependent manner. The

formation of typical giant syncytia induced by HIV Bal strain replication was inhibited by CP-96345 via antagonism of the neurokinin NK_1 receptor, a primary SP receptor. Substance P-enhanced HIV replication in MDMs was also inhibited by CP-96345 and anti-SP antibody. However, CP-96345 only prevented infection by HIV strains that enter cells via the CCR5 coreceptor, such as Bal, ADA, BL-6 and CSF-6. Infection by the X4 strain, which uses CXCR4 as its coreceptor, was not significantly inhibited. Moreover, CP-96345 markedly inhibited M-tropic ADA-pseudotyped HIV infection of MDMs, but did not affect murine leukemia virus-pseudotyped HIV. These findings suggest that CP-96345 intervenes in Env-determined early events in HIV infection of these cells. The compound also produced significant downregulation of CCR5 expression in MDMs at both protein and mRNA levels. These data suggest that CP-96345 inhibits HIV strains that enter cells using the CCR5 coreceptor either by interrupting the SP autocrine loop or by inhibiting SP-stimulated HIV replication at the transcriptional level (1).

Before infection with HIV, mononuclear phagocytes were treated with or without CP-96345 or the inactive enantiomer CP-96344 or with substance P and/or anti-substance P antibody to determine the effect of interruption of the substance P autocrine loop on HIV infectivity. CP-96345 was found to inhibit HIV replication by interrupting the SP autocrine loop, which resulted in downregulation of CCR5 expression. An increase in HIV LTR-driven CAT activity induced by substance P was also antagonized by the agent (2).

Intraperitoneal administration of CP-96345 to rats with colonic inflammation induced by dextran sodium sulfate was found to attenuate inflammation and oxidative stress, indicating a possible new therapeutic approach for treating chronic ulcerative colitis (3).

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3. Stucchi, A.F., Shofer, S., Leeman, S., Materne, O., Beer, E., McLung, J., Shebani, K., Moore, F., O'Brien, M., Becker, J.M. *NK-1 antagonist reduces colonic inflammation and oxidative stress in dextran sulfate-induced colitis in rats.* Am J Physiol - Gastrointest Liver Physiol 2000, 279(6): G1298.

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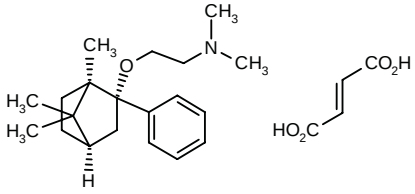
Deramciclane Fumarate

Anxiolytic

EN: 144469



$C_{20}H_{31}NO.C_4H_4O_4$

Egis; Orion Corp.; Pharmacia; Japan Tobacco

Orion Corporation and Pharmacia are going to jointly develop and commercialize deramciclane in the U.S. Under the terms of the agreement, phase III studies will be conducted in the U.S. and will be managed by Pharmacia, with funding provided by Orion. Both companies will be involved in the planning and supervision of the clinical development program. Deramciclane will be marketed in the U.S. by Pharmacia, which may also market the drug outside the U.S. and Europe. Deramciclane was discovered and initially developed by Egis Pharmaceuticals, which licensed the drug to Orion Pharma. Phase III studies of deramciclane for the treatment of generalized anxiety disorder are ongoing in Europe (1).

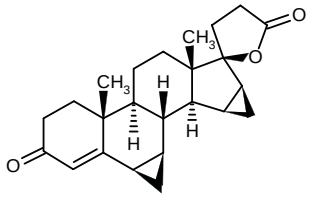
1. *Orion and Pharmacia agree to develop antianxiety treatment for the U.S. market.* DailyDrugNews.com (Daily Essentials) Aug 30, 2001.

Original monograph - Drugs Fut 1990, 15: 1174.

Drospirenone
ZK-30595
SH-470

Contraceptive
Hormone Replacement Therapy

EN: 169995



$C_{24}H_{30}O_3$

Schering AG

In two large, randomized, multicenter, open-label studies, both ethinylestradiol/drospirenone and ethinylestradiol/desogestrel provided effective contraception and good cycle control, but ethinylestradiol/drospirenone improved preexisting acne and seborrhea and more favorably affected body weight (1).

  CCC: 0377-8282/2001

In a 1-year pharmacokinetic evaluation of ethinylestradiol/drospirenone in healthy female volunteers, the absorption rate of drospirenone was found to be similar to that of other synthetic progestogens contained in different oral contraceptives, as demonstrated by similar t_{max} values (2).

A survey asked women involved in two major clinical trials to compare how they felt after treatment with either ethinylestradiol 30 μg/drospirenone 3 mg or ethinylestradiol 30 μg/desogestrel 150 μg to how they felt during treatment. The results indicate that ethinylestradiol/drospirenone may improve treatment compliance, as women who had taken the drug felt worse after their trial had ended and had returned to taking a conventional medication (3).

An open-label, multicenter study enrolling 322 healthy women found that ethinylestradiol 30 μg/drospirenone 3 mg may reduce premenstrual symptoms such as negative affect and water retention (4).

1. Foidart, J.M. *The contraceptive profile of a new oral contraceptive with antimineralocorticoid and antiandrogenic effects.* Eur J Contracept Reprod Health Care 2000, 5(Suppl. 3): 25.

2. Blode, H., Wuttke, W., Loock, W., Roll, G., Heithecker, R. *A 1-year pharmacokinetic investigation of a novel oral contraceptive containing drospirenone in healthy female volunteers.* Eur J Contracept Reprod Health Care 2000, 5(4): 256.

