Drugs of the Future 2001, 26(5): 491-520

CCC: 0377-8282/2001

Information Update

Volume 1-25, Number 5

Estimated developmental phase for this month's updated products:

Phase I

CR-2945 (antiulcer, CCK-B/gastrin antagonist; Rotta)
DAPD (anti-HIV, anti-HBV; Triangle Pharm., Abbott)

Phase II

A-007 (oncolytic, antiestrogen; Dekk-Tek)
FMdC (oncolytic; Matrix)
Hypericin (oncolytic, antiviral, photosensitizer; Yeda, Weizmann Inst. Sci.)
MCI-225 (antidepressant, 5-HT_3 antagonist; Mitsubishi Chem., Taisho)
Napsagatran (anticoagulant, thrombin inhibitor; Roche)
TAS-103 (oncolytic, topoisomerase I/II inhibitor; Taiho, Bristol-Myers Squibb)

Phase III

ABT-773 (ketolide antibiotic; Abbott, Taisho, Dainippon)
AS-101 (immunomodulator; Bar-Ilan Univ., Baker Norton)
Cilansetron (treatment of IBS, 5-HT_3 antagonist; Solvay)
Eplerenone (antihypertensive, treatment of heart failure, treatment of atherosclerosis, aldosterone antagonist; Pharmacia)
Pemetrexed disodium (oncolytic; Lilly)
ZD-4522 (hypolipidemic; Shionogi, AstraZeneca)

Preregistered

Emitefur (oncolytic; Otsuka)
Pimecrolimus (treatment of atopic dermatitis, antipsoriatic; Novartis)
Vorozole (oncolytic, aromatase inhibitor; Janssen, Kyowa Hakko)

Registered/Year

Amlexanox (treatment of aphthous ulcers, treatment of mucositis; Access, Paladin, Esteve, Strakan, Block Drug)/2000
Falecalcitriol (treatment of osteoporosis, antipsoriatic; Sumitomo, Taisho, YuYu, Bertek, Wisconsin Alumni Res. Found.)/2001
Trimegestone (prevention of osteoporosis, treatment of postmenopausal syndrome, oral contraceptive; Aventis Pharma, Wyeth-Ayerst)/2000

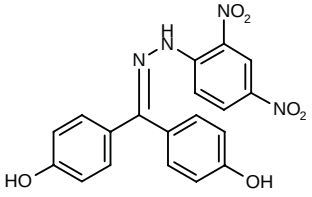
Launched/Year

Balsalazide disodium (treatment of IBD; Biorex Lab., Salix, Shire)/1997
Irbesartan (antihypertensive, treatment of heart failure, angiotensin AT_1 antagonist; Sanofi-Synthélabo, Bristol-Myers Squibb, Shionogi)/1997
Mitoxantrone hydrochloride (treatment of multiple sclerosis; Wyeth-Ayerst, Immunex)/2000
Pravastatin sodium (hypolipidemic, cardioprotectant; Bristol-Myers Squibb)/1989
Quetiapine fumarate (antipsychotic, dopamine D_2 antagonist; AstraZeneca, Fujisawa)/1997
Ramipril (antihypertensive, treatment of heart failure; Aventis Pharma, King Pharm.)/1989
Valganciclovir hydrochloride (anti-cytomegalovirus drug; Roche)/2001

A-007

Oncolytic
Antiestrogen

EN: 164886



$C_{19}H_{14}N_4O_6$ **Dekk-Tek**

A phase I trial conducted in 40 patients with metastatic cutaneous cancers (Kaposi's sarcoma, angiosarcomas, melanoma, breast and NHL) examined the efficacy of topical treatment with A-007 (0.25% gel b.i.d.). Skin itching was the only toxicity seen in 10 patients. The agent was not detected in plasma during treatment. Objective responses seen included 4 complete responses and 6 partial responses out of the 26 breast cancer patients, 2 partial responses out of the 5 melanoma patients, 2 partial responses out of the 6 Kaposi's sarcoma patients and 1 complete response out of the 3 NHL patients. Treated areas of responding patients with melanoma or breast cancer showed an increase in CD8+ cytotoxic T cells (1).

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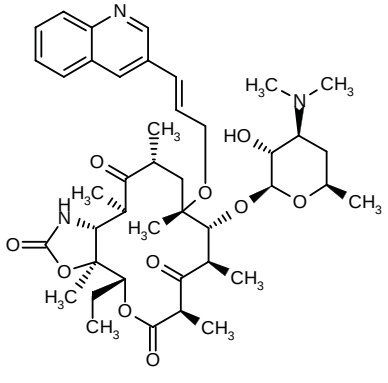
Original monograph - Drugs Fut 1992, 17: 369.

ABT-773
A-195773.0

Ketolide Antibiotic

EN: 265173



$C_{42}H_{59}N_3O_{10}$ **Abbott; Taisho; Dainippon**

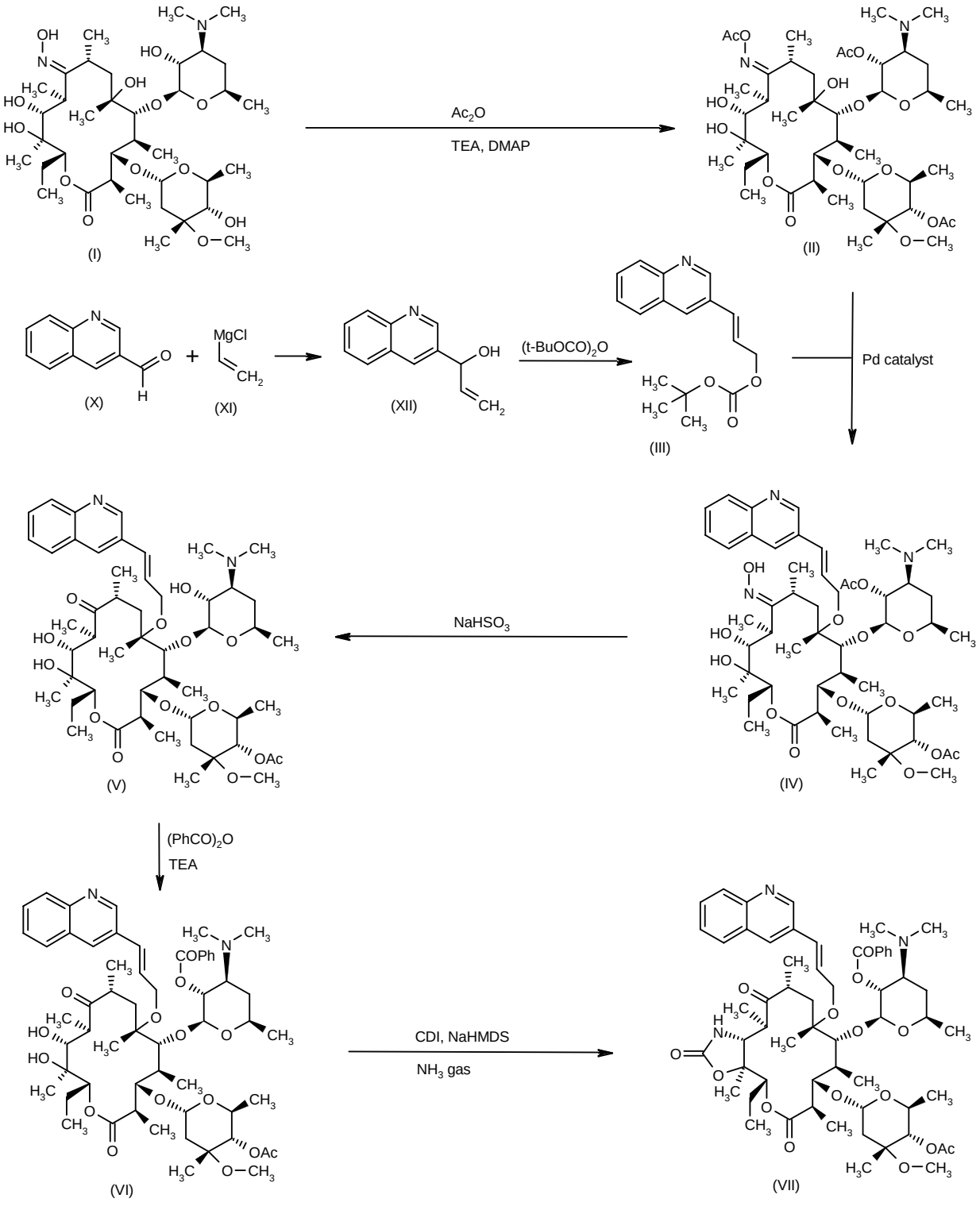
A new synthesis of ABT-773 has been reported: The acylation of erythromycin A 9-oxime (I) with acetic anhydride, TEA and DMAP in THF gives the 2',4'',9-tri-*O*-acetylerythromycin A 9-oxime (II), which is first condensed with 3-(3-quinolinyl)-2-propen-1-ol *tert*-butyl carbonate (III) by means of $Pd_2(dba)_3$ and dppb in toluene and then treated with NaOH to yield 2',4''-di-*O*-acetyl-6-*O*-[3-(3-quinolinyl)-2-propenyl]erythromycin A 9-oxime (IV). Reaction of oxime (IV) with $NaHSO_3$ and AcOH in water/THF affords 4''-*O*-acetyl-6-*O*-[3-(3-quinolinyl)-2-propenyl]erythromycin A (V), which is benzoylated with benzoic anhydride and TEA in isopropyl acetate/THF to provide 4''-*O*-acetyl-2'-*O*-benzoyl-6-*O*-[3-(3-quinolinyl)-2-propenyl]erythromycin A (VI). The reaction of compound (VI) with carbonyldiimidazole (CDI), sodium hexamethyldisilazide (NaHMDS) and ammonia gas in THF/DMF gives the 11-*N*,12-*O*-cyclic carbamate erythromycin A derivative (VII). The treatment of cyclic carbamate (VII) with HCl in ethanol produces the cleavage of the cladinosyl sugar moiety, resulting in the 3-hydroxyerythromycin derivative (VIII), which is oxidized with *N*-chlorosuccinimide (NCS) in dichloromethane to yield the 3-oxoerythromycin A derivative (IX). Finally, this compound is debenzoylated in refluxing methanol. The intermediate 3-(3-quinolinyl)-2-propen-1-ol *tert*-butyl carbonate (III) has been obtained by Grignard condensation of quinoline-3-carbaldehyde (X) with vinylmagnesium bromide (XI) in THF to give the secondary alcohol (XII), followed by esterification and simultaneous rearrangement with Boc_2O in the same solvent (1). Scheme 1.

The *in vitro* activity of ABT-773 was examined against 20 strains of *Chlamydia pneumoniae* and compared to activities of telithromycin, azithromycin, clarithromycin, erythromycin and levofloxacin. ABT-773 was the most active agent, with MIC_{90} and MBC_{90} values of 0.015 μg/ml (0.008-0.015 μg/ml) (2).

A comparison of ABT-773 and clarithromycin against *Mycobacterium avium* complex (MAC) infection has been conducted using *in vitro* assays and the beige mouse model of disseminated MAC infection. ABT-773 and clarithromycin MIC_{90}s were 16 μg/ml and 4 μg/ml, respectively. Cross-resistance to ABT-773 was found in 8 isolates resistant to clarithromycin. ABT-773 at doses of 100 and 200 mg/kg and clarithromycin 200 mg/kg, both by gavage, significantly decreased viable cell counts in the spleen and lungs of infected mice. At 200 mg/kg, the drugs showed comparable activity in the lungs, although ABT-773 was more active in the spleen. Thus, ABT-773 and clarithromycin were similarly effective *in vivo*, despite the higher *in vitro* activity of clarithromycin (3).

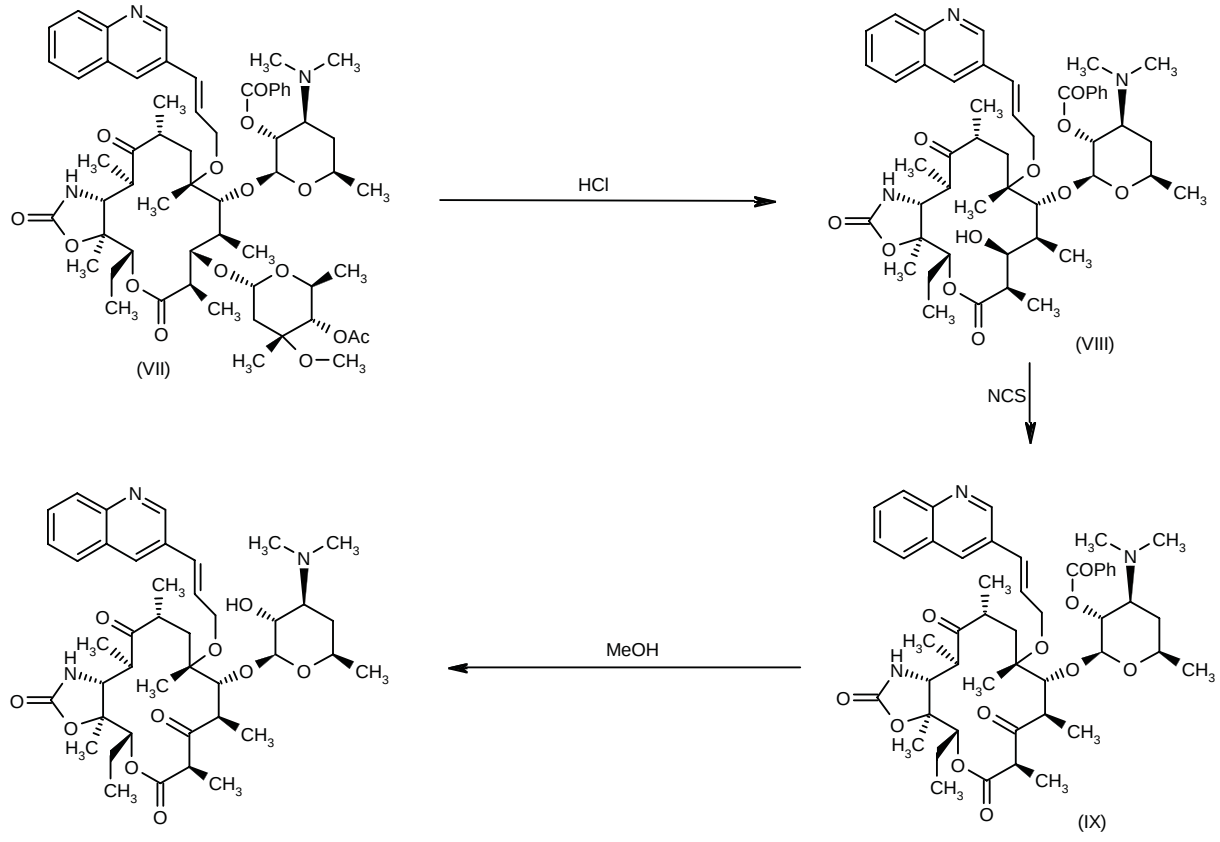
The intracellular activity and postantibiotic effect (PAE) of ABT-773 have been compared to clarithromycin, azithromycin and erythromycin against isolates of *Legionella*. The activity of the compounds in infected human monocytes and the PAE were determined following exposure to concentrations 4 times the MIC values. ABT-773 and clarithromycin inhibited the growth of erythromycin-susceptible and -resistant *Legionella pneumophila* and other *Legionella* species in human monocytes, but only ABT-773 was able to prevent the regrowth of *L. pneumophila* following removal of extracellular drug. A similar PAE was observed against erythromycin-

Scheme 1: Synthesis of ABT-773



(Continued)

Scheme 1: (Cont.) Synthesis of ABT-773



susceptible *L. pneumophila* for both ABT-773 and clarithromycin (over 3 h), but ABT-773 was significantly superior to clarithromycin against erythromycin-resistant *L. pneumophila*, with a PAE of 4.65 h, and against other erythromycin-resistant species of *Legionella*, with PAEs of over 6 h. *In vivo* studies of this ketolide are indicated to confirm these excellent *in vitro* results (4).

