Drugs of the Future 2002, 27(1): 61-103

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Cardiovascular Drugs

Since beginning publication in 1976, the aim of **Drugs of the Future** has been to provide product information on compounds in various stages of development. In 1977, the *Information Update* section of the journal was introduced to provide current information on drugs that were featured in monographs of the previous year's journal with the same issue number. *Update Information* followed the development of a drug up to its marketing date, from which point further information was presented in our journal **Drugs of Today**, in publication since 1958.

The time has come to introduce certain changes in the format of **Drugs of the Future**, and beginning this year *Information Update* will be replaced by *Annual Review*, which will present information on drugs grouped according to their therapeutic activity.

The Editor's decision to restructure drug information through *Annual Review* is based on two major objectives. The first, to provide our readers with the opportunity to better understand the competitive environment in which companies race to get their products to the marketing finish line. The second is to cover the progress of drugs through the development pipeline, with special emphasis on potential new therapeutic approaches to diseases for which no treatment is presently available, as well as improvements in current therapies.

Based on the screening of hundreds of journals and participation in conferences, our team of specialists prepare summaries that are integrated into each review. All of the information included in the reviews is available in electronic format in our drug discovery portal **Integrity**.

We hope the readers will enjoy this new section which begins with the following *Annual Review* of Cardiovascular Drugs.

J.R. Prous
Editor

Annual Review 2002: Cardiovascular Drugs

Drug	Source	Indication(s)	Phase
AC-3056	Amylin	Atherosclerosis	I
AGI-1067	AtheroGenics	Atherosclerosis	II
Aliskiren Fumarate[1]	Speedel/Novartis	Heart failure	I/II
		Arterial hypertension	II
Allopurinol	Johns Hopkins University	Heart failure	II
ALT-711	Alteon	Arterial hypertension	II
Ambrisentan	Myogen	Pulmonary hypertension	II
	Knoll/Myogen	Heart failure	II
		Arterial hypertension	I
AMP-579[1]	Aventis Pharma	Myocardial infarction	II
Atrasentan[1]	Abbott	Heart failure	Clinical
Avasimibe[1]	Pfizer	Atherosclerosis	III
Azelnidipine[1]	Sankyo/Ube	Arterial hypertension	Prereg
Azimilide Hydrochloride[1]	Procter & Gamble/Tanabe Seiyaku	Atrial fibrillation	Prereg
BG-9719/CVT-124	CV Therapeutics/Biogen	Heart failure	II
BGC-728	BTG	Myocardial infarction	I
Bidil™	NitroMed	Heart failure	Prereg
Bosentan[1]	Actelion/Genentech	Pulmonary hypertension	L-2001
	Roche	Arterial hypertension	III
	Actelion/Genentech	Heart failure	III
BRX-235	Biorex R&D	Atherosclerosis	II
	Biorex R&D	Myocardial infarction	II
BSF-302146	Knoll	Heart failure	I
		Arterial hypertension	I
Candesartan Cilexetil[1,2]	Takeda	Heart failure	III
Cariporide Mesilate[1]	Aventis Pharma	Myocardial infarction	III
CETi-1	Avant	Atherosclerosis	II
CI-1027	Pfizer	Atherosclerosis	II
Clamikalant Sodium[1]	Aventis Pharma	Arrhythmia	II
Conivaptan Hydrochloride[1]	Yamanouchi	Heart failure	II
CP-529414	Pfizer	Atherosclerosis	II
CS-505	Sankyo/Kyoto Pharmaceutical Ind.	Atherosclerosis	I
CS-780	Sankyo	Angina	I
CVT-510	CV Therapeutics	Atrial fibrillation	III
Darusentan[1]	Knoll/Aventis Pharma	Heart failure	II
	Knoll	Arterial hypertension	II
Dofetilide[1]	Pfizer	Atrial fibrillation	L-2000
Dronedarone Hydrochloride	Sanofi-Synthélabo	Atrial fibrillation	III
DTI-0009	Aderis Pharmaceuticals/Fujisawa	Arrhythmia/Atrial fibrillation	II
DTI-0017	Aderis Pharmaceuticals	Heart failure	I
Efaproxiral Sodium[3]	Allos	Angina	I
		Myocardial infarction	II
Eflucimibe	Pierre Fabre/Lilly	Atherosclerosis	I
Enrasentan	GlaxoSmithKline	Heart failure	II/Disc
Eplerenone[1]	Pharmacia	Heart failure	III
		Arterial hypertension	III
Esprolol Hydrochloride	Selectus Pharmaceuticals	Angina	II
ETC-216	Esperion	Atherosclerosis	II
ETC-588	Esperion	Atherosclerosis	II
ETC-642	Esperion	Atherosclerosis	I
Etomoxir[1]	Medigene	Heart failure	II
Ezetimibe[1]	Schering-Plough/Merck & Co.	Atherosclerosis	Prereg
F-1394[1]	UCB Japan	Atherosclerosis	II
Fasidotril[3]	Bioprojet/Lilly	Heart failure	II
		Arterial hypertension	II
Fasudil Hydrochloride[1,2]	Asahi	Angina	II
FM-VP4	Forbes Medi-Tech	Atherosclerosis	I/II
GT-102-279	GelTex/Sankyo	Atherosclerosis	II
GW-409544	GlaxoSmithKline/Ligand	Atherosclerosis	I
GW-473178	GlaxoSmithKline	Atrial fibrillation	I
GW-501516	GlaxoSmithKline	Atherosclerosis	I
GW-590735	GlaxoSmithKline	Atherosclerosis	I
HBS-107	Hisamitsu/Banyu	Atherosclerosis	II
Implitapide[1]	Bayer	Atherosclerosis	II
Irbesartan[1,2]	Sanofi-Synthélabo/Bristol-Myers Squibb	Heart failure	III
ITF-1697	Italfarmaco	Myocardial Infarction	II

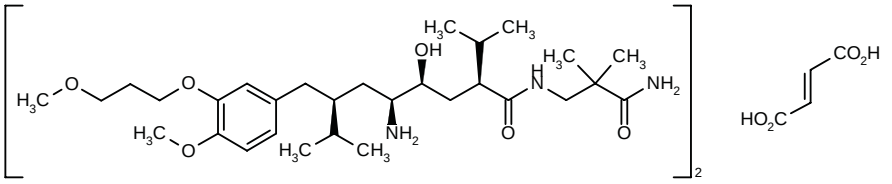
Continued

Annual Review 2002: Cardiovascular Drugs

Drug	Source	Indication(s)	Phase
J-104132	Merck/Banyu	Heat failure	II
JTT-705	Japan Tobacco	Atherosclerosis	II
JTV-519	Japan Tobacco	Myocardial Infarction	II
Landiolol	Ono	Arrhythmia	Prereg
Levosimendan[1]	Orion	Heart failure	L-2000
Lifibrol[1]	Klinge	Atherosclerosis	II
M-40403[1]	MetaPhore	Myocardial infarction	I
MC-1	Medicure	Myocardial infarction	I
MCC-135	Mitsubishi Pharma	Heart failure	II
MCI-154[1]	Mitsubishi Pharma	Heart failure	II
MDL-100240[3]	Aventis Pharma	Heart failure	II
		Arterial hypertension	II
Motexafin Lutetium	Pharmacyclics	Atherosclerosis	II
NCX-4016[1]	NicOx	Arterial hypertension	II
Nesiritide	Scios/GlaxoSmithKline	Heart failure	L-2001
NO-1886	Otsuka/TAP	Atherosclerosis	II
Nolomirole Hydrochloride[1]	Chiesi	Heart failure	III
Olmesartan Medoxomil[1]	Sankyo/Recordati/Menarini/Forest	Arterial hypertension	Prereg
Omapatrilat[1]	Bristol-Myers Squibb	Angina	II
		Arterial hypertension	Prereg
		Heart failure	II
OPC-31260[1]	Otsuka	Heart failure	II
Pexelizumab	Alexion/Procter & Gamble/Enzon	Myocardial infarction	II
Piboserod Hydrochloride[1]	GlaxoSmithKline	Atrial fibrillation	II
Pitavastatin Calcium[1]	Sankyo/Kowa	Atherosclerosis	Prereg
PMD-2850	Protherics	Arterial hypertension	II
Pranidipine[1]	Otsuka	Angina	Prereg
Ranolazine[1]	CV Therapeutics	Angina	III
		Heart failure	II
RC-552	Corixa/CoPharm	Myocardial infarction	Clinical
Rosuvastatin Calcium[1]	AstraZeneca/Shionogi	Atherosclerosis	Prereg
rPSGL-Ig	Genetics Institute	Myocardial infarction	II
RSD-1235	Cardiome	Atrial fibrillation	II
S-8921	Shionogi	Atherosclerosis	I
SB-237376	GlaxoSmithKline	Arrhythmia	II
SB-424323	GlaxoSmithKline	Atrial fibrillation	II
SB-480848	GlaxoSmithKline	Atherosclerosis	I
Sitaxsentan Sodium[1]	Icos-Texas Biotechnology	Pulmonary hypertension	II/III
		Heart failure	II
		Arterial hypertension	II
SLV-306[1]	Solvay	Heart failure	II
		Arterial hypertension	II
SPP-301	Roche/Speedel Pharma	Arterial hypertension	I
SR-121463A	Sanofi-Synthélabo	Heart failure	I
SSR-149744	Sanofi-Synthélabo	Arrhythmia	I
TBC-3711	Icos-Texas Biotechnology	Pulmonary hypertension	I
		Heart failure	I
		Arterial hypertension	I
Tedisamil Hydrochloride[3]	Solvay	Angina	III
		Atrial fibrillation	III
Tezosentan Sodium	Actelion/Genetech	Heart failure	III
TGL-749	Aventis Pharma	Atherosclerosis	I/II
Toborinone[1]	Ostuka	Heart failure	Prereg
Tolvaptan[3]	Otsuka	Heart failure	II
TP-10	Avant	Myocardial infarction	II
Trecetilide Fumarate	Pharmacia	Arrhythmia	II
Treprostinil Sodium[1]	United Therapeutics	Pulmonary hypertension	Prereg
Valsartan[2]	Novartis	Heart failure	Prereg
		Myocardial infarction	III
VAS-991	Vasogen	Heart failure	II
VEGF-2 Gene Therapy	Human Genome Sciences/Vascular Genetics	Myocardial infarction	I/II
Vepalimomab	BioTie Therapies	Myocardial infarction	I/II
Watanidipine Hydrochloride[1]	Mitsubishi Pharma	Arterial hypertension	Prereg
Z-13752A/GW-660511X	Zambon/GlaxoSmithKline	Arterial hypertension	I
Zelandopam Hydrochloride	Yamanouchi/Mochida	Arterial hypertension	II

Drugs in bold print are covered in the Review. [1]Previously published in Drugs of the Future. [2]Launched for another indication. [3]In preparation for Drugs of the Future.

Aliskiren Fumarate



Aliskiren fumarate (SPP-100) is an orally active renin inhibitor which has the potential to become the first renin inhibitor to provide a true alternative to ACE (angiotensin-converting enzyme) inhibitors and angiotensin II receptor blockers in the treatment of cardiovascular diseases. The compound is being developed by Speedel under license from Novartis and is in phase II trials for both hypertension and congestive heart failure (1).

An early clinical study demonstrated that aliskiren is able to effectively inhibit the renin-angiotensin system in healthy adults after both single and multiple oral doses. In this randomized, placebo-controlled, crossover study, escalating doses of SPP-100 were administered to two groups of patients as an oral solution once daily over 8 days: one group received SPP-100 40 or 80 mg, placebo or enalapril, and another group received SPP-100 100, 160 or 640 mg, placebo or enalapril. SPP-100 provided peak plasma concentrations at 0.5-6 h with a half-life of 20-45 h. Dose-dependent inhibition of plasma renin activity was obtained, with a maximum within 1 h of dosing and lasting for up to 24 h, and no attenuation of the effect was seen with multiple dosing. Dose-dependent decreases were also obtained in plasma angiotensin I and angiotensin II levels. The dose of 160 mg provided near-maximal effects. No significant changes in blood pressure were seen and the only drug-related adverse event was mild to moderate headache (2).