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Original monograph - Drugs Fut 2000, 25: 1247.

Edodekin Alfa
Interleukin-12

Oncolytic
Anti-HCV

EN: 164387

Genetics Inst.

Recombinant human interleukin-12 (rhIL-12) has a number of biological properties (broad-spectrum antiviral activity, stimulation of interferon gamma production and of the production and activity of cytotoxic/cytolytic T-cells and natural killer cells) which led researchers to evaluate its safety and efficacy in adult patients with chronic hepatitis C failing to achieve a sustained response on interferon alfa. Twenty-four patients were entered in this double-blind, randomized trial to receive placebo or rhIL-12 at doses of 30, 100 or 300 ng/kg s.c. twice weekly over 12 weeks. Whereas placebo-treated patients showed no response, 3 of 6 patients treated with the highest dose of rhIL-12 showed loss of detectable HCV RNA using the reverse transcription-polymerase chain reaction assay; 2 of the 3 patients also showed normalization of ALT values during treatment, which rebounded when edodekin alfa was stopped. All subjects relapsed by the end of the study, but it is suggested that this may be attributable to the short treatment period. rhIL-12 was well tolerated, headache and flu-like symptoms being the most frequently reported adverse events (1).

In a randomized, double-blind, placebo-controlled trial in patients with mild allergic asthma, treatment with increasing weekly injections of rhIL-12 (0.1, 0.25 and 0.5 μg/kg s.c.) reduced blood and sputum eosinophil counts but did not significantly affect airway hyperresponsiveness or the late asthmatic reaction after inhaled allergen challenge. The results raise questions regarding the activity of eosinophils in these reactions (2).

1. O'Brien, C.B., Moonka, D.K., Henzel, B.S., Caufield, M., DeBruin, M.F. *A pilot trial of recombinant interleukin-12 in patients with chronic hepatitis C who previously failed treatment with interferon-alpha.* Am J Gastroenterol 2001, 96(8): 2473.

2. Bryan, S.A., O'Connor, B.J., Matti, S. et al. *Effects of recombinant human interleukin-12 on eosinophils, airway hyperresponsiveness, and the late asthmatic response.* Lancet 2000, 356(9248): 2149.

Original monograph - Drugs Fut 1998, 23: 1331.

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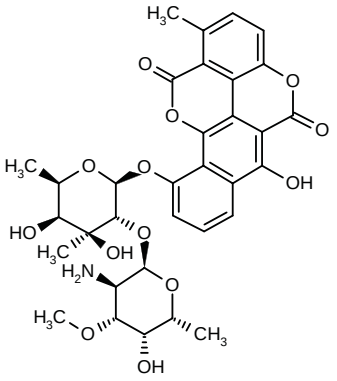
Hutson, T.E. et al. *Phase I trial of subcutaneously administered rHuIL-12 and rHuIFN-a2b in patients with metastatic renal cell carcinoma or malignant melanoma.* Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 1030.

Parihar, R. et al. *A phase I trial of Herceptin and interleukin-12 in patients with HER2-overexpressing malignancies.* Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 1031.

Elsamitrucin

Antineoplastic Antibiotic

EN: 108085



$C_{33}H_{35}NO_{13}$ **Bristol-Myers Squibb; NeoOncoRx**

NeoTherapeutics' NeoOncoRx subsidiary has signed an agreement with Bristol-Myers Squibb to develop and market elsamitrucin. The antitumor antibiotic has already shown promising activity in phase I and early phase II trials in patients with non-Hodgkin's lymphoma. NeoOncoRx intends to continue with phase II trials to identify the non-Hodgkin's lymphoma patient population most susceptible to the drug. Elsamitrucin's mechanism of action is based on its ability to induce single-strand DNA breaks as a result of drug intercalation between base pairs, with selectivity for the CG base pairs of DNA, which imparts a greater binding stability. It also inhibits topoisomerase II. Discovered by Bristol-Myers Squibb, elsamitrucin has been tested in approximately 300 patients to date in the U.S., Canada and Europe (1).

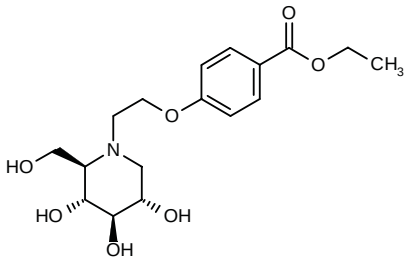
1. *NeoOncoRx to develop and market elsamitrucin.* DailyDrugNews.com (Daily Essentials) Nov 9, 2001.

Original monograph - Drugs Fut 1987, 12: 1104.

Emiglitate

Antidiabetic

EN: 100857



$C_{17}H_{25}NO_7$ **Mitsubishi-Tokyo Pharm.; Bayer**

Mitsubishi-Tokyo Pharmaceuticals is reportedly evaluating the possibility of discontinuing development of emiglitate, undergoing phase II trials in Japan for the treatment of diabetes (1).

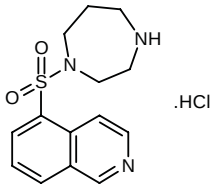
1. *Development of MKC-542 under consideration at Mitsubishi-Tokyo.* DailyDrugNews.com (Daily Essentials) Dec 22, 2000.

Original monograph - Drugs Fut 1986, 11: 1039.