The *in vitro* and *in vivo* efficacy of ABT-773 was shown against *Toxoplasma gondii*. The agent inhibited replication of RH tachyzoites in human foreskin fibroblasts *in vitro*. Mice infected i.p. with tachyzoites and treated with the agent for 10 days (25, 50 or 100 mg/kg/day p.o.) had significant survival of 20, 50 and 100% for the respective doses. ABT-773 treatment also resulted in significant survival of mice orally infected with strain C56 cysts (5).

An *in vitro* study examined the time kill kinetics and PAE of ABT-773 as compared to erythromycin against 12 recent clinical respiratory isolates including both macrolide-sensitive and -resistant strains of *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and *Staphylococcus aureus*. ABT-773 at 4 or 8 times the MIC was bactericidal against all strains except for 1 *S. aureus* strain. Bactericidal activity of ABT-773 was more marked and rapid against both macrolide-sensitive and -resistant *S. pneumoniae* and *H. influenzae* as compared to erythromycin. The PAE of ABT-773 was longer as compared to erythromycin (6).

The *in vitro* activity of ABT-773 was compared with that of cefuroxime and amoxicillin/clavulanate against community-acquired *S. pneumoniae* isolates including penicillin/erythromycin resistant strains. The MICs for ABT-773 were low for those strains carrying the ermB gene. All agents were bacteriostatic at 6 h. A decrease of 2.5-3.0 $\log_{10}$ was observed for ABT-773 at 24 h as compared to a > 3 $\log_{10}$ decrease for the other agents (7).

The *in vitro* activity of ABT-773 was shown against 268 aerobic and 148 anaerobic recent clinical bite isolates. Activity was compared to those of erythromycin, clarithromycin, cefuroxime, levofloxacin, penicillin G and tetracycline. The following MIC_{90} values (μg/ml) were obtained: 1 for *Pasteurella multocida* and *Pasteurella septica*; 0.5 for other *Pasteurella* spp.; 0.25 for *Neisseria weaveri*; 0.5 for *Moraxella* spp.; 0.015 for *Corynebacterium aquaticum* and other species; 0.06 for *S. aureus*; 0.25 for enterococci, 1 for *Eikenella corrodens*, 0.06 for *Bergeyella zoohelcum*; 0.125 for *Prevotella heparinolytica*; 0.06 for *Prevotella* spp.; 0.015 for *Porphyromonas*

spp.; ≥ 0.015 for *Porphyromonas gingivalis*; 8 for *Fusobacterium nucleatum*; 0.5 for other *Fusobacterium* spp.; 0.06 for *Bacteroides tectum*; and 0.03 for *Peptostreptococcus* spp. ABT-773 was more active than the other macrolides tested against *S. aureus*, *E. corrodens* and the anaerobes but showed little activity against *F. nucleatum*. ABT-773 was also found to be 4- to 8-fold more active than clarithromycin against *Pasteurella* spp (8).

The *in vitro* activity of ABT-773 was examined against 354 clinical isolates of anaerobic bacteria including *Peptostreptococcus*, *Propionibacterium acnes*, *Porphyromonas* spp., *Clostridium perfringens*, *Clostridium difficile*, *Bacteroides fragilis* and other species, *F. nucleatum* and *Prevotella* spp. When comparing the activities of ABT-776, azithromycin, clarithromycin, roxithromycin, erythromycin, cefoxitin, imipenem, clindamycin and metronidazole, ABT-776 and imipenem were the most active agents (9).

The *in vitro* activity of ABT-773 was compared to clarithromycin, amoxicillin, metronidazole and tetracycline against 15 *Helicobacter pylori* strains. The MIC_{90} of ABT-773 against all strains was 0.52 μg/ml. Neither synergy nor antagonism were observed when agents were combined. However, additive effects were seen when tetracycline, metronidazole and amoxicillin were combined in 100, 60 and 40% of the combinations, respectively (10).

Results from an *in vitro* study reported that ABT-773 avoids resistance mechanisms in *S. pneumoniae* through tighter ribosome binding as compared to erythromycin. In addition, ABT-773 was found to accumulate in macrolide-sensitive *S. pneumoniae* at a higher rate than erythromycin and was capable of binding with methylated ribosomes and accumulating in strains with efflux-resistant phenotype (11).

The *in vitro* activity of ABT-773 was examined against 238 microaerophilic and fastidious clinical isolates and compared to the activity of ampicillin/sulbactam, clindamycin, levofloxacin, metronidazole and penicillin G. Of all organisms tested, ABT-773 inhibited 96% at 2 μg/ml and 99% at 4 μg/ml. The following $MIC_{50/90}$ values (μg/ml) were obtained for ABT-773: 0.5/4 for *Campylobacter* spp. (34 strains); 2/4 for *Desulfovibrio* (14 strains); 0.5/1 for *Eikenella* (27 strains); 0.12/0.12 for *Actinomyces* (15 strains), *Capnocyptophaga* (20 strains), *Gemella* (25 strains) and *Streptococcus milleri* group (84 strains); and 0.12/2 for 19 strains of miscellaneous organisms including *Actinobacillus*, *Desulfomonas*, *Gardnerella*, *Mitsuokella*, *Prevotella*, *Propionibacterium propionicum* and *Sutterella*. Ampicillin/sulbactam and levofloxacin showed similar activity. Poor activity for clindamycin and penicillin G was observed against *Eikenella* and *Desulfovibrio* organisms, respectively, and metronidazole displayed poor activity against organisms from *Actinomyces*, *Eikenella*, *Gemella* and *S. milleri* groups (12).

The *in vitro* activity of ABT-773 was compared to 10 other antibacterial agents against 266 pneumococci isolates. The MIC_{50} and MIC_{90} values for ABT-773 against 78 ermB-containing and 44 mefE-containing strains were 0.016-0.03 and 0.125 μg/ml, respectively; clindamycin only had activity against mefE-containing strains (MIC_{50} = 0.06 μg/ml; MIC_{90} = 0.125 μg/ml) and the activity of pristinamycin (MIC_{90} = 0.5 μg/ml) and vancomycin (MIC_{90} = 0.25 μg/ml) was not affected by these resistant mutations. The ABT-773 MIC against 19 strains with L4 ribosomal protein mutations and 2 strains with mutations in domain V of 23S rRNA were 0.03-0.25 μg/ml as compared to > 16 μg/ml obtained for the macrolides and azalides tested. Bactericidal activity of ABT-7736 was noted at 2 times the MIC after 24 h for 8/12 strains and kill kinetics for ABT-773 against macrolide-susceptible strains were faster than those for erythromycin, azithromycin, clarithromycin and roxithromycin. PAE effects of ABT-773 were longer than the macrolides, azithromycin, clindamycin and β-lactams (13).

An *in vitro* study investigated the activity of ABT-773 against over 300 *S. pneumoniae* isolates, about half of which were resistant to beta-lactams, macrolides, lincosamides, tetracyclines, chloramphenical, fluoroquinolones, streptogramin or rifampin. Against the strains susceptible to macrolides, ABT-773 gave MIC values of < 0.004-0.008 μg/ml and values of 0.008-16 μg/ml against the macrolide-resistant strains; the MIC_{50} and MIC_{90} values were 0.008 μg/ml and 0.06 μg/ml, respectively. The activity of the new ketolide was affected by streptogramin resistance and, to a lesser extent, macrolide/lincosamide resistance (14).

The *in vitro* activity of ABT-773 was examined against type strains and 733 Gram-positive, Gram-negative, anaerobic and 4 *Chlamydia* clinical isolates and compared to the activity of 7 other antibiotics. ABT-773 activity was comparable to telithromycin. The MIC_{90} values for ABT-773 against all strains were ≤ 0.5 mg/l except against methicillin-resistant *S. aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, *H. influenza* and *Bacteroides* spp. ABT-773 was more active against the *Chlamydia* isolates than telithromycin, erythromycin and ciprofloxacin (15).

The *in vitro* activity of ABT-773 was shown against macrolide-sensitive (945 strains) and macrolide-resistant (213 strains with mefA or ermB genotypes) respiratory isolates of *S. pneumoniae* and was compared to the activities of clarithromycin, azithromycin, clindamycin, doxycycline and quinupristin/dalfopristin. ABT-773 was the most active agent examined against macrolide-resistant *S. pneumoniae* with equal potency observed against isolates carrying mefA and ermB genes ($MIC_{50/90}$ = 0.015/0.03 μg/ml). The $MIC_{50/90}$ for ABT-773 against erythromycin-susceptible strains was 0.004/0.008 μg/ml (16).

The *in vitro* activity of ABT-773 was compared to those of erythromycin, clarithromycin, ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, gatifloxacin and gemifloxacin against resistant respiratory tract pathogens. Against penicillin-resistant *S. pneumoniae* isolates, ABT-773 (MIC_{90} = 0.06 mg/l) was more active

than the quinolones (MIC_{90} = 4 mg/l) and macrolides (MIC_{90} 2 mg/l). ABT-773 was the most active against methicillin-resistant *S. aureus* (MIC_{90} = 0.06 mg/l) followed by the quinolones (MIC_{90} > 1 mg/l) and macrolides (MIC_{90} > 16 mg/l). Low activity was observed for ABT-773 and clarithromycin (MIC_{90} > 64 mg/l) against erythromycin-resistant *S. aureus*. ABT-773 (MIC_{90} = 4 mg/l) was more active than clarithromycin (MIC_{90} = 8 mg/l) and erythromycin (MIC_{90} = 16 mg/l) against β-lactamase positive *H. influenzae* although gemifloxacin, gatifloxacin and ciprofloxacin were the most active ($MIC_{90} \leq 0.01$ mg/l). Similar activity was observed for ABT-773 (MIC_{90} = 0.06 mg/l), levofloxacin (MIC_{90} = 0.06 mg/l) and gemifloxacin (MIC_{90} = 0.03 mg/l) against β-lactamase positive *M. catarrhalis* and this activity was superior to that seen with clarithromycin (MIC_{90} = 0.25 mg/l), gatifloxacin (MIC_{90} = 0.5 mg/l) or erythromycin (MIC_{90} = 0.5 mg/l) (17).

The *in vitro* activities for ABT-773, telithromycin, azithromycin, clarithromycin, roxithromycin, clindamycin, penicillin, levofloxacin and gatifloxacin were compared against 104 erythromycin-resistant *S. pneumoniae* strains isolated from the respiratory tracts of children. ABT-773 was the most active agent tested with MIC values 2- to 8-fold lower than those obtained for telithromycin. The MIC_{90} values for clarithromycin, erythromycin, roxithromycin and azithromycin were 16- to 62-fold greater than 128 μg/ml for strains carrying ermB. The MIC_{90s} for ABT-773 and telithromycin against strains with the mefE and ermB genotypes were 0.063 and 0.5 μg/ml and 0.032 and 0.125 μg/ml, respectively (18).

An *in vivo* study using the neutropenic murine thigh-infection model (*S. aureus* or *S. pneumoniae*) showed the efficacy of once-daily ABT-773 (0.625, 1.5, 2.5, 6, 10 or 24 mg/kg). Dose-dependent kinetics were obtained for the agent with dose-proportional AUC values seen with 1.5-24 mg/kg; the $t_{1/2}$ for this dose range was 0.8-2.6 h and protein binding was 90%. Dose-dependent PAEs of 1-11 h and 5-9 h were observed for *S. pneumoniae* and *S. aureus*, respectively. Results support once-daily dosing (19).

The safety and pharmacokinetics of ABT-773 (100-1200 mg p.o.) were examined in a single-dose, randomized, placebo-controlled, double-blind, parallel-group phase I study in 48 fasting healthy subjects. The mean $t_{1/2}$ was 3.6-6.7 h and the mean t_{max} increased from 0.9 h for 100 mg to 5.1 h for 1200 mg. The mean C_{max} and $AUC_{0-\infty}$ values over the dose range were 141-1174 ng/ml and 630-10955 ng·h/ml, respectively. While C_{max} appeared to be dose-proportional, $AUC_{0-\infty}$ was nonlinear, particularly with doses of 400 mg or less. Treatment was well tolerated with only mild or moderate adverse events observed, of which the most common were gastrointestinal (20).

Results of a randomized, placebo-controlled, double-blind, parallel-group phase I study in 24 healthy subjects showed that food did not affect the bioavailability of ABT-773 (400 mg p.o.). Subjects received a single dose under fasting or nonfasting (30 min after a standard breakfast) conditions. No significant differences in pharmacokinetics were observed between fasting and nonfasting subjects. The mean t_{max} values for fasting and nonfasted conditions were 2.7 ± 0.8 and 3.4 ± 1.5 h, respectively (21).

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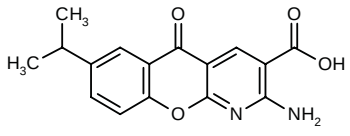
Amlexanox
OraRinse®
OraDisc®
Apthera®
Aphthasol®

Treatment of Aphthous Ulcers
Treatment of Mucositis

EN: 090210



$C_{16}H_{14}N_2O_4$

Access; Paladin; Esteve; Strakan; Block Drug

The Therapeutic Products Programme of Canada has granted Paladin marketing approval for amlexanox 5% paste (Apthera®) for the treatment of aphthous ulcers (canker sores). Approval for the product in the E.U. is anticipated for 2001 (1).

Access has announced the completion and initial results of the 400-patient, placebo-controlled, multicenter study evaluating OraDisc®, the company's new formulation of amlexanox in a polymer disc that adheres to the disease site, for the treatment of established canker sores. In the study, 3 groups were evaluated, including approximately 160 patients who were treated with amlexanox, 160 patients who received a placebo and 80 patients who received no treatment. Compared with both the placebo and no-treatment groups, the primary clinical endpoint which evaluated completed healing on day 5 was achieved, with statistically significantly accelerated healing on amlexanox. The full statistical analysis of the study has not been completed. Additional efficacy parameters, including the measurement of ulcer size and the subjective evaluation of pain by patients, will be analyzed. A second phase III study evaluating the ability of the drug to prevent the onset of the ulcerative phase of the disease is under way. A prevention study previously conducted with the 5% oral paste formulation confirmed that amlexanox has the ability to abort the onset of the disease (2).

Preliminary interim data, reflecting 23 evaluable patients, from a phase II randomized clinical trial comparing a 0.5% mucoadhesive solution of amlexanox (OraRinse®) to a mucoadhesive vehicle for the prevention and treatment of mucositis, did not disclose a statistically significant difference between the 2 arms of the study at any time point. However, in comparison to published historical data on mucositis, the mucoadhesive vehicle arm of the study showed interesting results. Of the 11 evaluable patients receiving the vehicle, 4 had only minimal evidence of mucositis (a score < 0.5 on a scale of 0-5) at any time during the course of treatment (3).

1. *Apthera for canker sores approved in Canada.* DailyDrugNews.com (Daily Essentials) Dec 22, 2000.

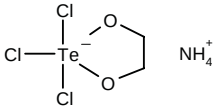
2. *Access reports positive phase III data for OraDisc canker sore treatment.* DailyDrugNews.com (Daily Essentials) Feb 21, 2001.

3. *Interim data from phase II mucositis trial presented by Access.* DailyDrugNews.com (Daily Essentials) Feb 26, 2001.

Original monograph - Drugs Fut 1984, 9: 311.