The results from a phase II dose-ranging study in 226 patients with mild to moderate hypertension were recently reported. The study was carried out as a multicenter, double-blind trial that consisted of parallel groups of randomized patients who were assessed at the end of a washout period and again after a 4-week treatment period. Treatment consisted of single daily oral doses of aliskiren (37.5-300 mg) or losartan (100 mg), a marketed angiotensin II receptor blocker. The data indicate good tolerability in all patients up to the highest dose tested, with no significant differences between the two compounds in terms of safety. A clear dose-response curve was observed for the reduction in blood pressure. Statistically significant lowering of systolic daytime blood pressure, the primary endpoint of the study, occurred with doses of 75, 150 and 300 mg aliskiren (3).

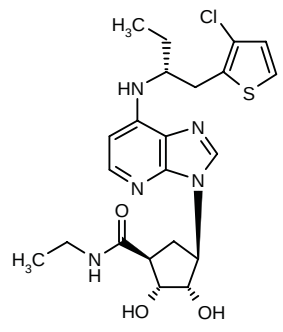
1. *Supplemental development program announced for oral renin inhibitor aliskiren.* DailyDrugNews.com (Daily Essentials) Sept 26, 2001.

2. Nussberger, J., Brunner, H., Jensen, C., Mann, J. *Tolerability, pharmacokinetics and pharmacodynamic effects of the renin inhibitor SPP 100 after repeated oral administration in healthy volunteers.* Eur Heart J 2001, 22(Suppl.): Abst P2294.

3. *Speedel reports promising data from aliskiren study in hypertension.* DailyDrugNews.com (Daily Essentials) Oct 16, 2001.

Original monograph - Drugs Fut 2001, 26(12): 1139.

AMP-579



The combined adenosine A_1/A_{2A} receptor agonist AMP-579 (RPR-100579; Aventis) was last reported to be in phase II trials as a potential therapy for acute myocardial infarction.

Experiments in rabbit hearts demonstrated that AMP-579 reduced myocardial contracture and infarction when given at reperfusion, with both effects requiring the adenosine A_2 receptor. Not all A_2 receptor agonists tested could duplicate the antiinfarct effect, however (1).

The mechanism of cardioprotection of AMP-579 was investigated using rat hearts subjected to ischemia and reperfusion. The hearts were perfused with AMP-579 beginning 5 min before reperfusion and PD-98059 was coperfused in some hearts to inhibit p42/p44 MAPK activation. AMP-579 increased coronary flow rate during early reperfusion, and this effect was not abolished by PD-98059. Transient bradycardia was also noted during the first 30 min of reperfusion with AMP-579. AMP-579 significantly reduced infarct size during early reperfusion in a neutrophil-independent manner, and this effect was abolished by inhibition of p42/p44 MAPK with PD-98059 (2).

Activation of the adenosine A_{2A} receptor during reperfusion was found to play a part in the protective action of AMP-579 in a rabbit model of acute myocardial infarction. Rabbits were treated with AMP-579 or vehicle. Two groups of rabbits were randomized to treatment with the A_{2A} antagonist ZM-241385 or vehicle and another group of animals was treated with the the A_{2A} agonist CGS-21680. Both AMP-579 and CGS-21680 similarly reduced mean arterial pressure during the infusion period. ZM-241385 pretreatment abolished the depressor effect of AMP-579 and attenuated the ability of AMP-579 to limit infact size, whereas CGS-21680 did not limit infarct size (3).

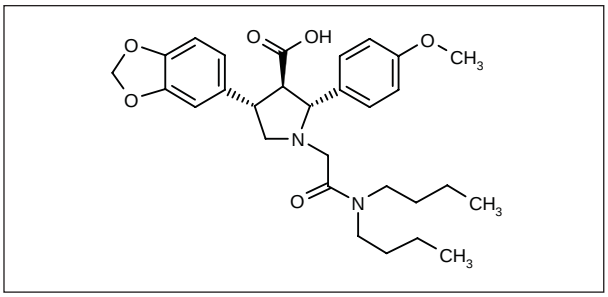
1. Xu, Z., Downey, J.M., Cohen, M.V. *AMP 579 reduces contracture and limits infarction in rabbit heart by activating adenosine A_2 receptors.* J Cardiovasc Pharmacol 2001, 38(3): 8474.

2. Baxter, G.F., Ebrahim, Z., Yellon, D.M. *AMP579, an adenosine A_1 and A_{2a} receptor agonist, attenuates lethal reperfusion injury in rat heart via the p42/p44 MAPK pathway.* Br J Pharmacol 2001, 133(Suppl.): Abst 7P.

3. Baxter, G.F., Kis, A., Yellon, D.M. *AMP579, an adenosine A_1 and A_{2a} receptor agonist, limits infarct size in rabbit heart in vivo when given at reperfusion: Role of A_{2a} receptor activation.* Br J Pharmacol 2001, 133(Suppl.): Abst 8P.

Original monograph - Drugs Fut 2000, 25(9): 900.

Atrasentan



Abbott's atrasentan (ABT-627) is a potent, selective, orally active, nonpeptide endothelin ET_A receptor antagonist which is undergoing clinical evaluation for several different indications, including heart failure and hormone-refractory prostate cancer.

Investigators conducted experiments in rabbit choroidal arteriolar smooth muscle where ET-1, through its activity on ET_A receptors, irreversibly activated oscillatory Ca^{2+}-activated Cl- currents and reversibly inhibited L-type Ca^{2+} channels. Further work indicated that these cells have two types of ET_A receptor, one where BQ-123 is an antagonist and atrasentan is an agonist, and the other where both compounds are antagonists (1).

The high mortality rate in newborns with congenital diaphragmatic hernia has been linked to pulmonary hypertension and right-to-left shunting. Based on evidence suggesting that ET_A receptor activation may be involved in the etiology of pulmonary hypertension, Abbott and Laval University researchers investigated the effects of atrasentan in near-term lambs with congenital diaphragmatic hernia. Compared to untreated newborn lambs, atrasentan displayed beneficial effects in terms of mean pulmonary artery pressure (MPAP)/mean blood pressure (MBP) ratio, pH, arterial partial pressure of carbon dioxide ($PaCO_2$), arterial partial pressure of oxygen (PaO_2) and postductal arterial oxygen saturation (SaO_2). According to these results, ETA receptor antagonists may represent a novel therapeutic approach to pulmonary hypertension in newborns with congenital diaphragmatic hernia, and the investigators also plan to evaluate the potential of *in utero* prophylaxis (2, 3).

In pigs, atrasentan prevented the increase in coronary vasa vasorum density brought about by a hypercholesterolemic diet. The endogenous endothelin system therefore appears to play a role in coronary vasa vasorum neovascularization in early coronary atherosclerosis (4).

Healthy volunteers received single oral doses (1-40 mg) of atrasentan or placebo in a randomized, double-blind phase I pharmacokinetic study of single and multiple doses. Administration of the highest dose was stopped due to adverse events. The remaining doses demonstrated dose- and time-independent pharmacokinetics after single- and multiple-dose administration (5).

In a placebo-controlled, double-blind study in 24 healthy male volunteers, single oral doses of atrasentan (1, 10 and 23.25 mg) demonstrated linear pharmacokinetics and oral clearance of 21-27 l/h. Volume of distribution was large (~ 6 l/kg) and harmonic mean terminal half-life was similar (20-25 h) across all doses studied (1, 10, 23.25 and 139.5 mg) (6).

1. Curtis, T.M., Scholfield, C.N. *Evidence for two endothelin ET_A receptor subtypes in rabbit arteriolar smooth muscle.* Br J Pharmacol 2001, 134(8): 1787.

2. Kavanagh, M., et al. *Effect of ABT-627 (A-147627), a potent selective ET_A receptor antagonist, on the cardiopulmonary profile of newborn lambs with surgically induced diaphragmatic hernia.* Br J Pharmacol 2001, 124(8): 1679.

3. Kavanagh, M., Battistini, B., Jean, S., Crochetiere, J., Fournier, L., Wessale, J., Opgenorth, T., Cloutier, R., Major, D. *Endothelin and congenital diaphragmatic hernia: Evaluation of an ET_A receptor antagonist (ABT-627) in the treatment of pulmonary hypertension associated with CDH in newborn lambs.* J Perinat Med 2001, 29(Suppl. I): 234.

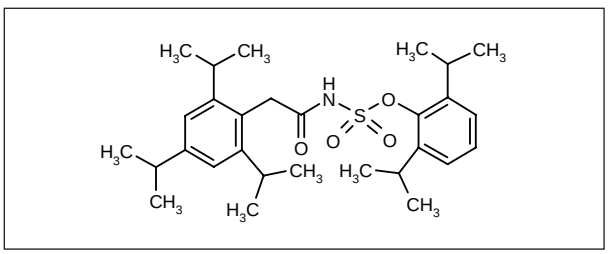
4. Herrmann, J., Best, P.J.M., Ritman, E.L., Richardson, D.M., Lerman, L.O., Lerman, A. *Chronic endothelin receptor antagonism prevents coronary vasa vasorum neovascularization in experimental hypercholesterolemia.* Circulation 2001, 104(17, Suppl. 2): Abst 881.

5. Dutta, S., Samara, E., Lam, W., Granneman, G.R., Leese, P.T., Padley, R.J. *Multiple-dose pharmacokinetics of atrasentan, an endothelin-A receptor antagonist.* Clin Drug Invest 2001, 21(2): 129.

6. Samara, E., Dutta, S., Cao, G., Granneman, G.R., Dordal, M.S., Padley, R.J. *Single-dose pharmacokinetics of atrasentan, an endothelin-A receptor antagonist.* J Clin Pharmacol 2001, 41(4): 397.

Original monograph - Drugs Fug 2001, 26(10): 939.

Avasimibe



The ACAT inhibitor avasimibe (Pfizer) is presently in phase III evaluation as a treatment for atherosclerosis (1).

The effect of avasimibe alone and in combination with atorvastatin on cholesteryl ester content in human macrophages and foam cells was studied. The results suggested that combining an ACAT inhbitor such as avasimibe with an HMG-CoA reductase inhibitor such as atorvastatin is a better approach to preventing cholesteryl ester accumulation and thus the formation of foam cells (2).

Rabbits fed a cholesterol-containing diet were treated with avasimibe, simvastatin or a combination of both drugs. Although the combination produced changes in plasma total and lipoprotein cholesterol exposure and lipoprotein composition similar to those resulting from monotherapy, it appeared to inhibit lesion progression and promote lesion regression (3).

The effects of atorvastatin alone and in combination with avasimibe were evaluated in Watanabe heritable hyperlipidemic (WHHL) rabbits. The combination was superior to controls and atorvastatin alone in reducing vessel wall area and staining of the neointima for MMP-1. Atorvastatin alone and in combination with avasimibe also reduced the extent of MMP-3 staining of the neointima (4, 5).

The antiatherosclerotic effects of avasimibe have been confirmed in the ApoE*3-Leiden transgenic mouse. Treatment of mice fed a high-cholesterol diet with avasimibe 0.01% (w/w) in the diet produced a 56% reduction in plasma cholesterol levels compared to untreated animals, with reductions mainly in VLDL and LDL cholesterol fractions. Avasimibe also markedly reduced atherosclerotic aortic lesion areas in these animals by 92%. Its antiatherosclerotic effect was then demonstrated to be independent of its cholesterol-lowering effect in a group of low-cholesterol animals, where it also markedly reduced aortic lesion area (78%), even after correction for the small difference in cholesterol exposure in the treated and untreated groups (73% reduction). Avasimibe reduced monocyte adhesion to endothelium, free cholesterol accumulation in the lesions and lesion severity, indicating that it may also increase plaque stability (6).