Fasudil Hydrochloride
Eril®
Fasdil®

Antiischemic
Antianginal

EN: 154989



$C_{14}H_{17}N_3O_2S.HCl$ **Asahi Kasei; Schering AG**

Schering AG has in-licensed fasudil from Asahi Kasei Corporation. The intravenous formulation of fasudil is approved and already on the market in Japan for the treatment of ischemia. Additionally, an oral formulation will be jointly developed by the two companies for the treatment of angina pectoris. Schering's licensing rights include the marketing and sales of fasudil in the U.S. and Europe (1).

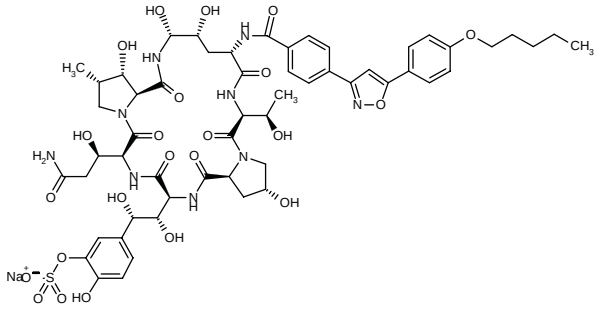
1. *Schering AG acquires rights to fasudil in the U.S. and Europe.* DailyDrugNews.com (Daily Essentials) Aug 10, 2001.

Original monograph - Drugs Fut 1989, 14: 1159.

FK-463
Micafungin

Antifungal

EN: 263634



$C_{56}H_{70}N_9NaO_{23}S$ **Fujisawa; Merck & Co.**

Fujisawa recently reported that it has filed for regulatory approval of FK-463 in Japan for the prevention and

treatment of fungal infections. The company intends to submit the product for approval with the FDA next year (1).

Micafungin is the proposed international nonproprietary name for FK-463 (2).

1. *Micafungin undergoing regulatory review in Japan.* DailyDrugNews.com (Daily Essentials) Oct 25, 2001.

2. *Proposed international nonproprietary names (Prop. INN): List 84.* WHO Drug Inf 2000, 14(4): 260.

Original monograph - Drugs Fut 1998, 23: 1273.

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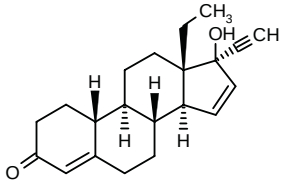
Nakai, T. et al. *In vitro pharmacological properties of the injectable antifungal agent micafungin (FK463) in 5 types of Candida.* Jpn J Med Mycol 2001, 42(Suppl. 1): Abst 126.

Gestodene
Avaden®
Convaden®

Hormone Replacement Therapy
Prevention of Osteoporosis

EN: 137511



$C_{21}H_{26}O_2$ **Schering AG**

The ability of oral activated charcoal to inhibit the enterohepatic recirculation of norethisterone acetate and gestodene was investigated in a randomized study with 13 volunteers. Bioavailability was not affected by the charcoal treatment and it was concluded that women on oral contraceptives can use activated charcoal for treating diarrhea when doing so 3 h after and at least 12 h before taking their contraceptive (1).

1. Elomaa, K., Ranta, S., Tuominen, J., Lahteenmaki, P. *The possible role of enterohepatic cycling on bioavailability of norethisterone and gestodene in women using combined oral contraceptives.* Contraception 2001, 63(1): 13.

Original monograph - Drugs Fut 1977, 2: 805.

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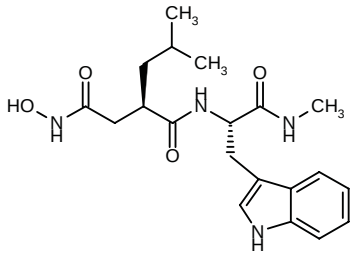
Ilomastat
Galardin®
Galardin MPI®

Treatment of Corneal Wounds
Antiasthmatic

EN: 194637



$C_{20}H_{28}N_4O_4$ **Ligand; Sankyo; Arriva Pharm.**

Arriva Pharmaceuticals has signed an agreement to develop and commercialize ilomastat (Galardin®) for the treatment of inflammatory respiratory diseases. Recently, evidence of matrix metalloprotease inhibitor (MMPI) involvement in the development of emphysema associated with cigarette smoking, as well as other pulmonary diseases such as asthma and cystic fibrosis, has emerged. Ilomastat is a broad-spectrum, small-molecule MMPI with potent biochemical activity against all of the damaging metalloproteinases involved in the progression of lung disease and demonstrated safety in humans. Originally developed by Ligand and licensed to Sankyo, ilomastat was last reported to be in phase II trials in Japan for corneal wound healing (1).

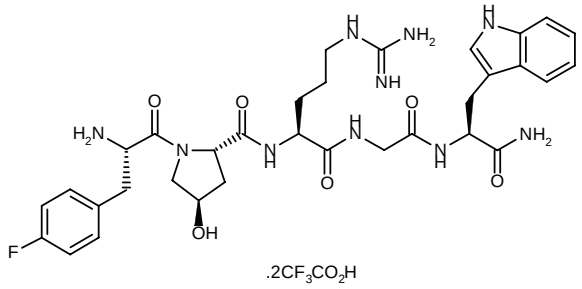
1. *Arriva to develop ilomastat as respiratory disease treatment.* DailyDrugNews.com (Daily Essentials) Feb 13, 2001.

Original monograph - Drugs Fut 1993, 18: 1109.

INN-00835

Antidepressant

EN: 244634



$C_{33}H_{43}FN_{10}O_6.2C_2HF_3O_2$ **Innapharma**

INN-00835 (0.2 mg/kg s.c. for 5 days) was the subject of a double-blind, placebo-controlled pilot study which included 52 subjects with major depression. Data

analysis revealed a strong pharmacodynamic correlation between plasma drug concentrations at 1 h postdosing and improved scores on psychiatric rating scales, although these promising results need to be confirmed in larger scale trials (1).