AS-101 *Immunomodulator*
Ossirene®

EN: 126952



$C_2H_8Cl_3NO_2Te$ **Bar-Ilan Univ. (IL); Baker Norton**

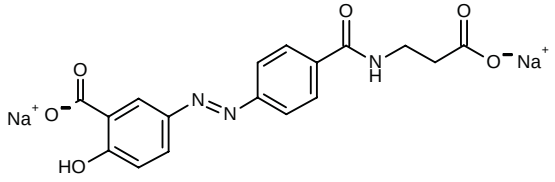
A study examining the effects of AS-101 on astrocyte cell lines *in vitro* showed that the agent (0.31-1 μg/ml) stimulated GDNF and IL-6 synthesis and secretion in a dose- and time-dependent manner. A 2-fold increase in IL-6, IL-1 and GDNF mRNA levels was observed *in vivo* when the agent was injected (2 μg/10 μl/10 min) into the substantia nigra (SN) or striatum of rats *in vivo*. In addition, when injected (15 μg for 3 days at 0.2 μl/μl/h) into diseased SN of partially 6-OHDA lesioned rats, apomorphine-induced rotation was decreased by 90%, spontaneous behavior was improved and dopamine, dopamine metabolites and IL-6 levels in the striatum and SN were higher as compared to controls. It was concluded that the agent may be an effective treatment for Parkinson's disease (1).

1. Geffen, R., Shalit, F., Thorne, R., Kinor, N., Sredni, B., Yalid, G. *A novel treatment for Parkinson's disease using an immunomodulator.* Soc Neurosci Abst 2000, 26(Part 1): Abst 27.1.

Original monograph - Drugs Fut 1989, 14: 410.

Balsalazide Disodium *Treatment of IBD*
Colazide®
Colazal®

EN: 090232



$C_{17}H_{15}N_3O_6$ **Biorex Lab.; Salix; Shire**

Salix has transferred to Shire the U.K. product license for balsalazide disodium (Colazal®), triggering a milestone payment from Shire to Salix. The payment was made in accordance with an agreement under which Shire purchased from Salix the exclusive rights to balsalazide for Austria, Belgium, Denmark, Finland, France, Germany, Iceland, the Republic of Ireland, Luxembourg, Norway, The Netherlands, Switzerland, Sweden and the U.K. Salix obtained worldwide license rights (except in Japan, Korea and Taiwan) to balsalazide from Biorex Laboratories and will share a portion of the milestone payments received from Shire in accordance with a license arrangement between Salix and Biorex. Colazal® was recently approved in the U.S. for the treatment of mildly to moderately active ulcerative colitis. Shire holds exclusive marketing rights to the product in a number of European countries, where it is marketed as Colazide® (1, 2).

1. *Salix receives milestone payment from Shire for balsalazide.* DailyDrugNews.com (Daily Essentials) Aug 18, 2000.

2. *Salix's Colazal approved in U.S. for ulcerative colitis.* DailyDrugNews.com (Daily Essentials) July 27, 2000.

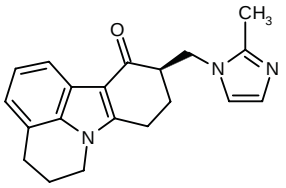
Original monograph - Drugs Fut 1984, 9: 313.

  CCC: 0377-8282/2001

Cilansetron
KC-9946

Treatment of IBS
5-HT$_3$ Antagonist

EN: 149826



$C_{20}H_{21}N_3O$ **Solvay**

A double-blind, randomized, placebo-controlled crossover study in 12 healthy volunteers examined the efficacy of cilansetron (4 or 8 mg t.i.d. for 7 days). Following 30-min baseline recording of activity from the sigmoid colon, subjects were given a meal and subsequently (90 min later) administered neostigmine (1 mg i.m.). While only a slight enhancement of meal-stimulated phasic motility was observed, a significant increase in neostigmine-stimulated phasic motility was evident. Treatment with the agent for 7 days was well tolerated and tended to increase stool consistency (1).

According to a recent shareholder report from Solvay, cilansetron entered phase III trials in September 2000 (2).

1. Stacher, G., Weber, U., Stacher-Janotta, G., Bauer, P., Huber, K., Holzäpfel, A., Krause, G., Steinborn, C. *Effects of the 5-HT$_3$ antagonist cilansetron vs placebo on phasic sigmoid colonic motility in healthy man: A double-blind crossover trial.* Br J Clin Pharmacol 2000, 49(5): 429.

2. *Cilansetron moves into phase III for IBS.* DailyDrugNews.com (Daily Essentials) Nov 8, 2000.

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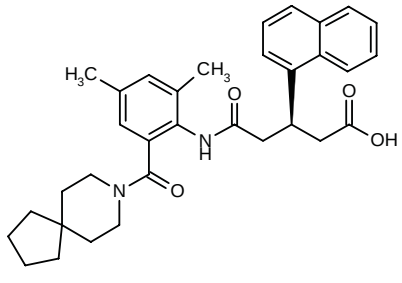
CR-2945
Itriglumide

Antiulcer
CCK-B/Gastrin Antagonist

EN: 261157



$C_{33}H_{38}N_2O_4$ **Rotta**

Itriglumide is the proposed international nonproprietary name for CR-2945 (1).

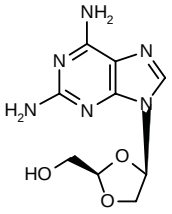
1. *Proposed international nonproprietary names (Prop. INN): List 82.* WHO Drug Inf 1999, 13(4): 279.

Original monograph - Drugs Fut 1999, 24: 483.

DAPD

Anti-HIV
Anti-HBV

EN: 257988



$C_9H_{12}N_6O_3$ **Triangle Pharm.; Abbott**

DAPD is a prodrug of the nucleoside reverse transcriptase inhibitor dioxolane guanosine (DXG) which is converted to the latter by adenosine deaminase. The 5'-triphosphate of DXG acts as a potent alternative substrate inhibitor of HIV reverse transcriptase (K_i = 0.019 μM). Several important findings emerged from kinetic studies with DXG-TP. For example, mutations conferring resistance to zidovudine or lamivudine did not affect the efficiency of incorporation of DXG-TP, and its lack of mitochondrial toxicity appeared to be related to its limited interaction with DNA polymerases (1).

In *in vitro* experiments with DAPD, a range of recombinant viruses and clinical isolates of HIV-1 from patients failing nucleoside or non-nucleoside reverse transcriptase inhibitor therapy, containing various single or multiple mutations, remained sensitive to DXG. Sensitivity to DXG was also seen in multidrug-resistant isolates. Drug-resistant mutant strains of HBV also showed no significant cross-resistance to DAPD (2).

Preliminary pharmacokinetic results from 5-6 treatment-naive, HIV-infected subjects were reported from a 14-day phase I/IIa study examining the efficacy and safety of DAPD (100, 200 and 300 mg b.i.d.). All doses were well tolerated and good antiviral activity has been observed. C_{max} was achieved 1-2 h postdosing and C_{max} and AUC values were dose-proportional for both DAPD and its active metabolite DXG. Plasma levels of DXG were higher than DAPD and a mean DXG/DAPD AUC ratio of 4-12 was obtained for the doses examined. $T_{1/2}$ values of 1 h for DAPD and 7 h for DXG were similar for all doses (3).

Pharmacokinetic results from a 2-week, open-label phase I/II dose-escalation trial of DAPD in therapy-naive and -experienced HIV-infected patients have been reported. In subjects given doses of DAPD of 100, 200, 300 and 500 mg b.i.d., rapid absorption and conversion to DXG were observed. Both DAPD and DXG reached peak plasma levels at 1-2 h after dosing, but the plasma levels of DXG were significantly higher than those of DAPD.

Pharmacokinetic parameters (C_{max} and AUC) of both DAPD and DXG showed large intersubject variability but increased with dose. Most of the dose absorbed was converted to DXG, which accounted for 20-30% of the dose recovered in urine *versus* 2-10% recovered as unchanged DAPD. These results indicating extensive conversion to and high plasma levels of the active compound provide further support for the continued development of DAPD (4).

Results from a nonrandomized, open-label phase I/II trial conducted in HIV-infected, treatment-naive patients (HIV RNA > 5000 copies/ml; CD4 cells > 50 cells/ml) showed the antiviral efficacy of short-term DAPD monotherapy (25, 100, 200, 300 or 500 mg b.i.d. for 15 days); each dose group included 5-7 patients. The maximum median decrease in HIV RNA was 0.5, 1, 1.14, 1.5 and 1.46 log_{10} for the respective doses. No genetic changes in reverse transcriptase coding regions of plasma HIV were observed on day 15 as compared to baseline. Treatment was well tolerated with no discontinuations due to adverse events (5).

The efficacy and tolerability of DAPD monotherapy (25, 100, 200 or 300 mg b.i.d.) were examined in a nonrandomized, escalating dose, 14-day phase I/II trial conducted in antiretroviral-naive HIV-infected subjects. Results from the 7-8 subjects treated at each dose level revealed maximal median decreases in HIV load (log_{10}) from baseline of –0.54,. –1, –1.14 and –1.49, respectively. All doses were well tolerated. Plasma levels of the agent were dose-proportional and DAPD was found to be converted to DXG. Similar HIV genotypes were seen at pretreatment and posttreatment in the 21 subjects examined. The trial is ongoing (6).

1. Feng, J., Jeffrey, J., Anderson, K., Copeland, W., Furman, P. *Mechanistic studies of dioxolane guanosine 5'-triphosphate: Implications for efficacy, lack of cross-resistance and selectivity of DAPD.* 8th Conf Retroviruses Opportunistic Infect (Feb 4-8, Chicago) 2001, Abst 306.

2. Furman, P.A., Chin, R., Borroto-Esoda, K., Mewshaw, J., Dent, B., Barthalomews, A., Locarnini, S. *DAPD: A novel inhibitor of HIV and HBV replication is active against drug-resistant viruses.* Antivir Ther 2000, 5(Suppl. 3): Abst 5.

3. Wang, L., Bigley, J.W., St. Claire, R.L., Sista, N.D., Rouseau, F. *Preliminary assessments of the pharmacokinetics of DAPD and its active metabolite DXG in HIV-infected subjects.* 13th Int AIDS Conf (July 9-14, Durban) 2000, Abst WePeA4056.

4. Wang, L.H., Bigley, J.W., Brosnan-Cook, M., Sista, N., Rousseau, F. *The disposition of DAPD and its active metabolite DXG in therapy-naive and -experienced HIV-infected subjects.* 8th Conf Retroviruses Opportunistic Infect (Feb 4-8, Chicago) 2001, Abst 752.

5. Eron, J.J., Kessler, H., Thompson, M., Deeks, S., Arduino, R., Jacobson, J., Sista, N., Quinn, J., Harris, J., Bigley, J., Rousseau, F. *Clinical HIV suppression after short term monotherapy with DAPD.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst I-690.

6. Kessler, H., Eron, J., Thompson, M. et al. *Anti-HIV activity and tolerability of DAPD, a novel dioxolane guanine RT inhibitor: Preliminary results of a phase I/II clinical trial.* 13th Int AIDS Conf (July 9-14, Durban) 2000, Abst TuPpA1146.

Original monograph - Drugs Fut 2000, 25: 454.

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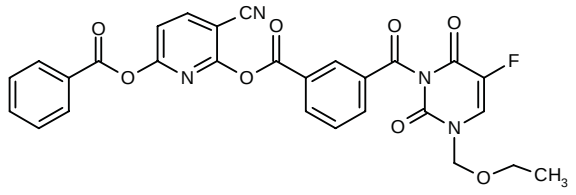
Emitefur *Oncolytic*
Last-F®

EN: 140773



$C_{28}H_{19}FN_4O_8$ **Otsuka**

The pharmacokinetics of multiple-dose emitefur (200 mg/m^2/day or b.i.d. p.o. for 14 days followed by a 7-day rest period) were examined in an ascending/descending dose, parallel-group study in 15 patients with colorectal cancer also given calcium leucovorin (30 mg p.o.). After only 1 day of dosing, 5-FU levels were higher than the minimum effective cytotoxic concentration required *in vitro*. The $t_{1/2}$ values for 5-FU were prolonged (8 h) due to codelivery of the dihydropyrimidine dehydrogenase inhibitor (DPD), CNDP, with emitefur administration. Since 5-FU concentrations were similar throughout dosing, it was concluded that the variability in circadian DPD activity was effectively suppressed (1).

An open-label, ascending/descending dose, parallel-group study in 19 patients with nonresectable solid tumors examined the metabolite (5-FU, EM-FU and CNDP) pharmacokinetics following treatment with oral emitefur (200 or 250 mg/m^2/day b.i.d., 200 or 300 mg/m^2/day t.i.d. for 14 days with a 7-day washout). Ten of the patients had received prior 5-FU therapy. The maximum tolerated dose (MTD) was determined to be 200 mg/m^2/day b.i.d. and steady state was achieved before day 7. The AUC_τ values for 5-FU, CNDP and EM-FU at the MTD were 723, 5374 and 46687 ng·h/ml, respectively; $t_{1/2}$ and C_{max} values at steady state for these metabolites were 13.6 h and 79 ng/ml, 11.6 h and 645 ng/ml and 21.6 h and 4326 ng/ml, respectively. It was concluded that emitefur treatment resulted in prolonged 5-FU exposure with sustained DPD inhibition and a suppression of DPD circadian variations (2).

  CCC: 0377-8282/2001

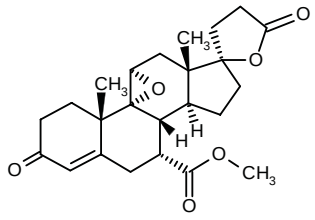
1. Corey, A.E., Twaddell, T.P.H., Mallikaarjun, S. *Emitefur (BOF-A2) metabolite pharmacokinetics and toxicodynamics following multiple oral doses, co-administered with calcium leucovorin, in man.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 2057.

2. Corey, A.E., Twaddell, T.P.H., Mallikaarjun, S. *Emitefur (BOF-A2) metabolite pharmacokinetics and toxicodynamics following multiple oral doses in man.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 2056.

Original monograph - Drugs Fut 1993, 18: 418.

Eplerenone

Antihypertensive
Treatment of Heart Failure
EN: 261466 *Treatment of Atherosclerosis*
Aldosterone Antagonist



$C_{24}H_{30}O_6$ **Pharmacia**

The preclinical efficacy of eplerenone was described in a recent review. The agent showed 10- to 100-fold higher affinity for the aldosterone receptor as compared to spironolactone and exerted similar potency in humans and rats *in vivo* (1).

The effects of selective aldosterone receptor blockade with eplerenone hve been investigated on endothelial function in rabbits with diet-induced atherosclerosis. After an initial 2-week period of normal chow or 1% cholesterol chow diet, 32 New Zealand white rabbits were randomized to saline or eplerenone (50 mg/kg twice daily) for 6 weeks. In rabbits on the 1% cholesterol chow diet, the peak relaxations to acetylcholine were 61 ± 4% in animals randomized to saline as compared to 82 ± 6% in animals randomized to eplerenone. Peak relaxations to nitroglycerin were 104 ± 3% and 112 ± 4% for saline and eplerenone, respectively. In rabbits fed 1% cholesterol chow, superoxide (O_2) generation was 3445 ± 863 O_2 counts for saline and 1400 ± 504 O_2 counts for eplerenone. Among animals receiving normal chow, the superoxide generation was 1478 ± 352 O_2 counts for saline and 1110 ± 373 O_2 counts for eplerenone. Since aldosterone receptor antagonism with eplerenone was shown to improve endothelial function and reduce superoxide generation in this rabbit model of diet-induced atherosclerosis, this compound may have applications in the treatment of this disease (2).