In an escalating-dose study of avasimibe (up to 1000 mg/kg b.i.d.) and in repeated-dose studies of the drug (300, 1000 and 1000 mg/kg once daily for 2, 13 and 52 weeks, respectively) in beagle dogs, minimal adrenal affects were observed and the dose-limiting toxicity consisted of reversible changes in hepatic function (7).

A double-blind, randomized, placebo-controlled trial was conducted to determine the efficacy and safety of the ACAT inhibitor in 130 patients with combined hyperlipidemia and hypoalphalipoproteinemia. Patients were administered placebo or avasimibe (50, 125, 250 or 500 mg) once daily for 8 weeks following an 8-week placebo and dietary control period. All doses of avasimibe effectively lowered plasma levels of total triglycerides and VLDL cholesterol, with respective mean reductions of up to 23% and 30%. These effects appeared to be independent of dose. Total cholesterol, LDL cholesterol, HDL cholesterol and apolipoprotein B (apo B) levels were unaffected by treatment. A significant decrease in plasma apo A1 was observed with the highest dose of avasimibe. Treatment was safe and well tolerated (8).

The potential of avasimibe to improve the LDL profile of hyperlipidemic patients was illustrated in a randomized, placebo-controlled study in 130 patients administered avasimibe 50, 125, 250 or 500 mg once daily for 8 weeks (9).

Avasimibe (250 and 500 mg) demonstrated a high degree of selectivity as well as activity on triglyceride-rich lipoproteins in an 8-week, placebo-controlled, double-blind trial in 72 patients, all of whom had LDL cholesterol of 140 mg/dl or more and triglycerides of 200-600 mg/dl (10).

Table I: Clinical study of avasimibe.

Indication	Design	Treatments	N	Conclusions	Ref.
Hypercholesterolemia	Randomized, double-blind, crossover	Avasimibe, 750 mg po od x 18 wks Atorvastatin, 80 mg po od x 18 wks AT, 80 mg po od + AV, 750 mg po od x 18 wks	27	Atorvastatin was better than avasimibe as monotherapy but the combined treatment had a potential benefit for patients with homozygous familial hypercholesterolemia. All treatments showed good tolerability	11

A total of 27 patients with homozygous familial hypercholesterolemia enrolled in an 18-week, double-blind, crossover trial were randomized to daily treatment with atorvastatin 80 mg, avasimibe 750 mg or atorvastatin 80 mg combined with avasimibe 750 mg. Monotherapy with atorvastatin was more effective in lowering lipids than avasimibe monotherapy and some benefit was noted in patients in the combination treatment group (11) (Table I).

A method for inhibiting monocyte-macrophage accumulation in atherosclerotic lesions consisting of the administration of an ACAT inhibitor such as avasimibe was recently claimed (12).

1. *Pfizer sees sustained, strong performance as broad and deep product line, new product pipeline, profit margin expansion and strategic alliances drive growth.* Pfizer Inc. Press Release 2000, Dec 11.

2. Llaverías, G., Jové, M., Diaz, C., Hernandez, G., Laguna, J.C., Alegret, M. *Avasimibe and atorvastatin reduce intracellular cholesteryl ester accumulation in human macrophages.* Atherosclerosis Suppl 2001, 2(2): Abst P180.

3. Bocan, T.M., Krause, B.R., Rosebury, W.S., Lu, X., Dagle, C., Bak Mueller, S., Auerbach, B., Sliskovic, D.R. *The combined effect of inhibiting both ACAT and HMG-CoA reductase may directly induce atherosclerotic lesion regression.* Atherosclerosis 2001, 157(1): 97.

4. Helft, G., Worthley, S.G., Corti, R., Fallon, J.T., Fuster, V., Beadimon, J.J. *Reduction of MMP-1 and -3 activity in the WHHL rabbit with atorvastatin and avasimibe.* Eur Heart J 2001, 22(Suppl.): Abst P1532.

5. Worthley, S.G., Helft, G., Osende, J.I., Corti, R., Fayad, Z.A., Fallon, J.T., Zaman, A.G., Fuster, V., Badimon, J.J. *Serial evaluation of atherosclerosis with in vivo MRI: Study of atorvastatin and avasimibe in WHHL rabbits.* Circulation 2000, 102(18, Suppl.): Abst 3906.

6. Delsing, D.J.M., Offerman, E.H., van Duyvenvoorde, W. et al. *Acyl-CoA:cholesterol acyltransferase inhibitor avasimibe reduces atherosclerosis in addition to its cholesterol-lowering effect in ApoE*3-Leiden mice.* Circulation 2001, 103(13): 1778.

7. Robertson, D.G., Breider, M.A., Milad, M.A. *Preclinical safety evaluation of avasimibe in beagle dogs: An ACAT inhibitor with minimal adrenal effects.* Toxicol Sci 2001, 59(2): 324.

8. Insull, W., Koren. M., Davignon, J. et al. *Efficacy and short-term safety of a new ACAT inhibitor, avasimibe, on lipids, lipoproteins, and apolipoproteins, in patients with combined hyperlipidemia.* Atherosclerosis 2001, 157(1): 137.

9. Lovalvo, J., Craig, W.Y., Heinonen, T. *The effects of the ACAT inhibitor, avasimibe on LDL diameter and subclass distribution in hyperlipidemic subjects.* 14th Int Symp Drugs Affect Lipid Metab (Sept 9-12, New York) 2001, 107.

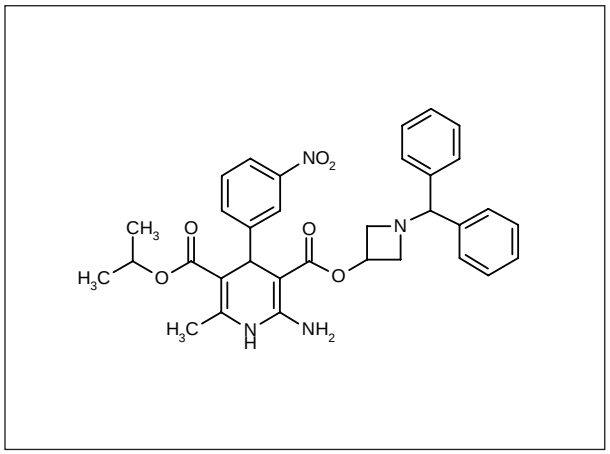
10. Klepack, E., Alaupovic, P., Heinone, T. *The effect of avasimibe on triglyceride-rich and cholesterol-rich lipoproteins.* 14th Int Symp Drugs Affect Lipid Metab (Sept 9-12, New York) 2001, 107.

11. Klepack, E., Raal, F.J., Marais, A.D., Heinonen, T. *Effects of avasimibe in patients with severe hypercholesterolemia.* 14th Int Symp Drugs Affect Lipid Metab (Sept 9-12, New York) 2001, 107.

12. Bocan, T.M.A. (Pfizer Inc.). *Prevention of plaque rupture by ACAT inhibitors.* WO 0134127.

Original monograph - Drugs Fut 1999, 24(1): 9.

Azelnidipine



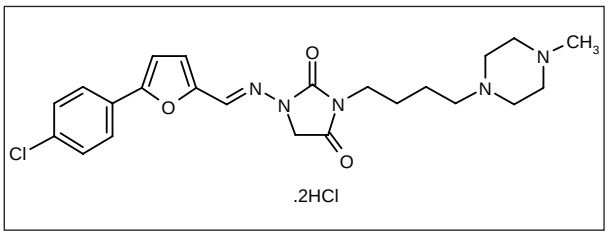
Azelnidipine is a dihydropyridine calcium antagonist developed by Sankyo and Ube which is undergoing regulatory review in Japan for the treatment of hypertension.

Immunohistochemical analysis of renal tissues from salt-sensitive rats fed a high-salt diet and treated with azelnidipine 3 mg/kg/day for 12 weeks revealed a renoprotective effect, which appeared to be mediated by the drug's effect on glycation (1).

1. Yamakado, M., Taguchi, J., Ohono, M. *Role of glycation in the mechanism of renoprotection of calcium antagonist.* J Hypertens 2000, 18(Suppl. 4): Abst P2.28.

Original monograph - Drugs Fut 1990, 15(7): 671.

Azimilide Hydrochloride



Azimilide is a unique class III antiarrhythmic agent under development by Procter & Gamble and Tanabe Seiyaku which blocks both slow and fast potassium channels in the heart.

Azimilide and *d,l*-sotalol have been compared for their electrophysiological effects in perfused canine and rabbit left ventricular wedge preparations. The results in rabbit preparations indicated that *d,l*-sotalol may be associated with a higher risk for torsade de pointes (1).

Different antiarrhythmic drugs have been studied for their effects in pigs with induced left atrial vulnerability (LAV), a model of atrial arrhythmia. The most effective was amiodarone (5 mg/kg i.v.), with a 72% decrease in the incidence of LAV, followed by *d,l*-sotalol (1.5 mg/kg; 53%), azimilide (5 mg/kg; 23%), flecainide (1 mg/kg; 17%), dofetilide (10 μg/kg; 14%) and esmolol (0.5 mg/kg; 10%) (2).

The proarrhythmic effects of dofetilide and azimilide were evaluated in a study in anesthetized dogs with a high incidence of torsade de pointes arrhythmias due to chronic complete AV block and bradycardia-induced volume overload. Both agents increased monophasic action potential duration, idioventricular rhythm cycle length and Q-T interval. Interventricular dispersion was also significantly increased after treatment with either agent due to the dissimilar lengthening of the left and right ventricular monophasic action potential duration. Early afterdepolarizations were observed in all animals, with ectopic ventricular beats seen in most of them. A comparable incidence of torsade de pointes arrhythmias was observed with both treatments (3).

Azimilide and dofetilide terminated atrial flutter and prevented reinduction in all dogs with surgically induced right atrial enlargement. Both drugs increased the effective refractory period in the slow conduction zone and increased flutter cycle length, resulting in interruption of the arrhythmia circuit (4).

A canine model of myocardial infarction was used to investigate the activity of azimilide on reentrant circuits causing ventricular tachyarrhythmias. Treatment prevented reentry and the consequent sustained ventricular tachycardia and ventricular fibrillation (5).

The pharmacokinetics and the relationship between pharmacokinetics and pharmacodynamics of azimilide were analyzed using data from three double-blind phase III trials. Patients had received placebo or azimilide 35, 50, 75, 100 or 125 mg/day for 6-9 months. Factors influencing pharmacokinetics included gender, tobacco use, weight and bilirubin. Pharmacokinetic parameters were independent of concomitant intake of digoxin, warfarin and cytochrome P450 3A4 inhibitors and inducers. Changes in Q-Tc interval were dependent on serum potassium (6).

Data from 4 double-blind, randomized, placebo-controlled trials including 1380 patients with atrial fibrillation, atrial flutter or both were subjected to meta-analysis to assess the dose-response relationship of azimilide 35, 50, 75, 100 and 125 mg once daily. While doses under 100 mg were not effective in controlling arrhythmia, the two higher doses studied were, with a significant prolongation in the time to arrhythmia recurrence and torsade de pointes occurring in less than 1% of these patients (7, 8). Further analyses of these ASAP (Azimilide Supraventricular Arrhythmia Program) trials were conducted to compare the effect of azimilide (100 and 125 mg) and placebo on the incidence of asymptomatic atrial fibrillation and flutter. This was observed in 18% of the placebo patients and 13% of those on therapeutic azimilide, for a stratified risk ratio of 0.74. These studies confirmed the high frequency of asymptomatic atrial fibrillation and flutter in untreated patients with a history of symptomatic atrial fibrillation and flutter, and also suggest that azimilide does not increase, and may even reduce, the incidence (9) (Table II).