1. Feighner, J.P., Ehresing, R.H., Kastin, A.J., Leonard, B.E., Nicolau, G., Patel, A., Hlavka, J., Abajian, H., Noble, J.F. *A double-blind, placebo-controlled, efficacy, safety, and pharmacokinetic study of INN 00835, a novel antidepressant peptide, in the treatment of major depression.* J Affect Disord 2000, 61(1-2): 119.

Original monograph - Drugs Fut 1997, 22: 1314.

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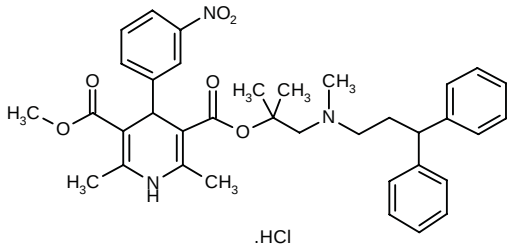
Lercanidipine Hydrochloride *Antihypertensive*
Lercan®
Zanidip®

EN: 090990



$C_{36}H_{41}N_3O_6.HCl$ **Recordati; Pierre Fabre; Zambon; Forest**

An NDA has been submitted to the FDA by Forest seeking marketing approval for lercanidipine hydrochloride for the treatment of hypertension. Lercanidipine is a member of the dihydropyridine calcium channel blocker class of drugs which prevent calcium from entering the muscle cells of the heart and blood vessels, enabling the vessels to relax and thereby lowering blood pressure. Lercanidipine is licensed from Recordati, which markets the product with its partners in 28 countries worldwide (1).

1. *Forest seeks FDA approval for new calcium channel blocker.* DailyDrugNews.com (Daily Essentials) Oct 3, 2001.

Original monograph - Drugs Fut 1987, 12: 1113.

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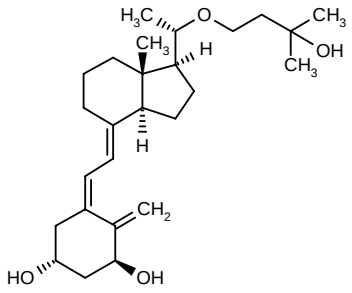
Maxacalcitol *Antipsoriatic*
Oxarol® *Treatment of Thyroid Disease*

EN: 127850



$C_{26}H_{42}O_4$ **Chugai; Maruho**

Chugai and Maruho have entered into a licensing agreement for the marketing of Oxarol® Ointment (maxacalcitol) for the treatment of psoriasis whereby Maruho will market the product for this indication in Japan. Chugai has been marketing Oxarol® Injection for the treatment of secondary hyperparathyroidism since September 2000 (1).

Results of a study of maxacalcitol (2.5, 5 or 10 μg) in 21 patients with secondary hyperparathyroidism indicated the potential of the drug for treatment of this disease, although the efficacy and risks of developing hypercalcemia with long-term treatment require further study (2).

1. *Licensing agreement signed for Chugai psoriasis therapeutic.* DailyDrugNews.com (Daily Essentials) June 20, 2001.

2. Izumi, M., Oda, M., Kitamura, R., Kotaki, Y., Naha, M., Itabana, R., Hiraoka, K., Inoue, T., Nakanishi, T., Takamitsu, Y. *Effects of 22-oxacalcitriol (OCT) on secondary hyperparathyroidism (2'HPT).* Jpn J Nephrol 2001, 43(3): Abst P-394.

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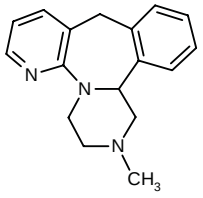
Mirtazapine *Antidepressant*
Remeron®
Remeron SolTab®

EN: 090918



$C_{17}H_{19}N_3$ **Organon; Solvay**

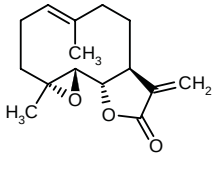
The Dutch Medicines Evaluation Board has approved Organon's antidepressant medication Remeron SolTab® (mirtazapine) for marketing, the first European marketing approval. This approval triggers the mutual recognition procedure in other European countries. Remeron SolTab® incorporates CIMA's OraSolv® technology to provide an orally disintegrating dosage form that dissolves quickly in the mouth without chewing or the need for water. The FDA approved Remeron SolTab® for the treatment of depression in January 2001 and the product has been available in the U.S. since the first quarter of this year (1).

1. *Dutch approval of Remeron SolTab.* DailyDrugNews.com (Daily Essentials) July 31, 2001.

Original monograph - Drugs Fut 1985, 10: 965.

Parthenolide *Urologic*

EN: 124002



$C_{15}H_{20}O_3$ **Cardiff Univ.**

Treatment of a hormone-sensitive prostate cancer cell line and a hormone-resistant prostate cancer cell line with parthenolide blocked proliferation of cancer cells. Greater nuclear factor κB DNA binding was seen in the hormone-resistant cell line, indicating a connection between hormone resistance and the transcription factor. DNA binding was decreased dose-dependently by parthenolide. Parthenolide treatment also demonstrated antiangiogenic activity through inhibition of capillary formation and cell proliferation in cultured human umbilical venous endothelial cells (1).

1. Sweeney, C.J., Sledge, G., Kelich, S., Nakshatri, P., Nakshatri, H. *Parthenolide: A nuclear factor κB inhibitor with in vitro antiangiogenesis and anti-cancer properties.* Proc Amer Assoc Cancer Res 2001, 42: Abst 4969.