A study using dogs examined the effect of food intake on the pharmacokinetics of eplerenone. Animals were implanted with a chronic portal vein access port and given [^{14}C]-eplerenone (15 mg/kg p.o., 100 mg tablet or 7.5 mg/kg i.v. [peripheral or portal vein] at an infusion rate of 0.5 mg/kg/min over 30 min) in the fed and fasted state. The mean AUC values for eplerenone infused through the peripheral vein in fed and fasted conditions were 18.2 ± 1.1 and 23.6 ± 2.4 h·μg/ml, respectively. These values following infusion via the portal vein were 13.3 ± 1.5 and 20.8 ± 3.1 h·μg/ml, respectively. The mean AUC values of the agent after oral administration were 31.2 ± 3.2 and 33 ± 2 h·μg/ml in peripheral plasma, respectively, and 33 ± 2.1 and 37.7 ± 2.9 h·μg/ml in portal plasma, respectively; the AUC values following oral administration of the tablet were 29.7 ± 3.6 and 23.8 ± 2.1 h·μg/ml, respectively. It was concluded that food intake influenced systemic exposure to eplerenone when the agent was infused via the peripheral or portal vein, while no interaction was observed following oral administration. The interactions observed with i.v. dosing may be due to increased biliary excretion of the agent with food (3).

A randomized study in 6 healthy adult volunteers examined the interaction of double strength grapefruit juice on the pharmacokinetics of eplerenone (100 mg after an overnight fast and followed by 4 h of postfasting or after fasting with 250 ml grapefruit juice). A significant 29% increase in the C_{max} for eplerenone and a 16% decrease in clearance were observed when the agent was administered with grapefruit juice; no differences in t_{max} (1.9 and 2 h) were seen. AUC values also increased with concomitant grapefruit juice. However, the interactions with grapefruit juice were concluded to be clinically insignificant (4).

1. Funder, J.W. *Eplerenone, a new mineralocorticoid antagonist: In vitro and in vivo studies.* Curr Opin Endocrinol Diabetes 2000, 7: 138.

2. Rajagopalan, S., Duquaine, D., Han, Z., Venturini, C., Pitt, B., Webb, C. *Selective aldosterone receptor blockade improves endothelial function in diet induced atherosclerosis.* J Am Coll Cardiol 2001, 37(2, Suppl. A): 303A.

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4. Tolbert, D.S., Karim, A., Nasafi, J., Ruckle, J.L., Qian, J. *Effect of double strength grapefruit juice on the pharmacokinetics of eplerenone.* Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 3456.

Original monograph - Drugs Fut 1999, 24: 488.

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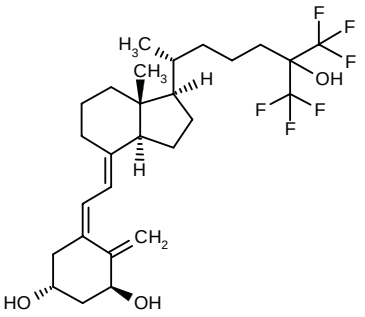
Falecalcitriol
Hornel®
Fulstan®

Treatment of Osteoporosis
Antipsoriatic

EN: 141273



$C_{27}H_{38}F_6O_3$

Sumitomo; Taisho; YuYu; Bertek; Wisconsin Alumni Res. Found.

As compared to calcitriol *in vitro*, falecalcitriol was 10-fold more potent and had 100-fold longer duration in inhibiting human normal and psoriatic keratinocyte proliferation. Falecalcitriol also more potently (100-fold) reduced the number of basal cells in a dose-dependent manner (1).

1. Chen, T.C., Holick, M.F. *Hexafluoro-1,25-dihydroxyvitamin D-3 has markedly increased potency in inhibiting proliferation of cultured human keratinocytes compared with 1,25-dihydroxyvitamin D-3.* Br J Dermatol 2000, 143(1): 72.

Original monograph - Drugs Fut 1997, 22: 473.

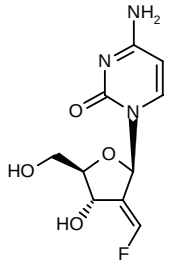
Additional Reference

Miyahara, T. et al. *Metabolism of 26,27-hexafluoro-1alpha,25-dihydroxyvitamin D_3 and 26,27-hexafluoro-1alpha,23(S)25-trihydroxyvitamin D_3 in ROS17/2.8 cells transfected with a plasmid expressing CYP24.* Xenobiotica 2000, 30(11): 1055.

FMdC
Tezacitabine

Oncolytic

EN: 165222



$C_{10}H_{12}FN_3O_4$

Matrix

A new synthesis of tezacitabine has been described: Protection of cytidine (I) with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (II) in pyridine gives the protected cytidine (III), which is oxidized with trifluoroacetic anhydride (TFAA)/DMSO in THF and treated with TEA to yield the 2'-deoxy-2'-oxocytidine derivative (IV). Condensation of (IV) with fluoromethyl phenyl sulfone (V) by means of diethyl chlorophosphate and lithium hexamethyldisilazide in THF affords the fluorovinyl sulfone (VI) as a mixture of (*E*)- and (*Z*)-isomers that is separated by flash chromatography. The desired (*Z*)-isomer (VI) is treated with tributyl tin hydride and AIBN in refluxing benzene to give the fluorovinyl stannane (VII), which is finally treated with KF in refluxing methanol (1). Scheme 2.

Results from an *in vitro* study using human leukemia and solid tumor cell lines have demonstrated that the cytotoxic effects of FMdC are due to incorporation of the nucleotide into DNA. Incorporation of the agent led to termination of DNA chain elongation and resistance to excision by exonucleases (2).

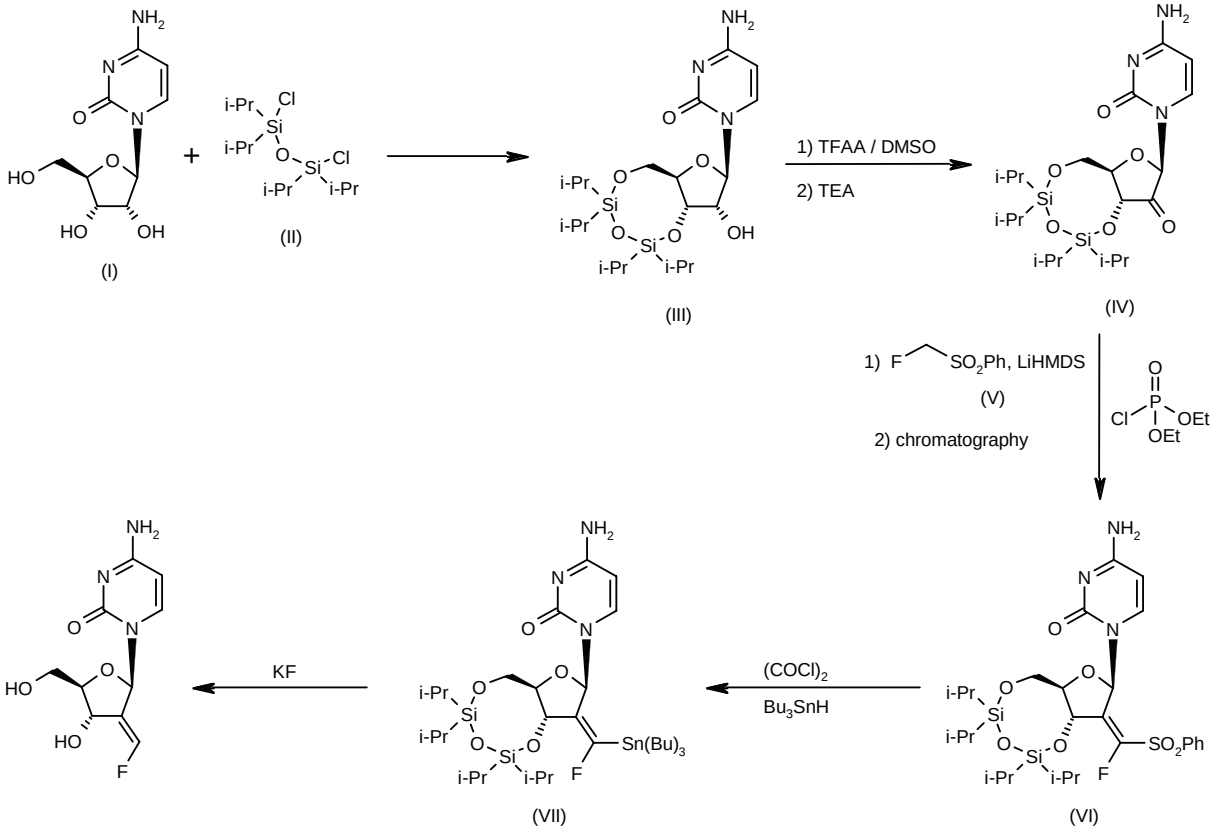
An *in vivo* study using nude mice bearing s.c. human pancreatic cancer (L3.6pL) xenografts showed that daily treatment with FMdC (15 mg/kg i.p. 5 days/week for 2 weeks) reduced tumor-associated VEGF expression, inhibited angiogenesis and inhibited tumor growth by 63% (3).

An *in vivo* study using nude athymic mice bearing human lung cancer (A549) tumors showed that treatment with FMdC (50 mg/kg for 5 days) caused tumor regression in 20% of the treated animals and tumor growth inhibition in all remaining treated animals. Regressed tumors were found to have significantly reduced VEGF protein as compared to nonregressed tumors from treated animals and from untreated animals. Results indicate that the antitumor effects of FMdC may be due to VEGF downregulation as well as direct cytotoxic effects (4).

An *in vivo* study using athymic mice bearing human xenografts (HCT116, HT29 or Capan-1) examined the effect of dosing frequency on the antitumor action of FMdC (100 mg/kg for 3 weeks or 300 mg/kg cumulatively i.p.). More frequent dosing was found to correlate with increased antitumor activity (daily > 3 times/week > 2 times/week > once weekly). Tumor regression also occurred with more frequent dosing. Daily (1-25 mg/kg 5 days/week for 4 weeks) and weekly (10-1500 mg/kg 5 days/week for 4 week) treatment of mice bearing HCT116 xenografts resulted in therapeutic indices of about 8-10 and ≤ 3, respectively (5).

A phase I trial of tezacitabine has been conducted in patients with relapsed/refractory hematological malignancies, including 13 patients with acute myeloid leukemia (AML), 4 with acute lymphocytic leukemia (ALL) and 3 with non-Hodgkin's lymphoma (NHL). These patients were treated at doses of 1, 2, 4 and 6 mg/m^2 by short i.v. infusion once daily for 5 days every 3-4 weeks. Grade 3/4 neutropenia was seen in all 3 NHL patients, while in the acute leukemia patients drug fever, gastrointestinal disturbances and skin rash were the most common adverse events. A partial response was obtained in 1 patient with

Scheme 2: Synthesis of FMdC



NHL and the other 2 had stable disease. Of those with acute leukemias, 1 complete remission was obtained at the highest dose and 1 patient showed transient disease stabilization followed by progression; significant reductions in blasts in peripheral blood and bone marrow were detected in 2 patients with ALL (6).

A phase I trial conducted in 6 patients with advanced cancer reported that the maximum tolerated dose (MTD) of FMdC infusion was 16 mg/m^2 (3 weeks of treatment followed by 1 week of rest). Dose escalation beyond this dose was impossible due to development of hematologic dose-limiting toxicities (*e.g.*, neutropenia). Other toxicities reported were grade 2 noninfectious fever, mucositis and anorexia. Stable disease was seen in a heavily pretreated patient with rectal cancer who exhibited a 38% decrease in indicator lesions lasting for 7 months (7).

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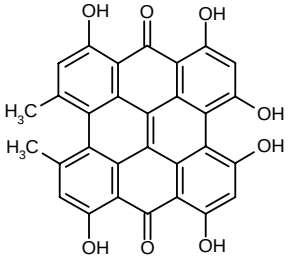

$C_{30}H_{16}O_8$ **Yeda; Weizmann Inst. Sci. (IL)**

An *in vitro* study using head and neck squamous carcinoma cells (SNU-486) showed that albumin (0.1-10%) inhibited hypericin dye (100 ng solution) uptake and laser phototherapy (532 nm green KTP laser light). An 8-fold decrease in phototoxicity was observed when the albumin concentration was increased from 0.1 to 10% (1).

A study using nude mice bearing human head and neck squamous cell carcinoma transplants compared the efficacy of hypericin as an *in situ* tumor photosensitizer with 2 anthracycline drugs (doxorubicin, daunorubicin) and 3 rhodamine dyes (123, 3G and 6G). Both anthracyclines were found to rapidly diffuse following intratumor administration; the agent was not detected in the tumor 24 h postdosing. In contrast, the rhodamines remained in the tumor with no evidence of diffusion. Hypericin (50 μg/0.05 ml) diffused slowly (over several hours) from the injection site to the tumor edges. The agent could be detected 10-14 days postinjection without evidence of diffusion into the surrounding normal tissue. Similar results were obtained for hypericin in mice bearing orthotopic human pancreatic tumors (2).

A study examined the effects of short-term (2 weeks) and long-term (8 weeks) administration of *Hypericum* extract (500 mg/kg), hypericin (0.2 mg/kg) and imipramine (15 mg/kg/day) on gene expression in brain areas involved in the hypothalamic-pituitary-adrenal axis in rats. All agents given long- but not short-term were found to decrease corticotropin-releasing hormone mRNA (16-22%) in the paraventricular nucleus of the hypothalamus and serotonin 5-HT_{1A} receptor mRNA (15-20%) in the hippocampus. Only long-term imipramine decreased tyrosine hydroxylase mRNA (23%) in the locus coeruleus. The effects of the agents on pituitary POMC mRNA were variable (3).

The pharmacokinetics of hypericin (20 mg/kg p.o.) were examined in nude mice bearing LNCaP prostate tumors. Levels of the agent were 3.9 μM at both 1 and 24 h postdosing. At 24 h postdosing, the agent was distributed in liver, kidney, spleen, brain and prostate tumor with higher concentrations of the agent detected in the brain and prostate tumor (4).

The disposition of the ingredients in St. John's wort (hypericin, pseudohypericin and hyperforin) were examined in a study involving 12 depressed patients and 12 healthy controls given a single dose of *Hypericum* extract (900 mg). Results indicate that depression may alter the disposition of hypericin and hyperforin. Plasma concentrations tended to be lower in controls as compared to depressed patients. The AUC_{0-36} values (μg/h/l) obtained in controls and depressed subjects (respectively) for hypericin, hyperforin and pseudohypericin were: 91 and 136, 6822 and 10302 and 60 and 66, respectively (5).

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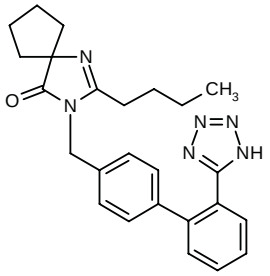

$C_{25}H_{28}N_6O$ **Sanofi-Synthélabo; Bristol-Myers Squibb; Shionogi**

The combination of an angiotensin II AT_1 receptor antagonist, preferably irbesartan, and an immunosuppressant, particularly ciclosporin, was found to be useful for the treatment or prevention of vascular complications after graft *versus* host reaction (1).

Bristol-Myers Squibb and Sanofi-Synthélabo have announced their intention to begin a worldwide clinical trial to evaluate once-daily treatment with irbesartan for the treatment of heart failure. The trial, expected to begin by September 2001, will evaluate the potential effect of irbesartan on morbidity and mortality in heart failure. The drug is currently indicated for the treatment of hypertension (2).

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MCI-225

Antidepressant
5-HT_3 Antagonist

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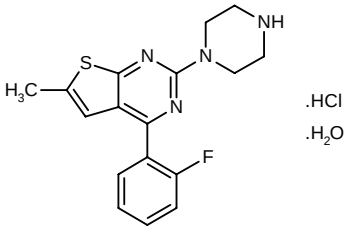

$C_{17}H_{17}FN_4S.HCl.H_2O$ **Mitsubishi Chem.; Taisho**

An *in vivo* study using stressed (20-min foot shock) and nonstressed rats examined the effects of acute (3 and 10 mg/kg p.o.) and chronic (3 or 10 mg/kg p.o. for 14 days) MCI-225 treatment on extracellular noradrenaline levels in hypothalamus. The results obtained suggest that the agent may have potential anxiolytic and/or antidepressant effects. Acute treatment dose-dependently and significantly increased extracellular noradrenaline levels in nonstressed and stressed rats. Chronic administration had no effect on basal extracellular noradrenaline levels in the hypothalamus but significantly decreased stress-induced increases in noradrenaline as compared to controls (1).