Findings from the AzimiLide post-Infarct surVival Evaluation (ALIVE) trial, a 1-year, double-blind, placebo-controlled study in 3717 recent postmyocardial infarction patients, were discussed at a late-breaking session of the November 2001 American Heart Association Scientific Sessions. The ALIVE trial was designed to measure the impact of 100 mg azimilide on all-cause mortality in post-MI patients with low left ventricular ejection fraction (LVEF) who are at risk of sudden death. Patients were stratified to those at high risk of sudden death (MI within the last 5-21 days, low LVEF of 15-35%, low heart rate

Table II: Clinical study of azimilide.

Indication	Design	Treatments	N	Conclusions	Ref.
Supraventricular arrhythmia	Multicenter	Azimilide, 100 mg x 6-9 mo Azimilide, 125 mg x 6-9 mo Placebo	1380	Azimilide did not increase the frequency of asymptomatic atrial fibrillation and flutter	9

variability of < 20 U) and those at risk (MI within the last 5-21 days and low LVEF). All-cause mortality in patients at high risk was 15.0% on placebo and 14.1% on azimilide, and it was 11.6% in both groups of at-risk patients. No difference in mortality was seen between those starting azimilide in or out of hospital. The overall incidence of serious cardiovascular adverse events and overall ventricular arrhythmic events was similar in the two groups, although a slightly higher incidence of torsade de pointes was seen on azimilide (0.3% *vs*. 0.1%). Both treatments were well tolerated. According to these results, azimilide does not appear to adversely affect mortality in post-MI patients (10).

1. Yan, G.X., Wu, Y., Liu, T., Wang, J., Marinchak, R.A., Kowey, P.R. *Phase 2 early afterdepolarization as a trigger of polymorphic ventricular tachycardia in acquired long-QT syndrome: Direct evidence from intracellular recordings in the intact left ventricular wall.* Circulation 2001, 103(23): 2851.

2. Knobloch, K., Wirth, K.J. *Effect of azimilide, dofetilide, d,l-sotalol, amiodarone, flecainide and esmolol on left atrial vulnerability in pigs: A new atrial arrhythmia model.* Naunyn-Schmied Arch Pharmacol 2001, 363(4, Suppl.): Abst 281.

3. Van Opstal, J.M., Leunissen, J.D.M., Wellens, H.J.J., Vos, M.A. *Azimilide and dofetilide produce similar electrophysiological and proarrhythmic effects in a canine model of torsade de pointes arrhythmias.* Eur J Pharmacol 2001, 412(1): 67.

4. Restivo, M., Hegazy, M., El-Haami, M., Yin, H., Caref, E.B., Assadi, M.A., Brooks, R.R., El-Sherif, N. *Efficacy of azimilide and dofetilide in the dog right atrial enlargement model of atrial flutter.* J Cardiovasc Electrophysiol 2001, 12(9): 1018.

5. Schmitt, H., Cabo, C., Coronillas, J.C., Wit, A.L. *Effects of azimilide, a new class III antiarrhythmic drug, on reentrant circuits causing ventricular tachycardia and fibrillation in a canine model of myocardial infarction.* J Cardiovasc Electrophysiol 2001, 12(9): 1025.

6. Phillips, L., Grasela, T.H., Agnew, J.R., Ludwig, E.A., Thompson, G.A. *A population pharmacokinetic-pharmacodynamic analysis and model validation of azimilide.* Clin Pharmacol Ther 2001, 70(4): 370.

7. Connolly, S.J., Schnell, D.J., Page, R.L., Wilkinson, W.E., Marcello, S.R., Pritchett, E.L.C. *Dose-response relations of azimilide in the management of symptomatic, recurrent, atrial fibrillation.* Am J Cardiol 2001, 88(9): 974.

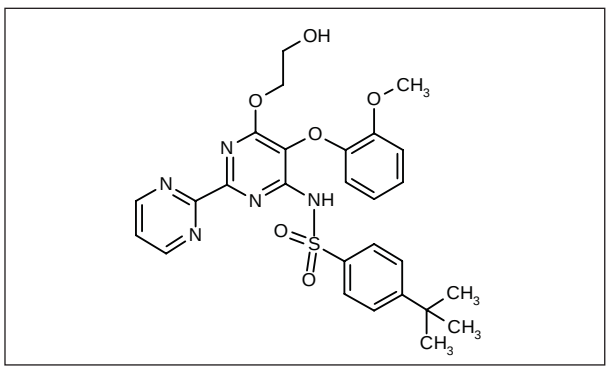
8. Connolly, S.J., Schnell, D.J., Page, R.L., Marcello, S.R., Wilkinson, W.E., Pritchett, E.L.C. *Dose response relationships of azimilide for control of atrial fibrillation/flutter: Meta-analysis of four randomized trials.* Circulation 2000, 102(18, Suppl.): Abst 3252.

9. Page, R.L., Tilsch, T.W., Schnell, D.J., Connolly, S.J., Marcello, S.R., Wilkinson, W.E., Pritchett, E.L.C. *Asymptomatic atrial fibrillation and flutter are common among patients with symptomatic arrhythmias: Lessons from the Azimilide Supraventricular Arrhythmia Program (ASAP) Trials.* Circulation 2000, 102(18, Suppl.): Abst 3255.

10. *Investigational antiarrhythmic azimilide demonstrates no adverse effect on mortality in post-myocardial infarction patients.* P&G Pharmaceuticals Press Release 2001, Nov 14.

Original monograph - Drugs Fut 1997, 22(6): 601.

Bosentan



Bosentan (Tracleer™), codeveloped by Actelion and Genentech and the first approved oral treatment for pulmonary arterial hypertension (PAH), is representative of a new class of drugs called endothelin receptor antagonists (ERAs). Bosentan works by blocking the binding of endothelin to its receptors, thereby preventing the deleterious effects of endothelin upon blood vessels. Bosentan is now commercially available in the U.S. and Canada for improving exercise capacity and decreasing the rate of clinical worsening in patients with PAH with significant limitation of physical activity (WHO class III and IV) (1, 2).

In the pivotal trials supporting the NDA for this product, twice-daily bosentan significantly improved exercise capacity in both primary and secondary PAH. The FDA based its approval on 2 randomized, placebo-controlled clinical trials involving 245 patients. Treatment with bosentan caused a significant increase compared to placebo in the 6-min walking distance: an additional 35-54 meters. This improvement was noted after 1 month of treatment, fully developed by 2 months and maintained for up to 7 months of treatment. Bosentan is currently under regulatory review in the E.U., Switzerland and Australia, and has received orphan drug status in the U.S., Europe and Australia as a treatment for PAH. Actelion is also studying bosentan in children with PAH, as well as in patients who receive concomitant intravenous prostacyclin therapy (3-5).

One of the pivotal trials – BREATHE-1 (Bosentan: Randomized trial of Endothelin receptor Antagonist THErapy for pulmonary hypertension) – was a multicenter, double-blind, randomized, placebo-controlled trial designed to evaluate the safety and efficacy of 2 dose levels of bosentan (125 and 250 mg b.i.d.) in 213 patients. The primary endpoint was the change from baseline in exercise capacity, as measured by a 6-min walk test at 16 weeks. Patients receiving bosentan were able to walk statistically significantly greater distances in the 6-min walk test after 16 weeks compared to placebo. The overall treatment effect for both doses of bosentan

combined was a 44-meter improvement in walking distance compared to placebo. This effect was statistically significant for both bosentan dose groups. Significant positive effects were also observed on clinically important secondary endpoints and the drug was well tolerated (6).

In Dahl salt-sensitive rats with left ventricular hypertrophy, bosentan and temocapril improved long-term survival and left ventricular (LV) fractional shortening to the same degree. Treatment with both drugs combined further improved survival without greater decreases in systolic pressure (7).

1. *Tracleer may now be prescribed for PAH patients in U.S.* DailyDrugNews.com (Daily Essentials) Dec 7, 2001.

2. *Second approval for first oral drug for the treatment of PAH.* DailyDrugNews.com (Daily Essentials) Dec 5, 2001.

3. *European authorities designate Tracleer an orphan product for pulmonary hypertension.* DailyDrugNews.com (Daily Essentials) March 6, 2001.

4. *FDA advisory committee recommends approval of Tracleer for PAH.* DailyDrugNews.com (Daily Essentials) Aug 13, 2001.

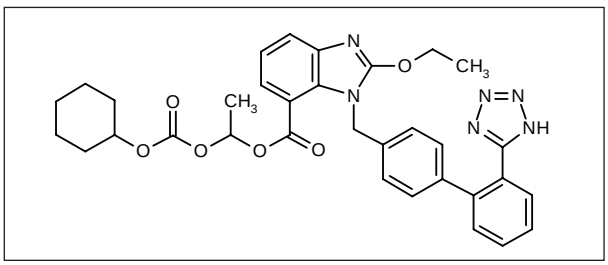
5. *Tracleer receives FDA approval for pulmonary arterial hypertension.* DailyDrugNews.com (Daily Essentials) Nov 23, 2001.

6. *Oral endothelin receptor antagonist achieves primary endpoint in phase III trial for PAH.* DailyDrugNews.com (Daily Essentials) May 3, 2001.

7. Iwanaga, Y., Kihara, Y., Inagaki, K., Onozawa, Y., Yoneda, T., Kataoka, K., Sasayama, S. *Differential effects of angiotensin II versus endothelin-1 inhibitions in hypertrophic left ventricular myocardium during transition to heart failure.* Circulation 2001, 104(5): 606.

Original monograph - Drugs Fut 2001, 26(12): 1149.

Candesartan Cilexetil



Candesartan cilexetil, an angiotensin AT_2 receptor blocker, has been available for several years for the treatment of hypertension and is now in late-stage development for use in heart failure.

Investigators treated normal dogs and dogs with pacing-induced heart failure with candesartan, LU-135252 (darusentan) and LU-302872 to analyze aldehyde levels in myocardial tissue. Aldehyde levels were increased in dogs with heart failure and were significantly decreased by drug treatment, suggesting that these agents function in part by reducing oxidative stress (1).

AstraZeneca has completed patient enrollment in the CHARM (Candesartan Heart Failure Assessment of Reduction in Mortality and Morbidity) clinical program, the largest angiotensin II receptor blocker (ARB) program in heart failure patients. The program has randomized more than 7500 patients from 26 countries, including approximately 1800 in the U.S. The objective of CHARM is to evaluate the effects of candesartan on survival, cardiovascular mortality and hospitalizations in patients with symptomatic heart failure. CHARM consists of three trials investigating a broad range of patient types and treatment scenarios. The first trial includes patients with impaired left ventricular systolic function who are intolerant of ACE inhibitors. This trial allows a comparison of candesartan and placebo without concomitant treatment with ACE inhibitors. The second trial will evaluate the use of candesartan in combination with conventional ACE inhibitor therapy, and the third trial will involve patients with congestive heart failure and preserved left ventricular systolic function, a population not previously studied (2).

During the year, the company also announced the completion of enrollment in the TRial Of Preventing HYpertension (TROPHY), an innovative study examining the use of the ARB candesartan in reducing the progression to established hypertension in people with high to normal blood pressure. Eight hundred subjects have been randomized to receive candesartan or placebo in this 4-year, multicenter, double-blind, placebo-controlled study taking place at 65 sites across the U.S.(3).