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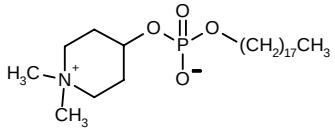
Perifosine *Oncolytic*
D-21266
NKA17

EN: 205357



$C_{25}H_{52}NO_4P$ **Asta Medica; Zentaris; Nippon Kayaku**

A phase I pharmacokinetic study has been conducted to determine the maximum tolerated dose and to characterize the pharmacokinetics of perifosine in patients with refractory neoplasms. In each cycle, loading doses were administered on day 1, followed by 21 days of treatment with maintenance doses and 7 days without treatment. In the first cycle, loading/maintenance doses were 300/50 mg for level I, 600/100 mg for level II and 900/150 mg for level III. In the subsequent cycles, these doses were 100/50, 200/100 and 300/150 mg, respectively. Pharmacokinetic analysis of the 9 patients enrolled in the study revealed linearity between dose and peak concentration at day 21. The $t_{1/2}$ was 151.3 ± 41.3 h, apparent total clearance was 1.173 ± 0.196 l/h, apparent volume of distribution was 257.9 ± 88.6 l and approximately 70% of day 21 peak concentration was achieved 48 h after the loading dose. The maximum tolerated dose has not yet been reached and dose escalation and patient accrual continues (1).

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Original monograph - Drugs Fut 2000, 25: 1257.

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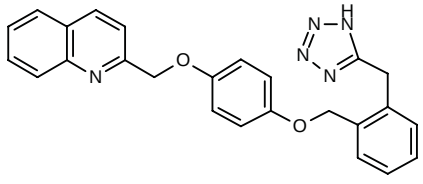
RG-12525

Antidiabetic
PPARγ Agonist

EN: 147690



$C_{25}H_{21}N_5O_2$ **Aventis Pharma**

RG-12525 was found to be a potent PPARγ agonist with potential utility in the treatment of diabetes and other PPAR-mediated diseases (1).

The importance of *N*-glucuronidation in the metabolism and overall pharmacokinetics of RG-12525 was investigated using several *in vitro* and *in vivo* approaches, primarily with human liver microsomes. High plasma levels of RG-12525 N^2-glucuronide previously seen in clinical trials with humans were found to be consistent with the high intrinsic clearance determined for human liver microsome studies (2).

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Original monograph - Drugs Fut 1991, 16: 1121.

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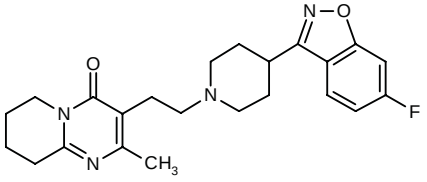
Risperidone
Risperdal®

Antipsychotic

EN: 127142



$C_{23}H_{27}FN_4O_2$ **Janssen; Organon; Alkermes**

Janssen has filed an NDA with the FDA for a long-acting injectable formulation of Risperdal® (risperidone), and similar filings are now being submitted to regulatory authorities worldwide. If approved, this would be the first atypical antipsychotic medication available in a formulation suitable for long-term use that requires administration just once every 2 weeks instead of daily. Using proprietary Medisorb® technology developed by Alkermes, the new formulation encapsulates risperidone in microspheres made of a biodegradable polymer, which is injected into the muscle. Laboratory and clinical research has shown that the microspheres gradually degrade at a set rate designed to provide consistent levels of the drug in the bloodstream. The polymer from which the microspheres are made breaks down into two naturally occurring compounds that are then eliminated by the body. Alkermes is scheduled to manufacture this long-acting formulation pending regulatory approval. Risperdal® tablets, first introduced in the U.S. in 1994, are indicated for the management of psychotic symptoms, such as those associated with schizophrenia. In its current tablet and oral solution formulations, Risperdal® has been shown in clinical trials to be effective and generally well tolerated (1).

1. *Janssen seeks FDA approval of new long-acting Risperdal formulation.* DailyDrugNews.com (Daily Essentials) Sept 10, 2001.

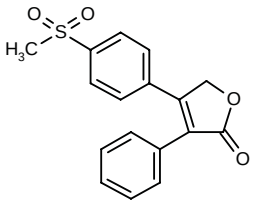
Original monograph - Drugs Fut 1988, 13: 1052.

  CCC: 0377-8282/2001

Rofecoxib
Vioxx®

Antiarthritic
COX-2 Inhibitor

EN: 221147



$C_{17}H_{14}O_4S$

Merck & Co.

Merck & Co. has received an approvable letter from the FDA for the company's application for changes to the prescribing information for rofecoxib, indicated for the treatment of osteoarthritis and acute pain. On June 29, 2000, the company submitted an sNDA to the FDA seeking changes to reflect results from the Vioxx® Gastrointestinal Outcomes Research (VIGOR) study, which the company believes support the excellent gastrointestinal and overall safety profile of Vioxx® compared to nonsteroidal antiinflammatory drugs (NSAIDs) (1).

An international multicenter trial is being carried out to determine if rofecoxib can safely and effectively prevent the recurrence of adenomatous polyps in the colon. Approximately 60 participants will take part in the study, which is a 3-year randomized trial. More than 2400 patients will be enrolled at 70 sites in the U.S., Canada and Europe. Study participants must be at least 40 years old and have had an endoscopic colon examination with removal of an adenomatous polyp within the previous 12 weeks prior to entry in the study. Following a 6-week run-in period, 60 patients will be randomized to treatment with either 25 mg of rofecoxib or placebo. Colonoscopy will be performed after the first and the third year to look for evidence of recurrence of colorectal adenomas. Participants will be closely monitored for any adverse events throughout the study (2).