Mitsubishi-Tokyo Pharmaceuticals has reportedly discontinued the development of MCI-225, which had reached phase II trials (2).

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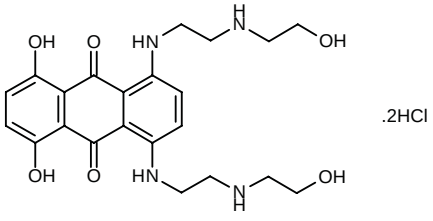

$C_{22}H_{28}N_4O_6.2HCl$ **Wyeth-Ayerst; Immunex**

A retrospective analysis of 24 patients with relapsing-remitting, secondary progressive and other types of multiple sclerosis (MS) receiving 34 total doses of mitoxantrone has been reported. Concurrent interferon β-1b (14 patients), interferon β-1a (4 patients) and/or steroids (29 patients) were also given. Relapse rates were reduced by over half on mitoxantrone and the treatment was well tolerated. Several cases of infection were seen but no serious adverse events were recorded. Short-term use of the drug both alone and in conjunction with other drugs thus appears safe in MS patients (1).

Results have been reported of a prospective analysis of the safety of mitoxantrone in 293 MS patients with relapsing-remitting, secondary progressive and primary progressive disease. Mitoxantrone was given monthly and/or every 3 months up to a maximum cumulative dose of 140 mg/m^2. No significant toxicity has been observed, including heart failure and severe infection, although 2 patients had decreases of over 50% in left ventricular ejection fraction after 6-10 courses and were withdrawn from the study. As 140 mg/m^2 is the maximum cumulative dose recommended by the FDA, these data support the safety of mitoxantrone in MS patients (2).

An ongoing, multicenter, placebo-controlled phase II trial of mitoxantrone (12 mg/m^2 i.v. every 3 months for up to 24 months) in patients with primary progressive MS has enrolled 37 patients who have completed up to 6 cycles. No cardiac dysfunction, secondary leukemia or other serious adverse events have been detected, the most frequent side effects consisting of mild nausea, fatigue and headache (3).

Pharmacoeconomic analysis of mitoxantrone therapy in patients with progressive relapsing and secondary progressive MS suggested that it compared favorably with other approved disease-modifying therapies (4).

The FDA has approved mitoxantrone hydrochloride (Novantrone®) for reducing neurological disability and/or the frequency of clinical relapses in patients with secondary progressive, progressive relapsing or worsening relapsing-remitting MS. The drug is currently marketed, in combination with corticosteroids, to treat pain in patients with advanced hormone-refractory prostate cancer and for initial therapy of acute nonlymphocytic leukemia in adults. This approval of the drug for expanded use marks the first approval of an anticancer drug for the treatment of MS (5).

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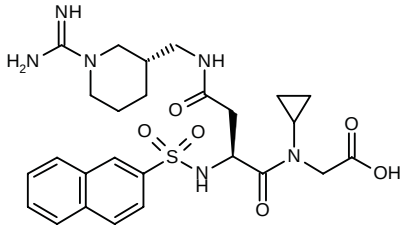

$C_{26}H_{34}N_6O_6S$ **Roche**

A randomized, 2-way crossover study in healthy male volunteers evaluated the effect of warfarin (25 mg p.o.) on the pharmacokinetics and pharmacodynamics of napsagatran infusion (80 µg/min over 48 h). Napsagatran concentrations and AUC values at steady state were not influenced by coadministration of warfarin (198 *vs.* 185 ng/ml for C_{max} and 569 *vs.* 535 mg·min/l for AUC). However, increases in both activated partial thromboplastin time (45%) and prothrombin time (438%) were found (1).

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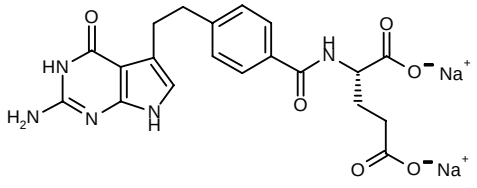

$C_{20}H_{19}N_5Na_2O_6$ **Lilly**

An *in vitro* study using a colon carcinoma cell line (LoVo) showed that pemetrexed disodium increased the cytotoxicity of gemcitabine in a dosing schedule-dependent manner. Pemetrexed disodium was only slightly cytotoxic when cells were treated with the agent alone for 48 h; thymidylate synthase and p53 protein expression and the bcl-2/bax ratio increased with pemetrexed disodium treatment although no apoptotic cells were detected. While an antagonistic effect was observed with simultaneous pemetrexed disodium + gemcitabine treatment, a synergistic effect was seen when cells were first exposed to gemcitabine for 48 h followed by pemetrexed disodium for another 48 h; a weaker synergistic effect was seen when cells were treated with pemetrexed disodium first followed by gemcitabine (1).

An *in vitro* study using human colorectal carcinoma cell lines (HT29, COLO 320 DM, and LoVo) examined the sequence dependence of combination treatment with pemetrexed sodium, gemcitabine and oxaliplatin. While oxaliplatin dose-dependently induced apoptosis in 2 of 3 cell lines, pemetrexed and gemcitabine had only minimal apoptotic effects. Maximum apoptotic responses were seen when HT29 and LoVo cells were treated with a sequence of pemetrexed, gemcitabine or both prior to oxaliplatin; no enhancing effects were observed when pemetrexed and gemcitabine were added after oxaliplatin (2).

The population pharmacokinetics of pemetrexed sodium (600 mg/m^2 10-min i.v. infusion every 21 days) were examined in 4 multicenter, open-label, nonrandomized phase II studies involving a total of 103 patients with cancer. A two-compartment model characterized the pharmacokinetics of the agent. Initial distribution and elimination $t_{1/2}$ values were 0.63 and 2.73 h, respectively. Volume of distribution, distributional clearance and peripheral volume were 11.3 l, 3.21 l/h and 5.20 l, respectively. Interpatient variability for these parameters was 15.6, 19.6 and 21.7%, respectively. Patient-specific factors significantly affecting clearance were creatinine clearance, body weight, alanine transaminase and folate deficiency. Central volume was significantly influenced by gender and body weight, and body surface area and albumin influenced peripheral volume (3).

The efficacy and tolerability of combination pemetrexed disodium (500 mg/m^2 over 10 min) and cisplatin (75 mg/m^2) given on day 1 of a 21-day cycle were shown in a phase II trial in 31 previously untreated patients with non-small cell lung cancer (Stage IIIB or IV, PS [performance status] 0, 1 or 2). Patients were also hydrated, administered mannitol diuresis and given dexamethasone (4 mg p.o. every 12 h starting 24 h before treatment and continuing for 6 doses after treatment) to prevent skin rash. Of the 30 evaluable patients, 1 complete response and 12 partial responses were seen for an overall response rate of 43%. Of the 4 PS-2 patients, 2 had a partial response, and of the 22 Stage IV patients, 9 partial responses and 1 complete response were achieved. Median survival was 7.3 months; 15 patients died. Adverse events included grade 3/4 anemia (5/1 cases), grade 3/4 granulocytopenia (7/3 cases), grade 3 nausea and vomiting (2 cases), grade 3/4 diarrhea (3 cases), grade 3 motor neuropathy (1 case), grade 2 infections (9 cases) and febrile neutropenia (1 case) (4).

An ongoing phase II study in 33 patients with locally advanced or metastatic breast cancer previously treated with anthracycline or anthracenedione + taxane examined the efficacy of third-line pemetrexed disodium (500 mg/m^2 i.v. once every 21 days); all patients received dexamethasone to prevent skin rash. No dose reductions or discontinuations have occurred and 4 patients have required dose delays due to conflicts in scheduling. The toxicities observed from the 24 evaluable patients have been manageable and reversible. They included grade 3 and 4 neutropenia (24 and 5%, respectively) and grade 3 elevated transaminases (11%), cutaneous toxicities (10%), neuromotor toxicities (5%), changes in hemoglobin (5%) and vomiting (5%). Of the 24 evaluable patients, 5 confirmed and 1 unconfirmed partial responses have been observed (5).

Results from a phase II trial involving 6 chemotherapy-naive patients with locally advanced or metastatic gastric cancer examined the efficacy and safety of pemetrexed disodium (500 mg/m^2 10-min infusion every 21 days for up to 6 weeks). Each patient developed at least 1 episode of grade 3/4 neutropenia (in 10/15 cycles). One patient discontinued and 3 died due to drug-related toxicities. A second subsequent part of the study involving 7 patients examined whether administration of folic acid (5 mg/day for 5 days starting 2 days before pemetrexed disodium) could reduce antifolate toxicity. No drug-related deaths or discontinuations occurred due to adverse events and only grade 2/3 neutropenia was seen in 4 cycles. One confirmed complete and 1 partial response were observed in 1 patient each, and an unconfirmed complete response was seen in another (6).

In a phase II trial, 53 patients with metastatic breast cancer failing anthracyclines and taxanes were administered pemetrexed (500 mg/m^2 i.v.) with dexamethasone to avoid skin rash. Treatment was well tolerated, grade 3/4 neutropenia being the major toxicity; no grade 3/4 thrombocytopenia was seen and other toxicities were mild and included rash, vomiting and fatigue. Of 32

evaluable patients, 6 have achieved partial response and 17 have had stable disease. Based on these results, a phase III trial is planned (7).

Pemetrexed disodium is in phase III clinical studies for the treatment of mesothelioma, and is also being studied for the treatment of non-small cell lung cancer and breast, colorectal, gastric and pancreatic cancers (8).

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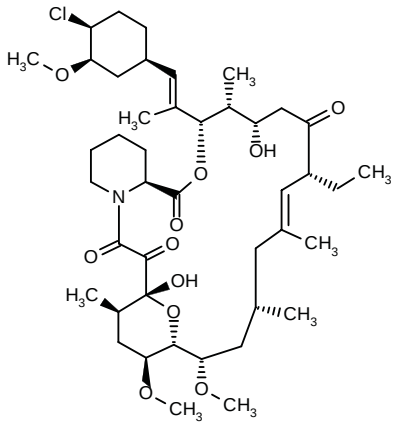

$C_{43}H_{68}ClNO_{11}$ **Novartis**

An *in vitro* study using an allogeneic mixed lymphocyte reaction (highly purified CD4+ T cells stimulated by human monocyte-derived dendritic cells) showed that SDZ-ASM-981 potently inhibited induction of coreceptors involved in dendritic cell-dependent activation of T cells. Treatment with the agent resulted in dose-dependent inhibition of upregulation of CD25, CD54, CD134 and CD137; an 80% inhibition was seen with a concentration of 10 nM. The agent was found to be 10-fold more potent that ciclosporin (1).

SDZ-ASM-981 was shown to be as effective as FK-506 (ED_{50} = 48 mg/kg p.) and superior to ciclosporin (ED_{50} = > 90 mg/kg p.o.) in a murine model of allergic contact dermatitis (ACD). In a rat model of ACD, the lowest doses of SDZ-ASM-981 and ciclosporin to induce effects were 12.5 and 50 mg/kg, respectively; FK-506 had no effect even at doses up to 25 mg/kg p.o. Following s.c. administration, SDZ-ASM-981 (ED_{50} = 20 mg/kg), FK-506 (E50 = 0.3 mg/kg) and ciclosporin (ED_{50} = 2.5 mg/kg) showed dose-dependent effects in models of localized graft *versus* host reaction; ciclosporin and FK-506 were 8 and 66 times superior to SDZ-ASM-981 in this model. Studies using an allogeneic kidney transplant model showed that the lowest dose of SDZ-ASM-981 required so that animals survived 100 days or longer was 15 mg/kg as compared to 5 mg/kg for ciclosporin and 1 mg/kg for FK-506. Thus, results show that SDZ-ASM-981

  CCC: 0377-8282/2001

is highly potent in skin inflammation models but less active in immunosuppression models indicating selective skin specificity for the agent (2).

A study genetically profiled blood cells from 9 patients with moderate to severe plaque psoriasis treated with SDZ-ASM-981 (30 mg b.i.d. p.o. for 13-14 days) or placebo. A common genomic profile was identified from SDZ-ASM-981-treated patients that included approximately 100 genes. Treatment with SDZ-ASM-981 was shown to downregulate expression of genes involved in the macrolactam pathway (macrophilin-12, calmodulin), cellular activation and proliferation (histone 2, histone 3.3, cyclin D2), chemotaxis and cellular migration (LFA-1, P-selectin ligand, L-selectin, RANTES) as well as genes expressing inflammatory mediators (leukotriene A_4 hydrolase, prostaglandin endoperoxide synthase) and HLA class II molecules (Ii invariant chain, CD74). Expression of genes associated with apoptosis, stress and enzymatic induction related to toxicity was not altered by treatment. Thus, oral SDZ-ASM-981 has broad antiinflammatory activity (3).

The efficacy of SDZ-ASM-981 against atopic dermatitis-like symptoms was shown in a study using hypomagnesemic hairless rats. Erythematous pruritic rash was inhibited within 1 day of oral SDZ-ASM-981 administration (12.5 mg/kg/day); decreases in histaminemia, leukocytosis, eosinophilia and serum nitric oxide levels were also seen. Prophylactic efficacy was observed when the agent was orally administered before rash onset. When the agent was applied topically to ears (0.4%) prophylactically or therapeutically, inflammatory changes were prevented and inhibited, respectively. Both routes of administration reversed histo- and immunopathological skin changes and normalized the numbers of dermal degranulated mast cells (4).

An *in vivo* study using Balb/c mice with oxazolone-induced allergic contact dermatitis reported differential actions following treatment with SDZ-ASM-981, FK-506 and ciclosporin. The agents were administered 4 times: 2 h before and 4, 24 and 48 h after the antigen challenge at doses of 30-90 mg/kg p.o., 10-30 mg/kg p.o. and 30-60 mg/kg for the respective agents. Doses of 3-90 mg/kg were used for all 3 agents at 2 and 4 h after the second exposure (*i.e.*, elicitation). None of the SDZ-ASM-981 doses impaired sensitization as compared to FK-506 (30 mg/kg, 4 times) and ciclosporin (60 mg/kg, 4 times) which inhibited sensitization by 71 and 60%, respectively. Inhibition was accompanied by a reduction in weight and cellularity (a decrease in cells expressing B-cell markers as compared to T cells) of draining lymph nodes. Both SDZ-ASM-981 and FK-506 inhibited elicitation with similar activities (ED_{50} = 48 mg/kg); ciclosporin also produced dose-dependent effects but to a lesser degree (ED_{50} > 90 mg/kg) (5).

The pharmacokinetic profile for single-dose (5, 15, 30 and 60 mg) and multiple-dose (5, 10 or 20 mg once daily or 20 or 30 mg b.i.d. for 28 days) oral SDZ-ASM-981 was reported in humans. The median t_{max} and apparent terminal $t_{1/2}$ after single dosing was between 0.7 and 1.4 h for all doses, respectively. A decrease in the concentration of the agent was observed following peak which occurred in 3 phases with an apparent $t_{1/2}$ value of about 30-40 h obtained for the 30 and 60 mg doses; the $t_{1/2}$ for the lower doses could not be determined due to sensitivity limitations of the assay. Mean apparent total body clearance and apparent volume of distribution was 71-91 l/h and 3452 and 4830 l for the 30 and 60 mg doses, respectively. C_{max} was dose-proportional and AUC values appeared to be over-proportional. The C_{max} and AUC_{τ} values following multiple dosing were dose-proportional. The mean AUC at steady state over 24 h for the 30 mg b.i.d. dose was 577 and 561 ng·h/ml on days 13 and 28, respectively. Steady state was reached after 5-10 days and the terminal $t_{1/2}$ was 30-66 h (6).