AstraZeneca has commenced another clinical trial to evaluate candesartan cilexetil as add-on therapy with the ACE inhibitor lisinopril (Zestril®) for lowering blood pressure. AMAZE (A Multi-center Trial using Atacand-Zestril versus Zestril to Evaluate the Effects on Lowering Blood Pressure) consists of 2 parallel, 8-week, multicenter, double-blind, randomized studies involving approximately 1000 hypertensive patients. The trial will evaluate the efficacy of adding candesartan to lisinopril compared to increasing the dose of lisinopril alone for lowering blood pressure. Results from another trial, ACTION, an open-label, large-scale study, showed that candesartan (16-32 mg/day) as add-on therapy further reduced systolic and diastolic blood pressure in patients on an ACE inhibitor (4).

1. Moe, G., Yazdanpanah, M., Konig, A., Romanova, M., Liu, P. *Elevated myocardial tissue aldehyde levels in heart failure: A novel marker of oxidative stress and its attenuation by neurohormonal blockade.* Eur Heart J 2001, 22(Suppl.): Abst P1656.

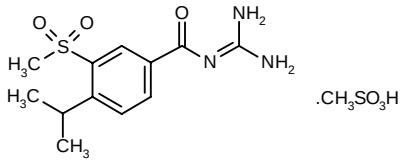
2. *Patient enrollment complete in AstraZeneca's CHARM program for heart failure.* DailyDrugNews.com (Daily Essentials) March 14, 2001.

3. *Enrollment completed in novel trial for prevention of hypertension.* DailyDrugNews.com (Daily Essentials) Aug 14, 2001.

4. *Atacand/Zestril combination trial begins.* DailyDrugNews.com (Daily Essentials) June 15, 2001.

Original monograph - Drugs Fut 1993, 18(7): 609.

Cariporide Mesilate



Cariporide (Aventis) is a late-stage investigational Na^+/H^+ exchange inhibitor with potential in the treatment of acute myocardial infarction and in coronary bypass surgery.

In rat hearts with left ventricular hypertrophy, cariporide reduced peak ischemic contracture and reperfusion contracture, demonstrating that the cardioprotective effects of the drug can be produced in clinically relevant models as well as in normal hearts (1).

Lifelong treatment with cariporide has been found to extend the life span of normotensive Wistar-Kyoto rats. Rats were randomized to receive placebo or cariporide 0.3% in their chow. The life span of the cariporide-treated rats was extended from 30 to 39 months, a change which was correlated with a delay in the onset of cancer. Cariporide also completely prevented age-related cardiac hypertrophy and improved the age-related endothelial dysfunction seen in the placebo group. Treatment also reduced muscular dystrophy, heart muscle fibrosis, tubulo-interstitial lesions in the kidney and retinal atrophy (2, 3).

Experiments in anesthetized dogs demonstrated that inhibition of the Na^+/H^+ exchanger with cariporide significantly blunted the decline in left atrial mechanical function from rapid atrial rates as compared to control and nifedipine-treated animals (4).

In postischemic rat hearts, cariporide and eniporide similarly reduced Ca^{2+} overload and improved contractile recovery. The compounds also reduced ischemic Na^+ overload and prolonged acidosis, which accounted for lower postischemic diastolic $[Ca^{2+}]_i$ and lower end-diastolic pressure (5).

Inflammatory cytokines were measured in 40 patients with unstable angina who were treated with placebo or cariporide (3 x 20, 80 or 120 mg for 2-3 days) following PTCA. Monocyte chemoattractant protein-1 (MCP-1) and IL-6 appeared to be involved in the pathogenesis of acute coronary syndrome. Cariporide demonstrated antiinflammatory as well as antiischemic effects (6).

1. Kevelaitis, E., Kevelaitiene, S., Mouas, C., Marotte, F., Menasche, P. *Sodium-hydrogen exchange inhibition by cariporide improves postischaemic recovery of hypertrophied myocardium.* Eur Heart J 2001, 22(Suppl.): Abst P391.

2. Linz, W., Lang, H.-J., Weichert, A., Albus, U. *Long-term treatment with the NHE-1 inhibitor cariporide extends the normal lifespan of Wistar Kyoto rats.* Naunyn-Schmied Arch Pharmacol 2001, 363(4, Suppl.): Abst 12.

3. Linz, W., Weichert, A., Albus, U. *Long-term treatment with the NHE-1 inhibitor cariporide extends the normal lifespan of Wistar Kyoto rats.* Eur Heart J 2001, 22(Suppl.): Abst P936.

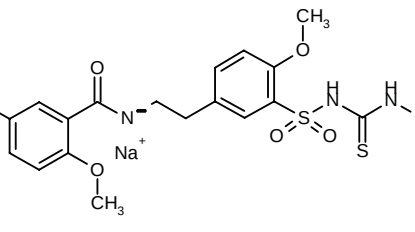
4. Altemose, G.T., Zipes, D.P., Weksler, J., Miller, J.M., Olgin, J.E. *Inhibition of the Na^+/H^+ exchanger delays the development of rapid pacing-induced atrial contractile dysfunction.* Circulation 2001, 103(5): 762.

5. ten Hove, M., Van Emous, J.G., Van Echteld, C.J.A. *Na^+/H^+ exchanger blockers cariporide and eniporide reduce post-ischaemic Ca^{2+}-overload.* Eur Heart J 2001, 22(Suppl.): Abst P2825.

6. Ries, M., Buerke, M., Lusch, A., Rupprecht H.-J., Meyer, J. *Sodium/H^+ exchange inhibitor (cariporide) reduces proinflammatory markers following PCTA in patients with unstable angina.* Eur Heart J 2001, 22(Suppl.): Abst P1597.

Original monograph - Drugs Fut 1997, 22(11): 1197.

Clamikalant Sodium



The antiarrhythmic agent clamikalant sodium (HMR-1098; Aventis), a cardioselective ATP-sensitive potassium channel blocker, is undergoing phase II trials for the prevention of sudden cardiac death.

Clamikalant has been reported to prevent ischemia-induced shortening of the action potential duration in Langendorff-perfused rabbit hearts and to reduce both ventricular repolarization dispersion and the window of vulnerability for ventricular fibrillation during ischemia (1).

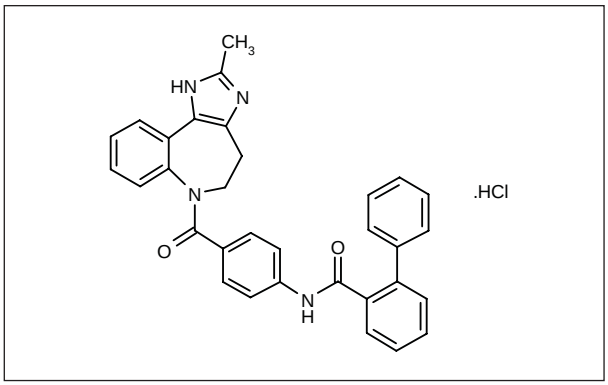
The effects of clamikalant on atrial effective refractory period shortening during atrial fibrillation were tested in dogs with autonomic blockade induced and maintained by atropine and propranolol and subjected to rapid right atrial pacing. Treatment with clamikalant had no effect on the shortening of high right atrial effective refractory period during the first 3 h, but was shown to prevent atrial electrical remodeling thereafter (2).

1. Behrens, S., Zabel, M., Janssen, A., Barbierato, M., Schultheiss, H.P. *Influence of a new ATP-sensitive potassium-channel antagonist (HMR 1098) on ventricular fibrillation inducibility during myocardial ischaemia.* Eur Heart J 2001, 22(Suppl.): Abst P2934.

2. Vereckei, A., Arnett, C.J.A., Goegelein, H.G., Zipes, D.P.Z. *The effect of the cardioselective K^+-ATP-channel blocker HMR 1098 in an acute rapid atrial pacing model of atrial electrical remodelling during atrial fibrillation.* Eur Heart J 2001, 22(Suppl.): Abst P1768.

Original monograph - Drugs Fut 2001, 26(10): 951.

Conivaptan Hydrochloride



Conivaptan is a dual vasopressin V_1 and V_2 receptor antagonist that is being codeveloped by Yamanouchi and Pfizer and is in phase II trials for the treatment of heart failure.

A multicenter, double-blind, randomized, placebo-controlled trial in 142 heart failure patients was designed to evaluate the efficacy and safety of conivaptan 10, 20 and 40 mg as single i.v. doses. Treatment was well tolerated and significantly decreased pulmonary capillary wedge pressure and right atrial pressure, without having significant effects on systemic blood pressure or heart rate. Conivaptan was also associated with an increase in urine output, effective water clearance and free water clearance, but no significant effect on urine or plasma sodium or potassium. The effects of the drug were independent of baseline arginine vasopressin (AVP) and sodium levels (1-4) (Table III).

A randomized pilot study assessed treatment of 24 heart failure patients with furosemide (40 or 80 mg q.i.d.) for 6 days followed by concomitant conivaptan (20 or 40 mg q.i.d.) for 3 days. The drug combination effectively increased free water clearance, indicating that the combination could make hyponatremia and hypokalemia less likely in these patients. Furosemide plus conivaptan also partially antagonized renal excretion of sodium and potassium (5) (Table III).

1. Udelson, J., Smith, W.B., Hendrix, G., Painchaud, C., Ghazzi, M.M., Thomas, I., Ghali, J., Selaru, P., Pressler, M., Konstam, M. *Haemodynamic effects of conivaptan hydrochloride (YM087, CI-1025) a combined vasopressin V_{1A} and V_2 receptor antagonist, in patients with advanced heart failure.* Eur Heart J 2001, 22(Suppl.): Abst P2150.

2. Painchaud, C., Bichet, D., Udelson, J.E., Ghazzi, M.M., Selanu, P., Chartier, K. *Urinary water clearance after infusion of conivaptan, a combined vasopressin V_{1A} and V_2 receptor antagonist, in patients with NYHA class III/IV heart failure.* Eur Heart J 2001, 22(Suppl.): Abst P2151.

Table III: Clinical studies of conivaptan.

Indication	Design	Treatments	N	Conclusions	Ref.
Heart failure	Randomized, double-blind, multicenter	Conivaptan, 10 mg iv infusion over 30 min (n = 37) Conivaptan, 20 mg iv infusion over 30 min (n = 32) Conivaptan, 30 mg iv infusion over 30 min (n = 35) Placebo (n = 38)	142	Conivaptan was well tolerated, induced dose-dependent favorable changes in hemodynamic outcomes (reduced pulmonary capillary wedge pressure without effects on systemic blood pressure or heart rate) and increased urinary output, effective water clearance and free water clearance without effects on electrolytes	1-4
Heart failure	Randomized, double-blind	Furosemide, 40 mg po od x 6 d → Conivaptan 20 mg po od x 3 d Furosemide, 40 mg po od x 6 d → Conivaptan 40 mg po od x 3 d Furosemide, 80 mg po od x 6 d → Conivaptan 20 mg po od x 3 d Furosemide, 80 mg po od x 6 d → Conivaptan 40 mg po od x 3 d	24	Conivaptan combined with furosemide was effective in clearing free water and partially antagonized renal excretion of sodium and potassium. Thus, this combination could reduce the risk of hyponatremia and hypokalemia in patients with chronic heart failure	5

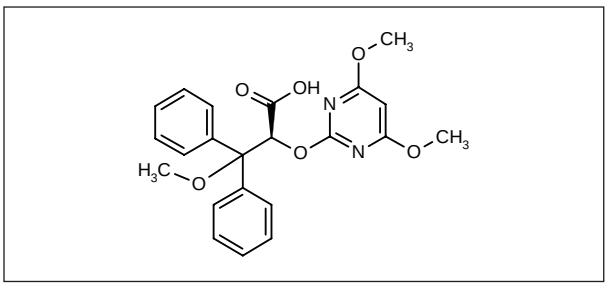
3. Udelson, J.E., Smith, W.B., Hendrix, G.H., Painchaud, C.A., Ghazzi, M., Thomas, I., Ghali, J.K., Selaru, P., Chanoine, F., Pressler, M.L., Konstam, M.A. *Acute hemodynamic effects of conivaptan, a dual V_{1A} and V_2 vasopressin receptor antagonist, in patients with advanced heart failure.* Circulation 2001, 104(20): 2417.