Researchers are currently testing the hypothesis that rofecoxib and celecoxib may increase the risk of obese patients developing type 2 diabetes. In obese patients being treated for osteoarthritis or other conditions, these agents may potentiate insulin resistance by inhibiting the synthesis of the endogenous insulin sensitizer 15dPGJ2 (3).

Two trials evaluated rofecoxib treatment in a total of 1429 patients with osteoarthritis of the knee or hip. One of the trials was a 6-week trial, in which rofecoxib 12.5 and 25 mg once daily demonstrated efficacy similar to ibuprofen 800 mg 3 times daily. In the second trial lasting 1 year, rofecoxib 12.5 and 25 mg once daily demonstrated efficacy similar to diclofenac 50 mg 3 times daily. The drug was well tolerated in both studies (4).

The combination of rofecoxib and montelukast was evaluated in a prospective open-label study in which 33 patients with migraine without aura were enrolled to receive rofecoxib 12.5 mg/day and montelukast 10 mg/day for 12 weeks. Twenty-five of the 31 evaluable patients experienced at least a 50% reduction in migraine frequency. The mean number of migraine attacks was reduced from 6.4 attacks per month at study entry to 2.3 attacks per month at the end of the study. Transient adverse events were reported by 2 patients but did not lead to withdrawal. Long-term use for up to 40 more weeks was not associated with either an increase in side effects or a decrease in response rate (5).

The utility of rofecoxib in the prophylaxis of migraine was investigated. The study included 25 patients with International Headache Society criteria for migraine headache who were given 25 mg/day drug in addition to their usual abortive medication. A significant reduction in headache frequency of at least 50% was reported by 64% of patients and similar efficacy was seen in all types of migraine. Only 2 patients discontinued the drug due to adverse events of pelvic pain and malaise, and 2 others stopped treatment due to poor response. Another patient discontinued rofecoxib following complete control of migraine; when the patient's headache recurred, rofecoxib was reintroduced and complete migraine control was achieved. Further evaluation of rofecoxib thus appears warranted (6).

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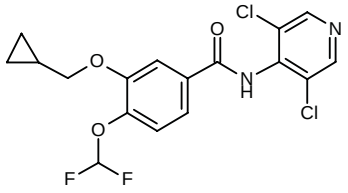
Roflumilast
BY-217

Antiallergy/Antiasthmatic
Treatment of COPD

EN: 224324



$C_{17}H_{14}Cl_2F_2N_2O_3$

Byk Gulden

Roflumilast, its major metabolite *N*-oxide, piclamilast, rolipram and cilomilast were evaluated for their antiinflammatory and immunomodulatory potential in various human leukocytes using neutrophil, eosinophil, monocyte, monocyte-derived macrophage, dendritic cell and CD4+ T-cell responses. The potencies of roflumilast, roflumilast *N*-oxide and piclamilast were similar across cell types and responses. The relative potencies of roflumilast and its metabolite for monocytes, CD4+ T cells and dendritic cells were much higher than those of cilomilast and rolipram in comparison to the potencies for neutrophils and eosinophils (1).

In studies in a sensitized Brown-Norway rat model of allergic asthma, intragastric roflumilast was shown to inhibit airways hyperresponsiveness to both acetylcholine and adenosine following antigen challenge (2, 3).

The cardiovascular safety of roflumilast (500 mg/day orally for 5 days) was examined in a double-blind randomized, placebo-controlled, crossover trial in 12 healthy volunteers. The results demonstrated no influence on cardiovascular function at therapeutic doses of roflumilast (4).

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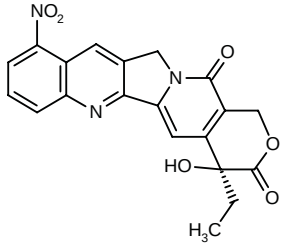

$C_{20}H_{15}N_3O_6$

Stehlin Found. Cancer Res.; SuperGen; Abbott

A study of rubitecan has demonstrated the drug's ability to inhibit by more than 95% the replication of HIV-1 in clinically relevant primary peripheral blood lymphocytes (PBLs). Equally important, the study showed that rubitecan induced apoptosis within 24 h of drug treatment in freshly infected, but not uninfected, PBLs. Similar results were observed whether rubitecan was applied in a single-, double- or triple-dose regimen. Furthermore, minimal toxicity was observed in both uninfected and infected PBLs. Rubitecan is currently in late-stage clinical trials for treating advanced pancreatic cancer (1).

Researchers tested the idea that 9-NC combined with trastuzumab would have additive inhibitory effects on tumor growth in HER2-neu-expressing pancreatic cells. In SCID mice bearing CFPAC-1 xenografts, 9-NC combined with trastuzumab more effectively slowed tumor growth rate than either agent alone or vehicle. The difference in tumor growth rate in mice treated with the drug combination and those in the vehicle group was significant. The combination will also be tested in a HER2-neu-negative pancreatic cell line (2).

SuperGen has completed patient enrollment in the second of three pivotal phase III clinical studies of rubitecan, its oral chemotherapeutic compound in development for the treatment of pancreatic cancer. This second pivotal study, which has enrolled more than 400 patients at 200 medical centers across the U.S., compares rubitecan to the most appropriate chemotherapy as third-line therapy for patients who have previously failed multiple types of chemotherapy. Enrollment for the first pivotal study, a gemcitabine-refractory study which compares rubitecan to 5-FU, has already been completed. The third pivotal study, comparing rubitecan to gemcitabine as first-line therapy, is more than 90% enrolled. Under a worldwide sales and marketing agreement with Abbott, SuperGen received an equity milestone payment. SuperGen anticipated filing an NDA with the FDA in the second half of this year (3).