The systemic exposure to SDZ-ASM-981 (1% cream b.i.d. for 3 weeks) was measured from blood samples (days 4 and 22 of treatment and 1 week posttreatment) taken from 10 young children (1-4 years) with atopic dermatitis (23-69% of the body surface affected) participating in an open noncontrolled trial. Of the 63 samples taken, SDZ-ASM-981 concentrations were < 0.5 ng/ml in 63% and the maximum concentration seen was 1.8 ng/ml. No accumulation was observed between days 4 and 22. SDZ-ASM-981 did not control the dermatitis of 2 patients who experienced flare. However, the Eczema Area Severity Index (EASI) of the remaining patients was improved by 8-89% at 3 weeks (7).

The efficacy and safety of topical SDZ-ASM-981 (1% cream b.i.d. for 6 weeks) were examined in 2 multicenter, randomized, double-blind, vehicle-controlled studies conducted in 403 pediatric subjects (mean = 6.8 years) with mild to moderate atopic dermatitis. Subjects completing the 6-week double-blind phase were subsequently enrolled in a 20-week open-label phase examining efficacy on an as-needed basis. Significantly improved Investigator's Global Assessment (IGA) scores were observed in the SDZ-ASM-981 group as soon as day 8. Mean reductions in EASI for the treated and vehicle groups were about 45 and 1%, respectively, and significantly more SDZ-ASM-981-treated subjects were determined to be treatment successes at the end of the double-blind phase. Significantly more treated subjects had little or no pruritus as compared to the vehicle. Treatment was well tolerated with less than 3% of the subjects discontinuing due to adverse events. Of the treated subjects, only 10% as compared to 13% in the vehicle group reported application site burning. No systemic or serious adverse events were observed (8).

Results of a randomized, double-blind study conducted in 16 healthy volunteers showed that topical SDZ-ASM-981 (1% cream b.i.d. 6 days/week for 4 weeks) applied to healthy forearm skin did not cause skin atrophy. Significantly less epidermal thinning was seen with SDZ-ASM-981 on day 29 as compared to betamethasone-17-valerate (0.1% cream) and triamcinolone acetonide (0.1% cream). The significant thinning of the skin observed with the 2 cortocosteroids started on day 8, in contrast to SDZ-ASM-981 which was not significantly different from the vehicle (9).

A randomized, double-blind, placebo-controlled, multiple oral dose trial conducted in 50 patients with moderate to severe chronic plaque psoriasis showed the safety and efficacy of SDZ-ASM-981 (5, 10 or 20 once daily [o.d.] or 20 or 30 mg b.i.d.).The agent was well tolerated with no serious adverse events observed. The most common adverse event was a transient mild to moderate feeling of warmth seen in 1, 1, 3 and 7 patients treated with 5 mg o.d., 20 mg o.d., 20 mg b.i.d. and 30 mg b.i.d. doses, respectively. No changes in blood pressure, serum creatinine, ECG, laboratory tests, glomerular filtration rate or renal function tests were seen. Only 1 patient had elevated glycemia after a glucose load during dosing. Doses of 20 and 30 mg b.i.d. resulted in median decreases in the Psoriasis Area Severity Index (PASI) on day 28 of 60 and 75%, respectively, as compared to 4% in placebo (10).

The efficacy of SDZ-ASM-981 (1% cream b.i.d. for up to 8 weeks) is being compared with triamcinolone acetonide (0.1%) as a treatment of atopic dermatitis on facial skin in a 2-phase trial involving 20 patients. The atrophogenic potential of the agents is being examined (11).

Results from a multicenter, randomized, vehicle-controlled study conducted in 183 infants (3-23 months) with atopic dermatitis showed the efficacy and safety of SDZ-ASM-981 (1% cream b.i.d. for up to 6 weeks). Results from the first 83 patients showed that more treatment successes were seen in the SDZ-ASM-981 group (62.7%) as compared to vehicle (16.7%). Effects were rapid with a significant difference seen by day 15 (47.5 *vs.* 16.7%). A significantly greater mean reduction in the EASI was observed for SDZ-ASM-981-treated patients as compared to vehicle and significantly more subjects treated with the agent had little or no pruritus early during treatment. Treatment was well tolerated and no serious or systemic adverse events were seen. Two patients from each group displayed adverse events at the application site (12).

An ongoing multicenter, randomized, double-blind, vehicle-controlled, parallel-group, 1-year study involving 713 children with atopic dermatitis is examining the efficacy and safety of long-term treatment with SDZ-ASM-981 (1% cream b.i.d.). To control refractory flares, a medium-high potency topical corticosteroid as a second-line medication was allowed (13).

An ongoing open-label study involving 20 infants (3-23 months) with atopic dermatitis (over at least 40% of their body surface area) is examining the tolerability and efficacy of SDZ-ASM-981 (1% cream for 3 weeks). Good local and systemic tolerability have been observed in the 12 patients treated so far and blood concentrations of the agent were low (< 0.1-1.8 ng/ml) (14).

A multicenter, double-blind, randomized study involving 294 adults with mild to moderate chronic hand dermatitis is examining the efficacy and safety of SDZ-ASM-981 (1% cream b.i.d. for up to 3 weeks). Following this first phase of the trial subjects will continue on to a 23-week open-label phase to examine the efficacy and safety of the agent on an as-needed basis. So far over 80% of the subjects have completed the randomized phase of the trial and have entered the open-label phase (15).

Novartis has submitted an NDA with the FDA for SDZ-ASM-981 cream 1%, the first ascomycin derivative under development specifically for the treatment of atopic dermatitis (eczema) (16).

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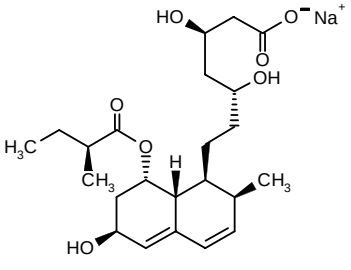

$C_{23}H_{35}NaO_7$ **Bristol-Myers Squibb**

A new microbial process for the preparation of pravastatin sodium has been claimed. The process comprises the biotransformation of the alkali or ammonium salts of compactin, preferably the sodium salt, by fermentation with a microorganism of the genus *Micromonospora*, such as *Micromonospora* sp. IDR-P3 [NCAIM P (B) 001268], able to 6β-hydroxylate compactin in aerobic conditions, separation of pravastatin performed by adsorption on an anionic ion exchange resin or by extraction with an organic solvent, and finally purification of the obtained pravastatin sodium (1).

Pravastatin appears to have important antiinflammatory activity, according to results from the Pravastatin Inflammation CRP Evaluation (PRINCE) study in over 2000 participants with and without a history of heart disease. The PRINCE trial included a randomized, double-blind, placebo-controlled primary prevention cohort of 1339 individuals with no history of cardiovascular disease and an open-label secondary prevention cohort of 898 patients with known cardiovascular disease. Using a new high-sensitivity C-reactive protein (CRP) test, researchers determined a significant 13% reduction in median CRP levels as early as 12 weeks in both cohorts with the administration of pravastatin (40 mg). Interestingly, the observed reduction in CRP levels appeared to be only minimally related to changes in LDL cholesterol levels (2).

The Demonstration of Regression of Atherosclerosis by ULtrasonographic Assessment (DRACULA) trial determined the effects of pravastatin on coronary plaque regression as assessed by intravascular ultrasound (IVUS). This prospective, multicenter trial included 50 patients presenting for angioplasty who had angiographically proven CAD and LDL cholesterol levels of 100 mg/dl or greater. IVUS with automated pull-back showed a slight increase in plaque mass despite the administration of 40 mg/day pravastatin for 1 year. The observed increase was caused by a rise in fibrocalcific plaque mass, with stabilization of soft plaques (3).

A 3-year poststudy follow-up of the West Of Scotland COronary Prevention Study (WOSCOPS) assessed the benefits of coronary disease prevention with pravastatin in 6595 men with no history of myocardial infarction. The total number of deaths both within the trial and during follow-up was 486 (223 cardiovascular, 259 noncardiovascular and 4 unclassifiable). Pravastatin therapy was associated with a proportional risk reduction of 27% for cardiovascular mortality, 6% for noncardiovascular mortality and 16% for all-cause mortality (4).

The results from the LIPID (Long-term Intervention with Pravastatin in Ischemic Disease) study evaluating lipid-modifying therapy with an HMG-CoA reductase inhibitor in almost 10,000 patients with previous unstable angina or myocardial infarction were previously presented. A substudy compared subsequent cardiovascular risks and the effects of pravastatin sodium in the 2 different groups qualifying for the entire study: those with unstable angina and those with previous acute myocardial infarction. Over 3000 patients were diagnosed with unstable angina and over 5700 with acute myocardial infarction 3-36 months before randomization to pravastatin 40 mg/day or placebo for a mean of 6 years. Survival

in the 2 groups receiving placebo was similar. A similar long-term prognosis was found in pravastatin-treated patients with previous acute myocardial infarction or unstable angina: the relative risk reduction for mortality on pravastatin was 20.6% in those with myocardial infarction and 26.3% in those with unstable angina. Treatment with pravastatin was associated with significant reductions in the rates of all coronary endpoints evaluated (coronary heart disease mortality, total mortality, stroke, myocardial infarction, nonfatal myocardial infarction, coronary heart disease death or nonfatal myocardial infarction, hospital admission for unstable angina, coronary artery bypass grafts and percutaneous transluminal coronary angioplasty) in patients with myocardial infarction, and those with previous unstable angina showed significant reductions in coronary heart disease mortality, total mortality, myocardial infarction, need for coronary revascularization, the number of admissions to hospital and the number of days in the hospital. The most frequent endpoint in both placebo and pravastatin groups was hospital admission for unstable angina, occurring in 24.6% of all placebo-treated patients and 22.3% of all pravastatin-treated patients. The results of this substudy thus provide evidence for a beneficial effect of lipid-modifying therapy as regards the prevention of death and major coronary heart disease in patients with previous unstable angina (5).

Data from almost 6000 middle-aged men with elevated cholesterol levels and no history of heart disease comparing pravastatin and placebo over 5 years demonstrated that a statin can reduce the risk of type 2 diabetes. Previous analyses of this trial demonstrated the ability of pravastatin to reduce the risk of a first heart attack in these subjects. Using the American Diabetes Association criteria, the researchers have shown that pravastatin therapy results in a 30% reduction in the risk of developing diabetes compared to placebo. Further investigations will be needed to clarify the exact mechanisms underlying this protective effect, as well as to determine if this effect is common to all members of the statin family or specific to pravastatin (6).

Coronary heart disease mortality in women with prior CHD and average cholesterol levels was reduced by long-term pravastatin treatment, according to additional 2-year follow-up data from the 6-year LIPID study. Compared to placebo, women initially assigned to pravastatin had a 31% lower CHD mortality, a 29% lower cardiovascular disease mortality and a 12% lower all-cause mortality. The relative risk reduction in CHD with pravastatin therapy was 16% in women and 23% in men, but this difference was not statistically significant. After adjustment for other risk factors, the overall risk of subsequent CHD events was lower in women than in men. The data included in this extended follow-up, which now include 126 deaths due to CHD in women, are sufficient to support the beneficial effects of pravastatin treatment in women with CHD and average cholesterol levels (7).

Pravastatin sodium was shown to reduce the risk of stroke in patients with previous myocardial infarction, according to a study conducted under the auspices of the National Heart Foundation of Australia. The primary objective of this double-blind, placebo-controlled trial was to assess the effect of pravastatin on mortality due to coronary heart disease, and secondary objectives were to evaluate the drug's effects on stroke from any cause and nonhemorrhagic stroke. Over the 6-year follow-up period, 419 strokes occurred in 373 patients (332 with single stroke and 41 with multiple stroke). Classification of the 419 strokes found that 309 were ischemic, 31 were hemorrhagic and 79 were of unknown type. Pravastatin led to a 19% relative reduction in risk of stroke from any cause and a 23% reduction in risk of nonhemorrhagic stroke, as compared to placebo. The drug did not appear to have an effect on hemorrhagic stroke. The results therefore support the use of pravastatin in patients with previous myocardial infarction, especially when coupled with the drug's reduction in the risk of heart attack, bypass surgery or angioplasty (8).

Pravastatin Pooling Project investigators examined the variation in long-term benefits associated with different degrees of alterations in LDL cholesterol, HDL cholesterol and triglycerides. Based on data from WOSCOPS, LIPID and the Cholesterol And Recurrent Events (CARE) trial, this analysis separated patients treated with pravastatin for 12 months into quintiles of changes in LDL cholesterol, HDL cholesterol and triglycerides, as well as quintiles of achieved LDL cholesterol levels. The percent changes in LDL cholesterol, HDL cholesterol and log triglycerides were not associated with alterations in the risk of a coronary event. Furthermore, achieved target levels of LDL cholesterol were not associated with risk reduction in the CARE trial, although a positive association was observed in the LIPID and WOSCOPS trials. The results from this analysis support the idea of a diminishing clinical benefit with greater reduction in LDL cholesterol. In addition, this study failed to demonstrate additional clinical benefit in patients with greater changes in HDL cholesterol and triglycerides (9).

Coronary heart disease patients with low levels of HDL cholesterol (40 mg/dl or less) and low levels of LDL cholesterol (140 mg/dl or less) from the LIPID trial were compared to similar patients in the VA-HIT trial in order to compare the efficacy of pravastatin and gemfibrozil, the study drugs used in the 2 respective trials. Baseline characteristics of the 2 trials were similar, with the exception of gender (LIPID: 81% male; VA-HIT: 100% male) and diabetes (LIPID: 8%; VA-HIT: 25%). The relative risk reduction for coronary events was 27% for pravastatin in the LIPID trial subgroup and 22% for gemfibrozil in the VA-HIT study. Therefore, according to this analysis, pravastatin and gemfibrozil caused similar reductions in the risk of major coronary events in patients with CHD and low HDL and LDL cholesterol (10).

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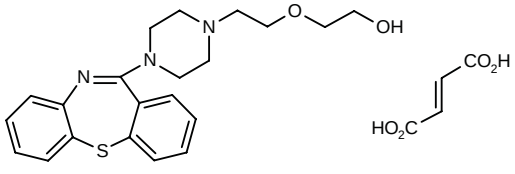


$C_{21}H_{25}N_3O_2S.C_4H_4O_4$ **AstraZeneca; Fujisawa**

The administration of quetiapine has been found to be associated with a small mean weight increase in the first 5-6 weeks of treatment and over 12 months of treatment only little further mean change was observed. Based on these findings, the use of quetiapine for the treatment of weight gain in patients suffering from psychoses has been claimed. This compound may also be of use for the treatment of psychoses in diabetic patients or patients with a risk of developing diabetes (1).

Data indicate that long-term treatment with quetiapine fumarate is associated with significant improvement in cognitive functioning among young people experiencing their first episode of acute schizophrenia. Preliminary results demonstrated that, compared with baseline assessments, improvements in important areas of cognitive function, including attention, language, memory and executive function, were seen in all 9 patients who have so far completed 1 year of quetiapine treatment (mean daily dose of 476 mg). Moreover, preliminary results indicate that quetiapine does not cause extrapyramidal symptoms and may correct underlying basal ganglia dysfunction (2).

Quetiapine fumarate (Seroquel®) has been introduced in Germany for the treatment of schizophrenia by AstraZeneca in the form of tablets containing 25, 100 and 200 mg quetiapine. The agent was also introduced in Japan by Fujisawa on February 6, 2001 (3, 4).