4. Smith, W.B., Russell, S., Ghali, J.K., Painchaud, C.A., Ghazzi, M.M., Konstam, M.A., Udelson, J.E., Selaru, P. *Conivaptan (CI-1025, YM087), a combined vasopressin V_{1A}/V_2 antagonist, reduces pulmonary capillary wedge pressure independent of baseline serum Na or vasopressin levels in heart failure.* Eur Heart J 2001, 22(Suppl.): Abst P2917.

5. Tonkon, M., Russell, S., Ghali, J.K., Painchaud, C.A., Ghazzi, M.M., Konstam, M.A., Udelson, J.E., Selanu, P. *Interaction between furosemide and oral conivaptan (YM087) in patients with heart failure.* Eur Heart J 2001, 22(Suppl.): Abst P2915.

Original monograph - Drugs Fut 2000, 25(11): 1121.

Darusentan



Most of the clinical trials on the selective endothelin ET_A receptor antagonist darusentan (LU-135252) published this past year were conducted in patients with heart failure. The compound is in phase II development at Abbott, through its acquisition of Knoll, in collaboration with Aventis for the treatment of congestive heart failure and hypertension.

The effects of darusentan were examined in a multicenter, double-blind, randomized, placebo-controlled study in 157 patients with NYHA class III congestive heart failure (CHF). The patients received placebo or darusentan at oral doses of 30, 100 or 300 mg/day over 3 weeks, in addition to standard therapy. The addition of darusentan was associated with a significant improvement in cardiac index compared to baseline and placebo, as well as dose-dependent increases in plasma ET-1 levels, but no neurohumoral activation was observed, even over the long term. Cardiac index was increased on acute administration of darusentan by 13%, 22% and 20%, respectively, at doses of 30, 100 and 300 mg/day, and even greater improvement was seen after long-term dosing, with respective increases of 17%, 35% and 25%. The two higher dose groups also experienced improvement in NYHA class and fatigue (1, 2) (Table IV).

Long-term treatment with darusentan in patients with heart failure was found to significantly reduce plasma brain natriuretic peptide (BNP) levels at doses of 100 and 300 mg/day, and to increase the cGMP/BNP ratio at doses of 30, 100 or 300 mg/day. The increase in cGMP/BNP ratio was correlated with the decrease in pulmonary vascular resistance. The investigators conclude that the improved cGMP/BNP ratio may be either a direct effect of treatment or a marker of improvement in CHF (3).

Chronic heart failure is associated with impaired endothelium-dependent vasodilatation and increased basal vascular tone, partly due to elevated plasma ET-1 levels. A study therefore evaluated the effects of darusentan on endothelial function in CHF patients. Twenty-one patients with CHF were randomized to receive darusentan (30 or 300 mg/day) or placebo for 3 weeks and assessed for baseline and end-of-treatment flow-mediated vasodilatation (FMD), as a measure of the ability of blood vessels to dilate, thereby increasing blood flow, using high-resolution ultrasound. All CHF patients showed impaired FMD at study entry compared to 11 control patients. This parameter significantly improved in all 14 darusentan-treated patients compared to baseline, but not in placebo-treated patients. However, subgroup analysis demonstrated a significant increase in FMD compared to baseline only in patients receiving the lower dose of darusentan. The lack of a significant effect on impaired FMD in those given the higher dose was suggested to be due to the significant increase seen in brachial artery diameter in this group. Big ET-1 plasma levels were elevated in the CHF patients compared to controls, but darusentan had no significant effect. Although preliminary and limited to assessing the effect

Table IV: Clinical study of darusentan.

Indication	Design	Treatments	N	Conclusions	Ref.
Chronic heart failure	Randomized, double-blind, multicenter	Darusentan, 30 mg po Darusentan, 100 mg po Darusentan, 300 mg po Placebo	157	Long-term treatment with darusentan improved hemodynamics without neurohormonal activation or impairment of renal function in patients with congestive heart failure	1, 2

on blood flow, this study indicates potential for selective ET_A receptor antagonists in improving endothelium-dependent vasodilatation in CHF (4).

The HEAT (Hypertension, Endothelin Antagonist Treatment) study, a multicenter, double-blind, randomized, placebo-controlled, parallel-group, dose-response trial, included 392 patients with moderate hypertension treated with placebo or darusentan at doses of 10, 30 and 100 mg/day for 6 weeks. Dose-dependent decreases in both diastolic and systolic blood pressure compared to placebo were obtained on darusentan, particularly at the highest dose (–8.3 mmHg diastolic, –11.3 mmHg systolic). A trend for more adverse events was noted in the active treatment groups, particularly at the highest dose (49.0% *vs*. placebo 30.3%). The most common adverse event was headache, and dose-dependent flushing and peripheral edema related to the vasodilator effect of darusentan were also seen (5).

Preclinical evaluation to further characterize the effects of darusentan also continues. In a study in rats with chronic heart failure, oral darusentan, trandolapril or the two agents combined was administered for 11 weeks. Trandolapril alone and in combination with darusentan attenuated left ventricular (LV) hypertrophy and expression of LV β-myosin heavy chain (MHC):α-MHC mRNA. The effect of the combination on right ventricular (RV) hypertrophy was better than that of trandolapril alone. The combination prevented the increase in RV β-MHC:α-MHC mRNA and the drugs were complementary in reducing LV collagen I and III mRNA levels and LV dilatation (6).

The results from a canine study indicated that the beneficial effects of darusentan in heart failure may be due in part to a reduction in oxidative stress (7).

Researchers compared darusentan, the combined endothelin-converting enzyme/neutral endopeptidase (ECE/NEP) inhibitor KC-12615 and the NEP inhibitor candoxatrilat in rats with hypoxia-induced pulmonary hypertension. In comparison with vehicle-treated animals under hypoxic conditions, mean pulmonary artery pressure decreased upon administration of all three agents. In addition, hypoxic rats treated with darusentan showed lower right ventricular mass than hypoxic rats treated with the other two drugs or vehicle. Pulmonary vascular remodeling was significantly reduced by all three agents (8).

Darusentan has been investigated for its ability to protect the myocardium in stroke-prone spontaneously hypertensive rats (SHRSP) subjected to myocardial infarction. Significantly more darusentan-treated animals survived following myocardial infarction (54% *vs*. 34% on placebo at 18 days; 17% *vs*. 11% at 6 weeks). Darusentan also significantly improved hemodynamics, reduced interstitial collagen content and induced marked left ventricular dilatation compared to placebo. The ET antagonist protected against the formation of transmural infarction scars and subendocardial arteriolar and capillary density was higher in these SHRSP than in placebo-treated animals (9).

Administration of darusentan in dogs did not negatively affect scar healing and was not associated with left ventricular remodeling 6 weeks after myocardial infarction (10).

Neointima formation was induced in wild-type, apolipoprotein E-deficient (apoE–/–), LDL receptor-deficient (LDLR–/–) and/or endothelial nitric oxide synthase-deficient (eNOS–/–) mice to determine the role of eNOS in the antiatherosclerotic effect of darusentan. The activity of darusentan appeared to be independent of eNOS, as well as effects on systolic blood pressure and plasma cholesterol levels (11-14).

A study in pigs subjected to ischemia-reperfusion and treated with darusentan, N^G-nitro-L-arginine (L-NNA), L-NNA plus darusentan or L-NNA plus L-arginine and darusentan compared the effects of endothelin antagonism alone to that with NO inhibition and stimulation. The results indicated that NO plays a role in the cardioprotection afforded by darusentan (15).

Piglets used as an animal model of acute lung injury were treated with 0.3 or 3 mg/kg of nebulized darusentan. Both doses resulted in comparable enhancements in gas exchange and hemodynamics; the lower dose may have been enough to block the majority of ETA receptors in ventilated regions of the injured lung (16).

1. Ruschitzka, F., Enseleit, F., Hurlimann, D., Pacher, R., Mitrovic, V., Schulze, M.R., Kiowski, W., Noll, G., Luscher, T.F. *Effects of long-term selective ET_A receptor blockade on neurohumoral activation in congestive heart failure.* J Am Coll Cardiol 2001, 37(2, Suppl. A): 171A.

2. Hurlimann, D., Ruschitzka, F., Enseleit, F., Pacher, R., Mitrovic, V., Schulze, M.R., Noll, G., Lüscher, T.F. *Effects of long-term selective ET_A receptor blockade on neurohumoral activation in congestive heart failure.* Eur Heart J 2001, 22(Suppl.): Abst 2080.

3. Monti, J. et al. *Improved cGMP generation correlates to hemodynamic improvement in heart failure patients after 21 days treatment with the ET_A-receptor antagonist LU 135252.* J Am Coll Cardiol 2001, 37(2, Suppl. A): 172A.

4. Berger, R., Hülsmann, M., Stanek, B., Frey, B., Heher, S., Pacher, R., Neunteufl, T. *Effects of endothelin A receptor blockade on endothelial function in patients with chronic heart failure.* Circulation 2001, 103(7): 981.

5. Nakov, R., Pfarr, E., Eberle, S. *LU 135252: An endothelin A receptor antagonist for treatment of hypertension, dose response, efficacy and safety. The HEAT study: Hypertension, Endothelin Antagonist Treatment.* Eur Heart J 2001, 22(Suppl.): Abst 3336.

6. Fraccarollo, D., Galuppo, P., Bauersachs, J., Erti, G., Kellner, M. *Effects of combined endothelin A receptor blockade plus ACE-inhibition in rats with chronic heart failure.* Eur Heart J 2001, 22(Suppl.): Abst P399.

7. Moe, G., Yazdanpanah, M., Konig, A., Romanova, M., Liu, P. *Elevated myocardial tissue aldehyde levels in heart failure: A novel marker of oxidative stress and its attenuation by neurohormonal blockade.* Eur Heart J 2001, 22(Suppl.): Abst P1656.

8. Clift, P.F.J., Wilkins, M.R. *Comparison of the effect of combined inhibition of endothelin-converting-enzyme/neutral endopeptidase activity and ET_A receptor blockade on hypoxia-induced pulmonary hypertension in the rat.* J Am Coll Cardiol 2001, 37(2, Suppl.): 225A.

9. Reinecke, A., Dorenkamp, M., Xia, Q., Bitterling, H., Penz, S., Storz, C., Haake, N., Simon, R., Unger, T. *Pre-treatment with the ET_A-receptor antagonist LU 135252 prevents transmural myocardial infarction in stroke-prone spontaneously hypertensive rats.* J Hypertens 2001, 19(Suppl. 2): Abst 4B.6.

10. Basso, C., Kirchengast, M., Thiene, G., Della Barbera, M., Angelini, A., Iliceto, S. *Chronic treatment with endothelin A-receptor antagonist after myocardial infarction in dogs: Early start does not affect scar healing and cardiac remodeling.* Eur Heart J 2001, 22(Suppl.): Abst P1047.

11. Ruetten, H., Tiemann, M. *Inhibition of endothelin ET_A receptors attenuates neointima formation in apolipoprotein E deficient mice independent of endothelial nitric oxide synthase.* Circulation 2001, 104(17, Suppl. 2): Abst 1310.

12. Ruetten, H., Tiemann, M., Dimmeler, S., Zeiher, A.M. *Endothelin ET_A receptors blockade inhibits neointima formation in apolipoprotein E deficient mice independent of endothelial nitric oxide synthase.* Eur Heart J 2001, 22(Suppl.): Abst P3546.