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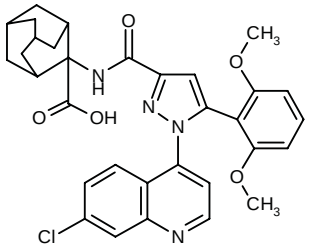

$C_{32}H_{31}ClN_4O_5$ **Sanofi-Synthélabo**

In vitro and *in vivo* experiments suggest that SR-48692 inhibits the growth of small cell lung cancer cells (1).

The regulation of striatal glutaminergic transmission by tridecapeptide neurotensin (NT) was blocked by SR-48692, indicating that this activity occurs via activation of local NT receptors. SR-48692 also inhibited NT-induced increases in basal and K^+-evoked endogenous glutamate release from cat cortical slices. Additionally, striatal NT receptor activation has been found to modulate the activity of the striatopallidal GABAergic pathway. These *in vivo* and *in vitro* findings indicate that NT has a role in modulating glutamate as well as GABA transmission in different brain regions (2).

Mutagenesis, structure-activity and computer-assisted modeling approaches were used to establish tridimensional models of SR-48692 and NT binding sites in the NT-1 receptor. This was done by creating a molecular model of the NT-1 receptor which explains the antagonist and inverse agonist behaviors of SR-48692 (3).

Studies *in vivo* suggested that chronic treatment with SR-48692 inhibits NT-1 receptor mRNA destabilization, resulting in increased NT-1 receptor synthesis and accumulation in submembrane pools (4).

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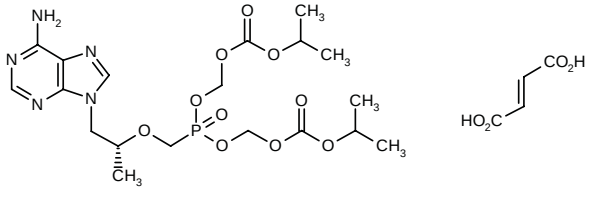

$C_{19}H_{30}N_5O_{10}P.C_4H_4O_4$ **Gilead**

A randomized, crossover, steady-state pharmacokinetic study investigated the possibility of drug interactions between tenofovir disoproxil fumarate (tenofovir DF; 300 mg q.i.d.), lamivudine (150 mg b.i.d.) and didanosine (400 mg q.i.d.). The agents were administered to healthy volunteers as tenofovir alone, tenofovir in combination with either lamivudine or didanosine and lamivudine or didanosine alone. The pharmacokinetics of tenofovir were unaffected when coadministered with either lamivudine or didanosine. Changes in the pharmacokinetics of lamivudine observed with coadministration of tenofovir DF were not considered to be clinically significant. Coadministration of tenovofir DF and didanosine resulted in increased didanosine exposure, the clinical significance of which is being examined (1).

Gilead has reported 24-week data which indicate that tenofovir DF 300 mg is associated with a statistically significant decrease in DAVG24, a measurement of the average postbaseline change in HIV RNA over 24 weeks, of –0.61 $\log_{10}$ copies/ml compared to –0.03 $\log_{10}$ copies/ml in the placebo group. These preliminary results, which meet the study's primary efficacy endpoint, are from an ongoing 48-week pivotal phase III clinical trial designed to investigate the safety and efficacy of tenofovir DF when used to intensify a stable background antiretroviral regimen in 552 treatment-experienced patients with HIV RNA levels of 400-10,000 copies/ml who were receiving stable antiretroviral therapy for at least 8 weeks prior to entering the study. In the trial, patients were randomized (2:1) to receive tenofovir DF (1 pill dosed once daily) or placebo in addition to their existing antiretroviral therapy. After 24 weeks of blinded, placebo-controlled dosing, patients assigned to tenofovir DF or placebo were allowed to receive tenofovir DF for the remainder of the 48-week study period. The study included sites in Australia, Europe and North America. At baseline, patients had a mean HIV RNA level of 3.36 $\log_{10}$ copies/ml and a mean CD4 cell count of 427 cells/mm^3. Prior to enrollment, patients had received antiretroviral therapy for a mean duration of 5.4 years. Approximately half of all study participants (n = 253) were randomly assigned to a virology substudy of this clinical trial. Baseline genotypic analysis of HIV isolates from these patients revealed that 94% of patients had evidence of nucleoside reverse transcriptase inhibitor resistance mutations, 58% had protease inhibitor resistance mutations and 48% had non-nucleoside reverse transcriptase inhibitor resistance mutations. The level of viral resistance seen in this cohort is consistent with the extensive prior treatment experience of this patient population. In terms of antiviral activity, the mean absolute change in HIV RNA at 24 weeks compared to baseline was –0.59 $\log^{10}$ copies/ml for the tenofovir DF group compared with a –0.01 $\log_{10}$ change in the placebo group. Additionally, 45% (155/346) of patients treated with tenofovir DF achieved HIV RNA reductions below 400 copies/ml at 24 weeks compared to 13% (23/172) in the placebo group. Reduction in HIV RNA to < 50 copies/ml was achieved by 22% (76/346) of patients in the tenofovir DF group compared to only 1% (2/172) in the placebo group. The DAVG24 for CD4 cells was an increase of 12.6 cells/mm^3 in the tenofovir DF group compared with a decrease of 10.6 cells/mm^3 in the placebo group. As far as safety is concerned, through the 24-week, placebo-controlled portion of the trial, the incidence of grade 3 and grade 4 laboratory abnormalities and clinical adverse events was similar between the placebo and tenofovir DF arms. Additionally, drug discontinuation at 24 weeks was 6% in both the placebo and tenofovir DF arms of the study. Following the 24-week phase of the study, 170 patients who received placebo rolled over to receive treatment with tenofovir DF. To evaluate the potential role of tenofovir DF in treatment-naive patients, Gilead initiated a phase III trial in June 2000. This trial is designed to compare the safety and tolerability of two treatment regimens, tenofovir DF, efavirenz and lamivudine versus stavudine, efavirenz and lamivudine. This randomized, double-blind, multicenter, active-controlled trial was fully enrolled in January 2001 with 601 treatment-naive patients (2).