AstraZeneca recently announced that it plans to launch 3 worldwide phase III clinical trials of quetiapine fumarate for the treatment of the symptoms of acute mania in patients with bipolar disorder. These trials will be conducted in addition to an ongoing U.S. trial evaluating quetiapine therapy as both adjunctive treatment and monotherapy. These 3 double-blind, randomized trials will involve over 800 patients in 28 countries. One of the trials will evaluate quetiapine as an adjunct to a mood-stabilizing drug in 200 patients with acute manic episodes of bipolar disorder in Eastern and Southern Europe, North America and Africa. A second trial will examine the efficacy of quetiapine and haloperidol as monotherapy in acute mania in bipolar disorder as compared to placebo in nearly 250 patients in Asia, Eastern Europe and South America. The third trial will include over 300 patients in Asia and Eastern Europe and will compare quetiapine and lithium monotherapy to placebo for the treatment of acute manic episodes (5).

1. Reinstein, M.J., Jones, A.M. (AstraZeneca AB). *Method of treatment.* WO 0071106.

2. *New data demonstrate cognitive benefits with quetiapine in treatment-naive schizophrenia patients.* DailyDrugNews.com (Daily Essentials) May 2, 2001.

3. *New market launch for Seroquel.* DailyDrugNews.com (Daily Essentials) Oct 25, 2000.

4. *Fujisawa begins marketing Seroquel in Japan.* DailyDrugNews.com (Daily Essentials) Feb 7, 2001.

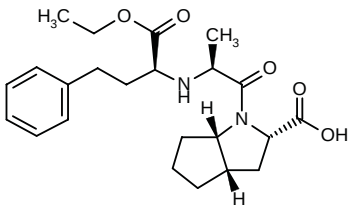
5. *Expanded phase III trial program in bipolar disorder announced for Seroquel.* DailyDrugNews.com (Daily Essentials) Jan 10, 2001.

Original monograph - Drugs Fut 1996, 21: 483.

Ramipril
Altace®

Antihypertensive
Treatment of Heart Failure

EN: 090507



$C_{23}H_{32}N_2O_5$ **Aventis Pharma; King Pharm.**

Health Canada has approved a new indication of Aventis's ramipril (Altace®), allowing the drug to be prescribed to reduce the risk of stroke, myocardial infarction and death from cardiovascular causes in patients 55 years of age and older with either a history of coronary artery disease, stroke or peripheral vascular disease, or with diabetes associated with another cardiovascular risk factor (*e.g.*, elevated cholesterol levels, cigarette smoking or elevated blood pressure). The new expanded indication is based on the results from the landmark HOPE (Heart Outcomes Prevention Evaluation) study in which 9297 patients from 19 countries were evaluated over a period of more than 4 years. During the study, researchers unexpectedly observed that ramipril also reduced by 34% the risk of new cases of diabetes. As a result, a new study is in progress in Canada to test the possibility that the drug can prevent type 2 diabetes. Altace® is currently available in the U.S. through Monarch Pharmaceuticals, a subsidiary of King Pharmaceuticals, for the treatment of hypertension and congestive heart failure postmyocardial infarction, as well as for the newly approved expanded indication. Altace® is marketed outside the U.S. by Aventis (1).

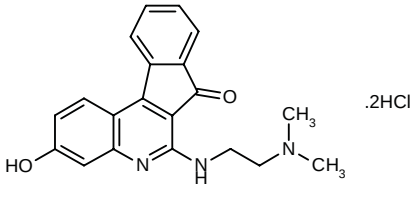
1. *Altace approved in Canada for expanded indication.* DailyDrugNews.com (Daily Essentials) Feb 20, 2001.

Original monograph - Drugs Fut 1985, 10: 400.

TAS-103
BMS-247615

Oncolytic
Topoisomerase I/II Inhibitor

EN: 231405



$C_{20}H_{19}N_3O_2.2HCl$ **Taiho; Bristol-Myers Squibb**

The mechanism of action of TAS-103 was examined in an *in vitro* study using 12 human cancer cell lines and acquired TAS-103-resistant cell variants (DLD/TAS14 and A549/C13). Cross-sensitivity of TAS-103 was seen with CPT-11 and doxorubicin in the 12 cell lines although TAS-103 was more active than the other two agents in the cells with acquired resistance. O^6-methylguanine-DNA methyltransferase (MGMT) gene expression and glutathione S-transferase activity correlated with cellular resistance while topoisomerase IIalpha, MRP1 and MRP2 expression inversely correlated with resistance. Results suggest that MGMT and topoisomerase IIalpha may be determinants of cellular sensitivity or resistance to TAS-103 (1).

Results from an *in vitro* study using a human myelogenous leukemia cell line (HL-60) showed that TAS-103 induced apoptosis via DNA topoisomerase inhibition, DNA damage, H_2O_2 production, mitochondrial injury and caspase-3 activation (2).

TAS-103 is a novel anticancer agent that targets both topoisomerase I and II and shows broad-spectrum antitumor activity. A phase I dose-escalation study has been conducted to determine the maximum tolerated dose (MTD) and pharmacokinetics of the compound given at doses of 20, 40, 60, 80 and 100 mg/m^2/day by short i.v. infusion for 5 days every 3 weeks. Ten patients with refractory solid tumors have received 30 cycles of drug so far and nonhematological toxicity has been mild. Grade 3/4 neutropenia and thrombocytopenia were seen in 2 patients at the highest dose. Treatment was associated with 4 cases of stable disease lasting for up to 12 cycles. Accrual continues at the dose of 80 mg/m^2 (3).

The safety and pharmacokinetics of TAS-103 (80, 120 and 160 mg/m^2/week; 1 cycle of 4 weeks) were reported from a phase I study in 16 patients with refractory solid tumors (colon, non-small cell lung cancer [NSCLC], head and neck, small cell lung cancer, sarcoma, pancreatic and carcinoma of unknown primary). The MTD was 120 mg/m^2/week. Dose-limiting toxicity (inability to dose patient with 80% or more of the planned dose) occurred in 2 of 3 patients treated with 160 mg/m^2/week. Myelosuppression was infrequent and transient with 3 cases of grade 3 neutropenia, 1 case of grade 4 neutropenia, 1 case of grade 3 anemia seen; no grade 3 or 4 thrombocytopenia was observed. Nonhematological toxicities reported were considered clinically insignificant. No major responses were observed although stable disease for 4 cycles was seen in 2 NSCLC patients. The preliminary mean total clearance steady-state volume and $t_{1/2}$ parameters obtained from 10 patients (3-4 patients/dose level) were 59 ± 29 l/h, 195 ± 96 l and 4.5 ± 3.6 h, respectively (4).

A phase I study in 32 patients with advanced cancer determined the MTD and dose-limiting toxicity (DLT) of TAS-103 (50-200 mg/m^2 i.v. over 1 h once weekly for 3 weeks). The DLT was grade 3 neutropenia seen in 5/12 and 3/6 patients at the 160 and 200 mg/m^2 doses, respectively. Pharmacokinetics obtained at the 130, 160 and 200 mg/m^2 doses showed a significant correlation

between the AUC values for TAS-103 and TAS-103-glucuronide and between the TAS-103 AUC value and absolute neutrophil counts. Clearance of the agent was not affected by the UGT1A1 genotype. The recommended dose for phase II studies was 130-160 mg/m^2 or 250-300 mg/m^2 once weekly (5).

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Original monograph - Drugs Fut 1998, 23: 513.

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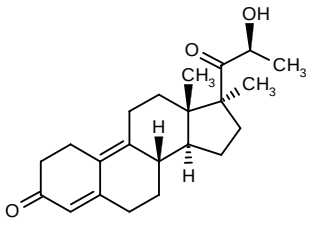
Trimegestone
Ru-27987
Ondeva®

Prevention of Osteoporosis
Treatment of Postmenopausal Syndrome
Oral Contraceptive

EN: 140296



$C_{22}H_{30}O_3$ **Aventis Pharma; Wyeth-Ayerst**

An *in vitro* study characterized and compared the steroid receptor selectivity of trimegestone and medroxyprogesterone (MPA). Both agents had comparable binding affinity for the human and rabbit progesterone receptor (PR), although trimegestone showed a higher affinity for rat PR (IC_{50} = 3.3 *vs.* 53.3 nM). Alkaline phosphatase activity and cell proliferation were increased in a similar manner in T47D cells treated with the agents (EC_{50} = 0.1 and 0.02 nM for trimegestone and MPA, respectively). Studies were also conducted using an immortalized human endometrial stromal cell line (HESC-T) which lacks the estrogen receptor (ER) and PR but has a glucocorticoid receptor (GR). When ER was transiently expressed in these cells, 17β-estradiol induced PR. Treatment of these transfected cells with either agent increased HRE-tk-luciferase activity 10-fold (EC_{50} = 0.2 nM). Although trimegestone had no effect in cells without ER or PR, MPA dose-dependently increased activity of the reporter gene (EC_{50} = 10 nM), possibly through a mechanism involving the GR. Trimegestone also had no effect on reporter activity in a human lung carcinoma cell line (A549) which has GR but no PR. In contrast, MPA increased reporter activity (EC_{50} = 30 nM) in these cells. Further studies showed that trimegestone displayed weak antiandrogenic activity as compared to MPA, which exerted androgenic activity in a HRE-tk-luciferase assay using mouse fibroblast cells (L929) expressing the androgen receptor but not the PR. Results indicate that trimegestone has a superior receptor selectivity profile as compared to MPA (1).

A study conducted in ovariectomized adult rats with osteopenia (2 months after ovariectomy) showed that treatment with trimegestone (1 mg/kg/day p.o.) in combination with 17beta-estradiol (10 μg/kg/day p.o.) for 2 months was superior to norethisterone (1 mg/kg/day p.o.) in preventing bone loss. Treatment with trimegestone also more effectively prevented estradiol-induced uterine atrophy as compared to norethisterone. However, although 17β-estradiol alone improved bone mass and turnover, neither of the progestins affected these parameters when administered alone (2).

American Home Products and Aventis have renegotiated their licensing agreement for trimegestone. Under the new agreement, Wyeth-Ayerst has exclusive development and worldwide marketing rights for trimegestone for all indications and formulations except transdermal products. The rights to combination use for hormone replacement therapy with conjugated estrogen tablets are included in the agreement. In addition, Wyeth-Ayerst will take full responsibility for development and marketing of combinations of trimegestone with 17β-estradiol for hormone replacement therapy. Swedish regulatory authorities recently approved the hormone replacement therapy product Totelle Sekvens®, the first commercial product using trimegestone. Totelle Sekvens® employs a cyclic regimen of 14 days of 2 mg of 17β-estradiol alone and 14 days in combination with 500 μg of trimegestone. The product, launched by Wyeth-Ayerst in Sweden last year, is indicated for the relief of vasomotor symptoms associated with menopause and provides improved and

predictable cycle control and a better lipid profile in comparison to existing products (3).

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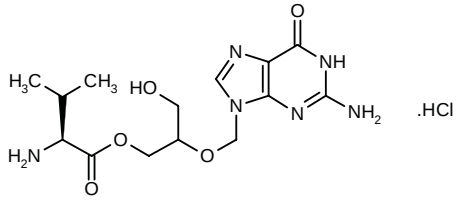
3. *American Home Products and Aventis renegotiate agreement.* DailyDrugNews.com (Daily Essentials) Oct 24, 2000.

Original monograph - Drugs Fut 2000, 25: 465.

Valganciclovir Hydrochloride

Cymeval® *Anti-Cytomegalovirus Drug*
Valcyte®
Valcyt®

EN: 233109



$C_{14}H_{22}N_6O_5.HCl$ **Roche**

An *in vitro* study examined the interaction of valganciclovir and ganciclovir with intestinal peptide transporter PEPT1 and the renal peptide transporter PEPT2. The K_i values for valganciclovir for PEPT1 in Caco-1 cells and PEPT2 in SKPT cells were 1.68 ± 0.30 and 0.043 ± 0.005 mM, respectively. Valganciclovir inhibition was found to be competitive for both PEPT1 and PEPT2, while ganciclovir did not interact with either transporter. Studies using cloned PEPT1 and PEPT2 produced similar results. Only valganciclovir was found to induce inward currents in PEPT1-expressing *Xenopus* oocytes (1).

A study examining the emergence of resistance mutations in leukocytes from HIV-infected patients with CMV retinitis administered valganciclovir (900 mg b.i.d. p.o. for 3 weeks followed by 900 mg once daily for 1 week) or ganciclovir (5 mg/kg b.i.d. for 3 weeks followed by 5 mg/kg once daily for 1 week) showed that the rate of ganciclovir resistance was similar for both treatments. Of those patients with genotypic evidence of ganciclovir resistance, 2.79% displayed a UL97 mutation at codons 594, 595 or 460 (2).

Exposure to oral valganciclovir (450 or 900 mg p.o. once daily) was found to be similar to that of ganciclovir (1 g p.o. t.i.d. or 5 mg/kg/day i.v. over 1 h) in an open-label, randomized study with a 3- to 7-day washout period conducted in 28 liver transplant recipients. Exposure to 450 mg valganciclovir (20.56 μg·h/ml) was similar to oral ganciclovir (20.15 μg·h/ml) and exposure to 900 mg valganciclovir (42.69 μg·h/ml) was similar to i.v. ganciclovir (47.61 μg·h/ml). Results suggest that valganciclovir may be effective as CMV prophylaxis and safe for transplant recipients (3).

The FDA has approved valganciclovir hydrochloride (Valcyte®) for the treatment of cytomegalovirus (CMV) retinitis in AIDS patients. Valganciclovir is the oral prodrug of ganciclovir, which was launched in the U.S. in 1989. The two treatments showed comparable efficacy for induction therapy in clinical studies (4).

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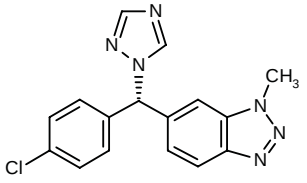
4. *Valcyte approved by FDA for AIDS-related CMV.* DailyDrugNews.com (Daily Essentials) April 3, 2001.

Original monograph - Drugs Fut 2000, 25: 474.

Vorozole

Rivizor® *Oncolytic*
Aromatase Inhibitor

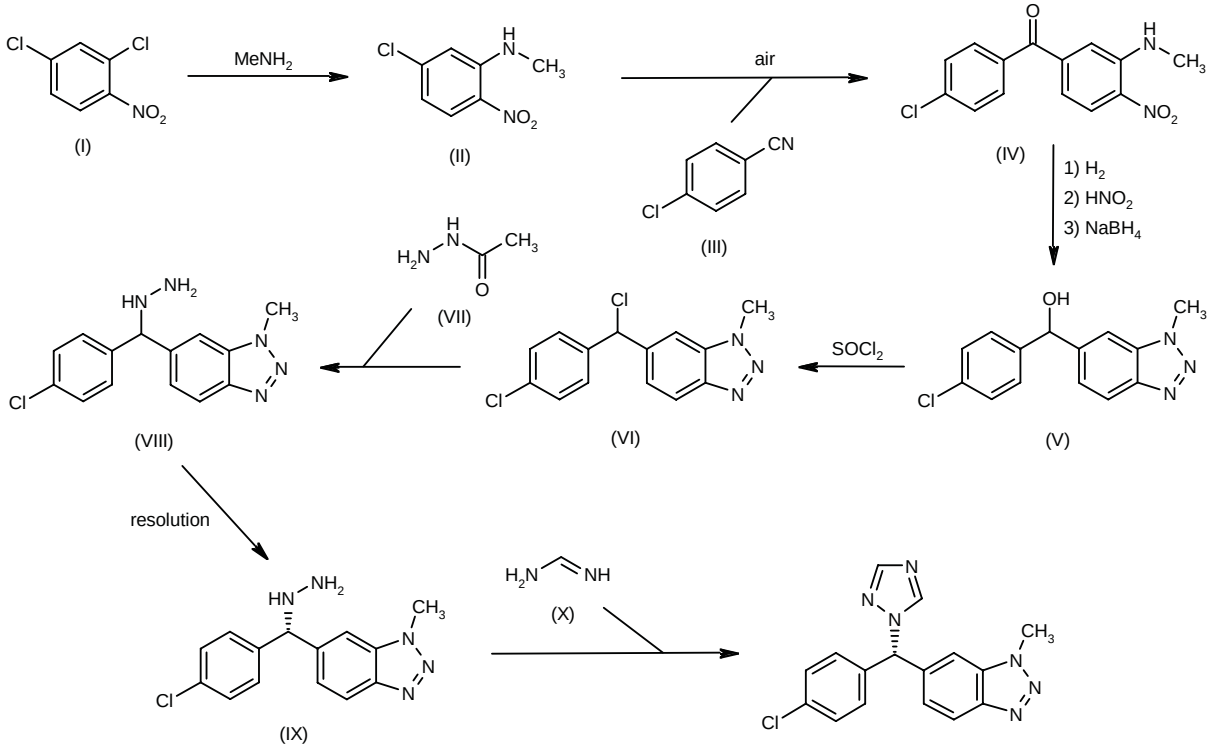
EN: 172112



$C_{16}H_{13}ClN_6$ **Janssen; Kyowa Hakko**

A scaleable process to produce vorozole has been reported: The reaction of 2,4-dichloronitrobenzene (I) with methylamine gives 5-chloro-*N*-methyl-2-nitroaniline (II), which is condensed with 4-chlorobenzonitrile (III) and oxidized with air to yield 4'-chloro-3-(methylamino)-4-nitrobenzophenone (IV). The hydrogenation of compound (IV), followed by cyclization by means of nitrous acid and reduction of the carbonyl group with $NaBH_4$ affords the benzotriazole (V). Reaction of the OH group of (V) with $SOCl_2$ provides the corresponding chloro derivative (VI), which is treated with acetohydrazide (VII) to give the racemic hydrazine derivative (VIII). Optical resolution of (VIII) by chiral chromatography yields the (*S*)-isomer (IX),

Scheme 3: Synthesis of Vorozole



which is finally cyclized with formamidine to afford vorozole (1). Scheme 3.