13. Ruetten, H., Tiemann, M., Ihling, C. *Enhanced atherosclerosis in mice deficient for low density lipoprotein/endothelial nitric oxide synthase is ameliorated by inhibition of endothelin ET_A receptors.* Circulation 2001, 104(17, Suppl. 2): Abst 1309.

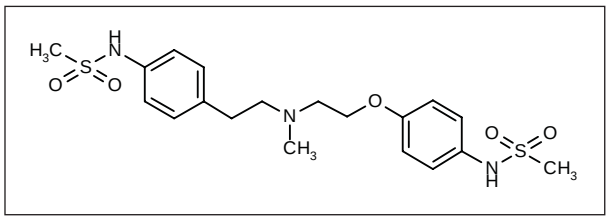
14. Ruetten, H., Tiemann, M., Ihling, C., Zeiher, A.M., Dimmeler, S. *Enhanced atherosclerosis in low density lipoprotein/endothelial nitric oxide synthase deficient mice is ameliorated by inhibition of endothelin ET_A receptors.* Eur Heart J 2001, 22(Suppl.): Abst 1394.

15. Gourine, A.V., Gonon, A.T., Pernow, J. *Involvement of nitric oxide in cardioprotective effect of endothelin receptor antagonist during ischemia-reperfusion.* Am J Physiol - Heart Circ Physiol 2001, 280(3): H1105.

16. Busch, T., Deja, M., Wolf, S., Lohbrunner, H., Boemke, W., Falke, K.J., Kaisers, U. *Effects of the inhaled endothelin-A-receptor antagonist LU-135252 at various doses in experimental acute lung injury.* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A817.

Original monograph - Drugs Fut 1999, 24(2): 141.

Dofetilide



Dofetilide was launched in the U.S. by Pfizer as Tikosyn® during the first quarter of 2000 as a new drug for atrial fibrillation (1).

The proarrhythmic effects of dofetilide and azimilide were examined in a study in anesthetized dogs with a high incidence of torsade de pointes due to chronic complete AV block and bradycardia-induced volume overload. Both agents increased monophasic action potential duration, idioventricular rhythm cycle length and Q-T interval. Interventricular dispersion was also significantly increased after treatment with either agent due to the dissimilar lengthening of the left and right ventricular monophasic action potential duration. Early afterdepolarizations were observed in all animals, with ectopic ventricular beats seen in most of them. A comparable incidence of torsade de pointes was observed with both treatments (2).

Azimilide and dofetilide terminated atrial flutter and prevented reinduction in all dogs with surgically induced right atrial enlargement, respectively. Both drugs increased the effective refractory period in the slow conduction zone and increased flutter cycle length, resulting in interruption of the arrhythmia circuit (3).

A multicenter, randomized, double-blind, placebo-controlled study compared dofetilide 500 μg b.i.d. with propafenone 150 mg t.i.d. in preventing the recurrence of paroxysmal supraventricular tachycardia (PSVT) in 122 patients. At 6 months, the treatments demonstrated equivalent efficacy in preventing PSVT (4).

Patients (n = 341) with chronic heart failure and left ventricular dysfunction enrolled in the Danish Investigation of Arrhythmia and Mortality on Dofetilide (DIAMOND-CHF) study were randomized to dofetilide or placebo and the effects of treatment on Q-T dispersion were evaluated. Between randomization and day 4, Q-T dispersion was not significantly affected by dofetilide treatment as compared to placebo (5).

A double-blind, randomized, placebo-controlled, parallel-group study in 14 healthy male volunteers showed that treatment with dofetilide did not significantly influence the steady-state pharmacokinetic parameters of digoxin. Thus, dofetilide dose adjustments should not be necessary with concomitant digoxin treatment (6).

1. *Pfizer updates late-stage product pipeline at annual meeting.* DailyDrugNews.com (Daily Essentials) May 22, 2000.

2. Van Opstal, J.M., Leunissen, J.D.M., Wellens, H.J.J., Vos, M.A. *Azimilide and dofetilide produce similar electrophysiological and proarrhythmic effects in a canine model of torsade de pointes arrhythmias.* Eur J Pharmacol 2001, 412(1): 67.

3. Restivo, M., Hegazy, M., El-Haami, M., Yin, H., Caref, E.B., Assadi, M.A., Brooks, R.R., El-Sherif, N. *Efficacy of azimilide and dofetilide in the dog right atrial enlargement model of atrial flutter.* J Cardiovasc Electrophysiol 2001, 12(9): 1018.

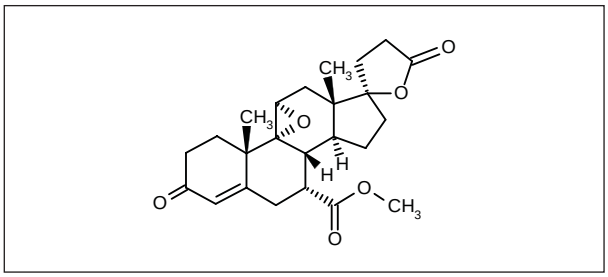
4. Tendera, M., Wnuk-Wojnar, A.M., Kulakowski, P. et al. *Efficacy and safety of dofetilide in the prevention of symptomatic episodes of paroxysmal supraventricular tachycardia: A 6-month double-blind comparison with propafenone and placebo.* Am Heart J 2001, 142(1): 93.

5. Brendorp, B., Elming, H., Kober, L., Jun, L., Torp-Pedersen, C. *Effect of dofetilide on QT-dispersion in patients with congestive heart failure.* Eur J Heart Fail 2001, 3(Suppl. 1): S95.

6. Kleinermans, D., Nichols, D.J., Dalrymple, I. *Effect of dofetilide on the pharmacokinetics of digoxin.* Am J Cardiol 2001, 87(2): 248.

Original monograph - Drugs Fut 1991, 16(6): 521.

Eplerenone



Eplerenone is a selective aldosterone receptor antagonist developed at Pharmacia which is scheduled for NDA filing for the treatment of hypertension by the first quarter of 2002. Pharmacia is also completing phase III studies in heart failure and anticipates filing an NDA by the first quarter of 2003 (1).

Two separate studies in rats with licorice-induced hypertension have compared the effects of eplerenone and spironolactone or verapamil on endothelial function. All treatments normalized blood pressure, while vascular ET-1 levels and endothelium-dependent relaxation were restored by eplerenone and spironolactone, but not verapamil (2, 3).

The effect of eplerenone on infarct healing and left ventricular remodeling was examined after myocardial infarction in rats. Collagen deposition and the thinning ratio were not affected by eplerenone and at 28 days postmyocardial infarction, treatment had reduced reactive fibrosis in the viable myocardium as compared with vehicle-treated animals (4).

Aldosterone, eplerenone and spirolactone were administered to pigs to examine their effects on remodeling and collagen accumulation after angioplasty. Collagen accumulation appeared to be a major factor in constrictive remodeling of coronary arteries and was most effectively reduced by eplerenone (5).

The effects of selective aldosterone receptor blockade with eplerenone have been investigated on endothelial function in New Zealand white rabbits with diet-induced atherosclerosis. Eplerenone was shown to improve endothelial function and reduce superoxide generation in this rabbit model, suggesting that it may have application in the treatment of this disease (6).

The predictive value of active plasma renin and serum aldosterone levels for response to eplerenone was examined in a multicenter, double-blind, randomized, placebo-controlled trial. Eplerenone 50-100 mg once daily or placebo was added to a fixed dose of an ACE inhibitor or an angiotension II receptor blocker (ARB) in patients with hypertension not controlled on ACE inhibitor or ARB therapy. The results showed that addition of eplerenone to either treatment modality safely and effectively reduces systolic and diastolic blood pressure, but this response could not be predicted from baseline renin-angiotensin-aldosterone system status (7). The combination of eplerenone 50 once daily with a fixed dose of an ACE inhibitor or an angiotensin II receptor antagonist was the focus of another multicenter, double-blind, randomized, placebo-controlled study. Patients (n=388) with mild to moderate hypertension were enrolled and treated for 8 weeks. The addition of eplerenone was found to be safe and effectively reduced blood pressure in these patients (8) (Table V).

Eplerenone 50 mg/day and losartan 50 mg/day were compared in 551 black and white patients in a randomized, double-blind, 16-week trial. Eplerenone treatment produced significant reductions in blood pressure and was superior to losartan in black patients (9).

1. *Pharmacia outlines plans and priorities for delivering growth*. DailyDrugNews.com (Daily Essentials) Dec 11, 2001.

2. Quaschning, T., Ruschitzka, F., Shaw, S., Luscher, T.F. *Aldosterone receptor antagonism normalizes vascular function in liquorice-induced hypertension*. Hypertension 2001, 37(2, Part 2): 801.

3. Hurlimann, D., Lüscher, T.F., Shaw, S.G., Ruschitzka, F., Quaschning, T., Enseleit, F. *Eplerenone normalizes vascular function in liquorice-induced hypertension*. Eur Heart J 2001, 22(Suppl.): Abst 3337.

4. Delyani, J.A., Robinson, E.L., Rudolph, A.E. *Effect of a selective aldosterone receptor antagonist in myocardial infarction*. Am J Physiol - Heart Circ Physiol 2001, 281(2): H647.

5. Ward, M.R., Kanellakis, P., Ramsey, D., Funder, J., Bobik, A. *Eplerenone suppresses constrictive remodeling and collagen accumulation after angioplasty in porcine coronary arteries*. Circulation 2001, 104(4): 467.

Table V: Clinical study of eplerenone.

Indication	Design	Treatments	N	Conclusions	Ref.
Hypertension	Randomized, double-blind, multicenter	Eplerenone, 50-100 mg od x 8 wks + fixed doses of ACE-I or ARB Placebo	388	Response to eplerenone combined with an ACE inhibitor or ARB could not be predicted by active plasma renin or serum aldosterone levels. Nevertheless, it was a safe and effective treatment for reducing systolic and diastolic blood pressure	7, 8

6. 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.

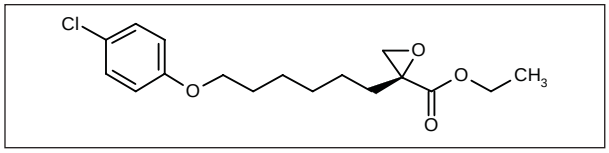
7. Prisant, L.M., Krum, H., Roniker, B., Krause, S., Fakouhi, K., Workman, D. *Endocrine relationships of eplerenone coadministration with an angiotensin converting enzyme inhibitor or an angiotensin II receptor antagonist in hypertensive patients.* J Clin Pharmacol 2001, 41(9): Abst 66.

8. Krum, H., Nolly, H., Roniker, B., Fakouhi, K., Krause, S., Flemng, C. *Coadministration of eplerenone with an angiotensin converting enzyme inhibitor or an angiotensin II blocker in patients with mild to moderate hypertension.* Eur Heart J 2001, 22(Suppl.): Abst 3338.

9. Saunders, E., Oparil, S., Roniker, B., Kleiman, J., Krause, S., Workman, D. *Eplerenone vs. losartan in black compared to white hypertensive patients.* 24th Annu Sci Meet Jpn Soc Hypertens (Oct 25-27, Osaka) 2001, Abst O-078.

Original monograph - Drugs Fut 1999, 24(5): 488.