In vitro data further characterizing the resistance profile of tenofovir DF has been presented. The resistance profile was created using almost 5000 clinically derived HIV samples from predominantly treatment-experienced patients, which were provided and analyzed by Tibotec-Virco. Results of the *in vitro* analysis indicate that reduced susceptibility to tenofovir is infrequent and is not closely correlated with crossresistance to commercially available drugs from the nucleoside reverse transcriptase inhibitor (NRTI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) classes. Specifically, results indicate that over 88% of the samples were fully susceptible to tenofovir and over 97.5% were within the normal 3-fold susceptibility range. Decreases in tenofovir susceptibility were infrequent, with 7% of samples having between a 3- and 5-fold decrease, 4% of samples having greater than a 5-fold decrease and only 1% having greater than a 10-fold decrease. In contrast, 40%, 17% and 49% of these samples showed over a 10-fold reduction in susceptibility (resistance) to 3TC, zidovudine or at least one NNRTI, respectively. In two additional presentations, Gilead described data on the unique structural and enzymological features of tenofovir which may explain the compound's favorable resistance profile. One study, which analyzed the crystal structure of HIV-1 reverse transcriptase bound to tenofovir, revealed that the unique acyclic chemical structure of tenofovir may contribute to the infrequent development of crossresistance and resistance. The other study compared the removal of nucleosides (zidovudine, stavudine, zalcitabine, didanosine and lamivudine) *versus* nucleotides (tenofovir) using the ATP-dependent chain-terminator removal mechanism. Results demonstrated that chain-terminator removal occurs more

readily with nucelosides than nucleotides and may contribute to the higher level of resistance associated with nucleosides (3).

The E.U.'s Committee for Proprietary Medicinal Products (CPMP), the scientific committee of the European Medicines Evaluation Agency, has recommended that marketing authorization be granted for tenofovir DF (Viread®) in the 15 member states of the E.U. The European Commission will consider granting final marketing authorization on the basis of the CPMP's recommendation, which Gilead anticipates will be granted in early 2002. On the basis of the safety and efficacy data submitted for the agent, the committee recommended the granting of a marketing authorization under exceptional circumstances. The indication recommended by the CPMP is for the drug taken in combination with other antiretroviral agents in HIV-infected patients over 18 years of age experiencing early virological failure. Viread(R) is taken as 1 tablet once daily with food as part of antiretroviral combination therapy and works by blocking reverse transcriptase, an enzyme crucial to the replication of HIV (4).

According to a company spokesperson, Gilead began launch of Viread® immediately following FDA approval of the drug at the end of October of this year. The drug has been approved for the treatment of HIV-1 infection in combination with other antiretroviral drugs and is supplied as tablets containing 300 mg of tenofovir disoproxil fumarate, equivalent to 245 mg tenofovir disoproxil (5).

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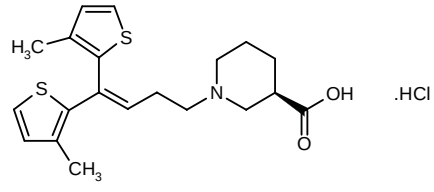

$C_{20}H_{25}NO_2S_2.HCl$

Novo Nordisk; Sanofi-Synthélabo; Cephalon

The GABA reuptake inhibitor tiagabine has been assessed for its effects on bladder function in rats based on the working hypothesis that increasing endogenous

GABA would inhibit micturition. When administered i.v. at doses of 5 and 20 mg/kg, tiagabine significantly reduced micturition pressure, decreased micturition volume and slightly decreased bladder capacity. The higher dose also significantly increased residual volume. Following intrathecal administration (100 μg), tiagabine significantly decreased micturition pressure and increased bladder capacity and residual volume, without affecting micturition volume. In *in vitro* studies, tiagabine produced a concentration-dependent (10-100 μM) inhibition of electrical field stimulation-induced rat bladder contractions, but had no effect on carbachol-induced contractions. Thus, the increase in endogenous GABA levels induced by tiagabine via GABA reuptake inhibition results in decreased micturition and may be a useful treatment approach to detrusor overactivity. The findings also suggest that tiagabine acts on micturition via both spinal and peripheral effects, and possibly also supraspinal effects (1).

Case reports from 4 patients with neuropathic pain treated with tiagabine have been presented. The patients received tiagabine because of either intolerable side effects or incomplete efficacy on gabapentin and although they were also receiving other medications, the doses of these remained the same during the trial. All 4 patients, suffering from neuropathic pain at a variety of sites and of different etiologies, experienced a marked reduction in their pain while taking tiagabine. Further research is needed to investigate the effect of this drug in the treatment of neuropathic pain (2).

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