A multicenter, randomized, single-blind study in 53 postmenopausal patients with ER-positive breast tumors compared the effects of vorozole (2.5 mg/day p.o. for 12 weeks) and tamoxifen (20 mg/day p.o. for 12 weeks). While tamoxifen-treated patients displayed a significant decrease in serum markers of bone resorption after 12 weeks, no changes were observed in the vorozole group. Tumor Ki67 levels were decreased significantly more in patients treated with vorozole as compared to tamoxifen (58 *vs.* 43% between baseline and 2 weeks and 73 *vs.* 57% between baseline and 12 weeks). A significant decrease in apoptosis was observed in tumors from the vorozole-treated patients while no changes were seen in tumors from tamoxifen-treated patients; the Ki67/apoptosis ratios were decreased by 48 and 35% at 2 weeks and 63 and 69% at 12 weeks in tumors from the tamoxifen and vorozole groups, respectively. A significant reduction in serum IGF-1 was observed in the tamoxifen group as compared to the vorozole group which tended to have increased levels (2).

A multicenter, single-blind, randomized trial in 79 patients with ER-positive breast tumors (> 2 cm in diameter) compared the efficacy of tamoxifen (20 mg/day p.o.) with vorozole (2.5 mg/day p.o.) for 12 weeks. The tamoxifen group showed a significant decrease in serum markers of bone resorption at 12 weeks; these levels were unchanged in the vorozole group. A significant decrease in apoptosis was observed at 2 weeks as compared to baseline in the vorozole group. Significant decreases in Ki67 of 58 and 30% were observed in vorozole- and tamoxifen-treated patients, respectively, at 2 weeks as compared to baseline although no significant difference was observed between the 2 treatment groups. Significant decreases in Ki67 levels were also observed for the vorozole (73%) and tamoxifen (49%) groups between 2 and 12 weeks. These results indicate a more rapid effect of vorozole on proliferation. A positive correlation was found between the reductions in Ki67 at 2 weeks and reductions in tumor volume in both groups. In the vorozole group, the reduction in Ki67 at 2 weeks was significantly greater in objective responders as compared to nonresponders at 12 weeks (3).

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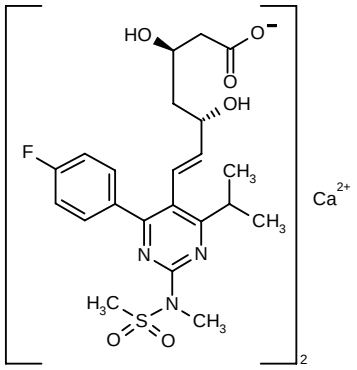
ZD-4522
Rosuvastatin Calcium
Crestor®

Hypolipidemic

EN: 243619



$C_{44}H_{54}CaF_2N_6O_{12}S_2$ **Shionogi; AstraZeneca**

An *in vitro* study examined the kinetics of rosuvastatin-induced inhibition of HMG-CoA reductase. Results showed that the agent exhibited slow binding inhibition in that its catalytic activity was decreased over minutes. Rosuvastatin displayed competitive kinetics for HMG-CoA reductase as compared to noncompetitive kinetics seen with NADPH. High affinity of the agent for HMG-CoA reductase was observed with an overall K_i value of about 0.1 nM obtained. When HMG-CoA inhibition by other statins was compared, rosuvastatin (IC_{50} = 5 nM) was as effective as atorvastatin, cerivastatin and simvastatin (IC_{50} = 8-11 nM) but was more potent than fluvastatin and pravastatin (IC_{50} = 28-44 nM). Results also showed that the replacement of the HMG-CoA reductase amino acid Ile-638 with Val had no effect on rosuvastatin inhibitory activity (1).

Results from a study using human hepatic microsomes showed that ZD-4522 (50 mcM) had no effect on cytochrome (CYP) 1A2, 2C19, 2D6, 2E1 and 3A4 enzyme activity, indicating that metabolic interactions *in vivo* are unlikely. A slight 10% reduction in CYP2C9 was observed but was considered clinically insignificant. Although human hepatic microsomes and heterologously expressed human CYP enzymes did not metabolize [^{14}C]-ZD-4522 (1-4 μM for 3 and 1 h, respectively), slow metabolism producing a single *N*-desmethyl product was observed by cultured human hepatocytes (5-50% over 3 days). This metabolism was inhibited by sulphaphenazole and less potently by omeprazole, indicating that CYP2C9 and CYP2C19 were involved (2).

Results from a study in rats examining the mechanisms of action of rosuvastatin showed that the agent (0.5 and 1.25 mg/kg i.p.) attenuated thrombin-induced leukocyte rolling, adherence and transmigration in mesenteric microvasculature following pretreatment (18 h prior to the study). Mevalonic acid (25 mg/kg 18 h before) reversed the effects of rosuvastatin. Rats treated with 1.25 mg/kg rosuvastatin displayed a 70% decrease in P-selectin expression on endothelial cells and enhanced nitric oxide (NO) release from vascular endothelium. In contrast, the agent had no effect on leukocyte-endothelium interactions in the peri-intestinal venules of eNOS–/– mice. Results suggest that the antiinflammatory effects of the agent are via inhibition of endothelial cell adhesion molecule expression and they were dependent on NO release (3).

The preclinical and clinical pharmacology of rosuvastatin was summarized. The agent is relatively hydrophilic and was shown to potently inhibit HMG-CoA reductase in *in vitro* studies using the catalytic domain of the human form of the enzyme or in rat and human hepatic microsomes. The agent was significantly more active in inhibiting cholesterol synthesis in rat hepatocytes as compared to 5 other statins and was 1000-fold more potent in rat hepatocytes as compared to rat fibroblasts. Further studies using human hepatic microsomes and human hepatocytes revealed little or no metabolism of the agent by the CYP450 3A4 isoenzyme. The agent was shown to be taken up into rat hepatocytes via a high-affinity active uptake process and was selectively taken up by the liver following i.v. dosing in rats. Oral administration to rats and dogs resulted in potent and prolonged inhibition of HMG-CoA reductase. The C_{max} and AUC values of the agent were linear following oral dosing (5-80 mg) in humans and the $t_{1/2}$ value was about 20 h (4).

The pharmacokinetics and elimination of ZD-4522 were examined in a study in 6 healthy subjects administered a single oral dose of the [^{14}C]-labeled compound (20 mg/1.85 Mbq). Peak plasma concentrations (6.06 ng/ml) were achieved at 5 h postdosing and ZD-4522 accounted for about 50% of the radioactivity at C_{max}. Of the total dose, 90 and 10% was recovered in feces and urine, respectively. Of the total radioactivity recovered in feces, 92, 6 and 2% were the parent compound, *N*-desmethyl metabolite and 5S-lactone metabolite, respectively, and in urine, 50% was the parent compound, 20% was the *N*-desmethyl metabolite and 10% was the 5S-lactone metabolite. A single 20 mg dose was well tolerated (5).

An open-label, randomized, 2-period, crossover trial examined the pharmacokinetics of ZD-4522 (10 mg o.d. at 7 a.m. or 6 p.m. for 14 days) after a.m. and p.m. administration in 24 healthy subjects. A washout period of 28-35 days was included between treatments. Multiple dosing was well tolerated and improvements in serum lipids were significant and comparable after both a.m. and p.m. dosing. No significant differences in changes in LDL cholesterol were observed with a.m. or p.m. dosing (–41.3 *vs.* 44.2%). Urinary excretion rates and plasma $AUC_{0\text{-}24h}$ values for mevalonic acid at steady state were decreased by about 30% following a.m. or p.m. dosing (6).

A multicenter, randomized, placebo-controlled, parallel-group, 2-phase study conducted in 206 patients with hypercholesterolemia who underwent a 6-week dietary lead-in, examined the efficacy of double-blind rosuvastatin (5 or 10 mg once daily for 6 weeks) and open-label atorvastatin (10 or 80 mg once daily for 6 weeks). A follow-up trial increased rosuvastatin doses to 80 mg. All treatments were well tolerated. All doses of rosuvastatin significantly reduced LDL cholesterol in a dose-dependent manner (34-65%) and improved lipid ratios as compared to placebo. No statistical comparison was made between rosuvastatin and atorvastatin although it appeared that greater improvements were observed with the former agent (7).

Results from a randomized, double-blind study showed an up to 65% reducion in LDL cholesterol levels and an up to 14% increase in HDL cholesterol levels with administration of ZD-4522 at 80 mg. In the first stage of the dosing program, 142 patients aged 18-70 years were randomized to receive 1 of 6 doses of ZD-4522 (1-40 mg) or placebo. In the second stage, 64 patients were randomized to treatment which included an 80-mg dose of ZD-4522. Compared to placebo, ZD-4522 produced a dose-dependent decrease in mean LDL cholesterol and total cholesterol at all dose levels. Furthermore, after 6 weeks, the 80-mg dose caused an average 65% reduction in triglycerides, as well as a 9-14% increase in HDL-cholesterol. Moreover, 90% of the LDL cholesterol reduction occurred during the first 2 weeks of therapy. The compound was well tolerated, with gastrointestinal disorders and headache being the most frequent adverse effects (8).

A study compared rosuvastatin with diet and maximal lipid therapy ("usual care") in patients with severe HeFH and baseline LDL cholesterol levels of > 220 mg/dl. At the time of screening, patients were receiving high-dose statin therapy, as well as resin and niacin in many cases. After undergoing a 6-week washout period with the AHA Step I Diet alone, patients were randomized to rosuvastatin or atorvastatin (20, 40 and 80 mg daily). Following an 18-week, double-blind trial period, patients continued in an open-label extension trial with 80 mg/day rosuvastatin. Results from the open-label phase of the trial were presented for 47 patients after 6 weeks of therapy. Rosuvastatin therapy reduced total cholesterol, LDL cholesterol and triglyceride levels more than diet or usual care. LDL cholesterol levels of < 160 mg/dl, 130 mg/dl and 100 mg/dl were achieved in 92, 70 and 21%, respectively, of patients on rosuvastatin therapy and in 51, 20 and 7%, respectively, of patients receiving usual care. In all 4 trials, rosuvastatin was well tolerated (9).

Results from a multicenter, randomized, double-blind, force-titration, parallel-group, 18-week study conducted in 622 patients with heterozygous familial hypercholesterolemia who underwent a 6-week dietary lead-in, showed that once-daily rosuvastatin was superior to atorvastatin at 6, 12 and 18 weeks in improving lipid levels. Patients received an initial dose of 20 mg that was then titrated to 40 mg at 6 weeks and then to 80 mg. Patients treated with rosuvastatin had significantly greater reductions in LDL cholesterol, total cholesterol and apolipoprotein B levels and greater increases in HDL cholesterol as compared to patients treated with atorvastatin; lipid ratios were also significantly improved with rosuvastatin over atorvastatin. More rosuvastatin-treated patients (including high-risk patients) reached their LDL cholesterol target level as compared to atorvastatin (47 *vs.* 24%). Similar incidence of adverse events was seen for the 2 treatment groups (10).

Results from a randomized, placebo-controlled, double-blind, parallel-group, dose-ranging trial with a 6-week dietary run-in period conducted in 142 patients with primary hypercholesterolemia showed the efficacy of ZD-4522 (1, 2.5, 5, 10, 20 or 40 mg for 6 weeks) as compared to open-label atorvastatin (10 or 80 mg for 6 weeks). All doses of ZD-4522 significantly and dose-dependently decreased LDL cholesterol (36 and 63% with 1 and 40 mg, respectively, at week 6) as compared to placebo. Atorvastatin reduced these levels by 44 and 59% with doses of 10 and 80 mg, respectively. ZD-4522 was found to have a rapid onset of action with 90% of the reductions occurring in the first 2 weeks. The agent was also well tolerated. Similar incidence of adverse events was seen for placebo and treatment groups (11).

A study compared rosuvastatin with pravastatin and simvastatin in patients with primary hypercholesterolemia. This randomized, double-blind, multicenter trial included 502 patients with LDL cholesterol levels of 160-250 mg/dl and triglyceride levels of 400 mg/dl or less. Patients were randomized to rosuvastatin, pravastatin or simvastatin for 12 weeks. The reductions in LDL cholesterol for the different treatment groups were 42% (rosuvastatin 5 mg), 49% (rosuvastatin 10 mg), 28% (pravastatin 20 mg) and 37% (simvastatin 20 mg). Similarly, the percentages of patients achieving the NCEP goals in each group were 71% (rosuvastatin 5 mg), 87% (rosuvastatin 10 mg), 53% (pravastatin) and 64% (simvastatin). The high-risk group showed especially marked benefits with rosuvastatin: target LDL cholesterol levels were achieved in 42% and 67% of patients receiving rosuvastatin 5 mg and 10 mg, respectively, as compared to 7% and 19% in the pravastatin and simvastatin groups, respectively (12).

A study compared the efficacy of rosuvastatin calcium with that of other statin therapies in patients with hypercholesterolemia. In a multicenter, randomized,

double-blind, placebo-controlled trial, rosuvastatin was found to be superior to atorvastatin in decreasing LDL cholesterol and in increasing HDL cholesterol in patients with type IIa or IIb hypercholesterolemia. In this trial, 516 patients with primary hypercholesterolemia (LDL cholesterol 160-250 mg/dl and triglycerides 400 mg/dl or less) received placebo, atorvastatin (10 mg) or rosuvastatin (5 mg or 10 mg) once daily for 12 weeks following a 6-week dietary lead-in period. In each of the rosuvastatin groups, NCEP target goals for LDL cholesterol were achieved by 84% of patients, as compared to 73% of those in the atorvastatin group. Among high-risk patients, NCEP targets were achieved by 42% (5 mg) and 47% (10 mg) of patients receiving rosuvastatin, as compared to 19% of patients in the atorvastatin group. Rosuvastatin was also more effective than atorvastatin in lowering triglyceride and apolipoprotein B levels and in raising HDL cholesterol and apolipoprotein A levels (13).

Rosuvastatin calcium is the proposed international nonproprietary name for ZD-4522 (14).

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