Etomoxir



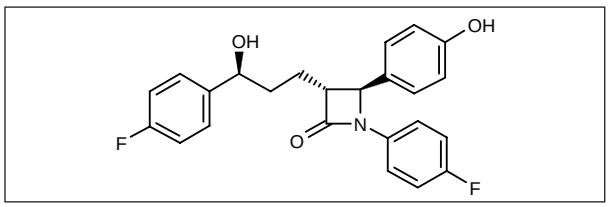
Etomoxir is a highly active and specific inhibitor of carnitine *O*-palmitoyltransferase 1 (CPT1), a key enzyme in mitochondrial fatty acid oxidation. The inhibition of this enzyme leads to a shift from fatty acid oxidation to glucose oxidation, a more efficient supplier of energy in the diseased heart. It is currently being evaluated in a phase II trial in patients with congestive heart failure by MediGene, which holds a license to the drug from Byk Gulden.

Investigators measured myocardial lipid levels and myocardial function in diabetic rats and evaluated the effects of etomoxir on lipid second messengers and myocardial function in diabetic rat hearts. 1,2-Diacylglycerol appeared to have a role in ameliorating myocardial dysfunction. Ceramide did not appear to play a role in either cardiomyopathy or the improvement in cardiac contractility seen in etomoxir-treated rats (1).

1. Hayashi, K., Okumura, K., Matsui, H., Murase, K., Kamiya, H., Saburi, Y., Numaguchi, Y., Toki, Y., Hayakawa, T. *Involvement of 1,2-diacylglycerol in improvement of heart function by etomoxir in diabetic rats.* Life Sci 2001, 68(13): 1515.

Original monograph - Drugs Fut 1986, 11(12): 1034.

Ezetimibe



Merck & Co. and Schering-Plough are collaborating on the development and marketing of ezetimibe (Zetia™), an investigational cholesterol absorption inhibitor discovered by Schering-Plough, as well as a once-daily combination tablet containing ezetimibe and Zocor® (simvastatin), Merck's best-selling cholesterol medicine. Ezetimibe has completed phase III studies both as monotherapy and for use in combination with statins, and has been shown to inhibit the absorption of cholesterol in the intestine. A regulatory filing in the U.S. for these indications was recently submitted and international regulatory filings will begin in the first half of 2002. Clinical trials are currently under way with ezetimibe and simvastatin as a once-daily combination tablet for the treatment of elevated cholesterol levels (1-3).

Ezetimibe has been shown to reduce plasma cholesterol levels in animals and humans, but its effects on the combined dyslipidemia (hypercholesterolemia and hypertriglyceridemia) typical of type 2 diabetes and obese insulin-resistant subjects have not been established. A preclinical study was therefore performed in which hamsters were made obese, hyperinsulinemic, hypercholesterolemic, hypertriglyceridemic and hyperleptinemic by feeding with a cholesterol- and triglyceride-containing diet. The animals treated with ezetimibe in the diet for up to 84 days showed no change in body weight, insulin or leptin but had normalized VLDL + LDL cholesterol and triglyceride levels and a significant decrease in LDL cholesterol to below levels in animals fed normal chow. The treatment also significantly increased the HDL:LDL cholesterol ratio. The hepatic accumulation of cholesteryl ester and free cholesterol was completely reversed by ezetimibe. According to these findings, ezetimibe may represent an effective pharmacological intervention in patients with combined dyslipidemia, thereby reducing the risk of cardiovascular disease in this patient population (4).

The combination of ezetimibe or Sch-48461 and HMG-CoA reductase inhibitors in chow-fed dogs resulted in synergistic reductions in plasma cholesterol (5).

In vivo studies conducted in monkeys fed a high-cholesterol diet assessed the efficacy of ezetimibe in decreasing hypercholesterolemia. In rhesus monkeys, the agent prevented the doubling of plasma cholesterol levels seen in untreated controls. Treatment dose-dependently reduced LDL cholesterol without affecting plasma triglycerides or HDL cholesterol levels. A significant reduction in chylomicron apolipoprotein (apo) B-100 content was also observed, with no affects on apo B-48. Experiments conducted in cynomolgus monkeys fed a single cholesterol-containing meal showed that a single dose of ezetimibe significantly reduced cholesterol in chylomicrons during the postprandial phase; chylomicron triglyceride content was unaffected. Thus, it was concluded that ezetimibe-induced reductions in chylomicron cholesterol content indirectly lead to decreases in LDL cholesterol (6).

A pharmacokinetic study of oral ezetimibe 10 mg given to 18 healthy children for 7 days found that the drug was well tolerated and rapidly absorbed, extensively glucuronidated and slowly eliminated in this population. It was concluded that dose adjustments would not be necessary in adolescents with hypercholesterolemia (7).

Several studies have examined the potential pharmacokinetic/pharmacodynamic interactions between ezetimibe and statins and other frequently administered drugs. No interaction was seen with atorvastatin (8), lovastatin or hydroxylovastatin (9), glipizide (10), triphasic oral contraceptives (ethinylestradiol and norgestrel) (11), warfarin (12), gemfibrozil (13) or vitamin A, vitamin D, vitamin E, α- and β-carotenoids and vitamin K (14).

Analysis of data from 2 double-blind, placebo-controlled phase II studies of ezetimibe (0.25-10 mg/day for 12 weeks) in 409 patients indicated that the 10-mg dose was optimal for treating hypercholesterolemia. This dose had the greatest likelihood of maintaining ezetimibe trough concentrations high enough to reduce LDL cholesterol by more than 15% (15).

Results from a double-blind, randomized, placebo-controlled, parallel-group study conducted in 827 subjects with primary hypercholesterolemia on the National Cholesterol Education Program (NCEP) Step I or a stricter diet demonstrated the safety and efficacy of ezetimibe (10 mg p.o. once daily in the morning for 12 weeks). Similar safety profiles were reported for ezetimibe and placebo. Ezetimibe significantly decreased

Table VI: Clinical studies of ezetimibe.

Indication	Design	Treatments	N	Conclusions	Ref.
Hypercholesterolemia	Randomized, double-blind, multicenter	Ezetimibe, 10 mg po od x 12 wks (n = 85) Placebo (n = 28)	113	Ezetimibe had no effect on serum concentrations of lipid-soluble vitamin	14
Hypercholesterolemia	Randomized, double-blind,	Ezetimibe, 10 mg po od x 12 wks (n = 666) Placebo (n = 226)	892	Ezetimibe was well tolerated and effective in reducing mean plasma concentrations of LDL-cholesterol and improving other lipid parameters in primary hypercholesterolemia	16, 17
Hypercholesterolemia	Randomized, double-blind, multicenter	Study I: Ezetimibe, 0.25 mg po od x 12 wks (n = 44) Ezetimibe, 1 mg po od x 12 wks (n = 46) Ezetimibe, 5 mg po od x 12 wks (n = 49) Ezetimibe, 10 mg po od x 12 wks (n = 43) Placebo (n = 50) Study II: Ezetimibe, 5 mg po od x 12 wks (n = 33) Ezetimibe, 10 mg po od x 12 wks (n = 32) Placebo (n = 34)	432	Ezetimibe dose-dependently reduced LDL-cholesterol and improved other lipid parameters within 2 weeks and throughout the treatment, with no effect of time of dosing. Efficacy and safety of ezetimibe was demonstrated, a daily 10-mg dose being the optimal therapeutic dose	15, 18
Hypercholesterolemia	Randomized, single-blind	Ezetimibe, 10 mg po od x 14 d Fluvastatin, 20 mg po od x 14 d Ezetimibe, 10 mg po od + Fluvastatin, 20 mg po od x 14 d Placebo	32	Ezetimibe plus fluvastatin produced clinically significantly greater reductions in LDL-cholesterol than either drugalone, with a favorable safety profile	19
Hypercholesterolemia	Randomized, single-blind	Ezetimibe, 10 mg po od x 14 d (n = 8) Fenofibrate, 200 mg po od x 14 d (n = 8) Ezetimibe, 10 mg po od + Fenofibrate, 200 mg po od x 14 d (n = 8)	32	The ezetimibe plus fenofibrate combination was more effective in reducing apolipoprotein levels and LDL subfractions in hypercholesterolemia than either drug alone	20, 21
Hypercholesterolemia	Randomized, single-blind	Ezetimibe, 10 mg po od x 14 d Cerivastatin, 0.3 mg po od x 14 d Ezetimibe, 10 mg po od + Cerivastatin, 0.3 mg po od x 14 d	32	Ezetimibe combined with cerivastatin produced significantly greater reductions in LDL-cholesterol than cerivastatin alone	22

LDL cholesterol by week 2 and throughout the dosing period, and also produced significant improvements in total cholesterol, apo B, HDL cholesterol and lipoprotein(a) levels as compared to placebo. A trend toward a decrease in triglycerides was also seen. Moreover, no differences in the LDL cholesterol-lowering effect were found in risk factor, race, gender, age or baseline lipids subgroups (16, 17).

Ezetimibe treatment was analyzed in two 12-week, multicenter, double-blind, randomized, placebo-controlled studies carried out in a total of 432 patients with primary hypercholesterolemia. Patients received ezetimibe 0.25, 1, 5 or 10 mg once daily (trial 1) or ezetimibe 5 or 10 mg once daily (trial 2). In both trials, ezetimibe produced significant reductions in LDL cholesterol, increased HDL cholesterol and demonstrated tolerability comparable to placebo (18).

The efficacy and safety of ezetimibe in combination with another cholesterol-lowering drug, mostly statins, have also been evaluated in placebo-controlled trials in hypercholesterolemic patients on an NCEP Step I diet. Combinations with fluvastatin, fenofibrate, cerivastatin or atorvastatin were not associated with serious adverse events or pharmacokinetic interactions. In all cases, combination therapy was able to reduce LDL cholesterol to a greater extent than monotherapy (19-23).

Results of the above clinical studies of ezetimibe are summarized in Table VI.

1. *Worldwide expansion of Merck/Schering-Plough cholesterol partnership.* DailyDrugNews.com (Daily Essentials) Dec 27, 2001.

2. *Merck & Co. announces new pipeline candidates.* DailyDrugNews.com (Daily Essentials) Dec 19, 2001.

3. *Merck/Schering-Plough seeks FDA approval for Zetia in elevated cholesterol.* DailyDrugNews.com (Daily Essentials) Jan 3, 2002.

4. van Heek, M., Austin, T.M., Farley, C., Cook, J.A., Tetzloff, G.G. *Ezetimibe, a potent cholesterol absorption inhibitor, normalizes combined dyslipidemia in obese hyperinsulinemic hamsters.* Diabetes 2001, 50(6): 1330.

5. Davis, H.R. Jr., Pula, K.K., Alton, K.B., Burrier, R.E., Watkins, R.W. *The synergistic hypocholesterolemic activity of the potent cholesterol absorption inhibitor, ezetimibe, in combination with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in dogs.* Metab Clin Exp 2001, 50(10): 1234.

6. van Heek, M., Compton, D.S., Davis, H.R. *The cholesterol absorption inhibitor, ezetimibe, decreases diet-induced hypercholesterolemia in monkeys.* Eur J Pharmacol 2001, 415(1): 79.

7. Kosoglou, T., Kakar, T., Statkevich, P., Anderson, L., Pai, S., Boutros, T., Vletri, E.P., Affrime, M.B. *Multiple-dose safety and pharmacokinetics of ezetimibe in adolescent children.* Clin Pharmacol Ther 2001, 69(2): Abst PII-77.

8. Zhu, Y., Starkevich, P., Kosoglou, T., Maxwell, S.E., Anderson, L., Patrick, J.E., Batra, V. *Lack of a pharmacokinetic interaction between ezetimibe and atorvastatin.* Clin Pharmacol Ther 2001, 69(2): Abst PIII-15.

9. Reyderman, L., Kosoglou, T., Statkevich, P., Anderson, L., Boutros, T., Batra, V., Seiberline, M. *No pharmacokinetic drug interaction between ezetimibe and lovastatin.* Clin Pharmacol Ther 2001, 69(2): Abst PIII-8.

10. Statkevich, P., Reyderman, L., Kosoglou, T. et al. *Ezetimibe does not affect the pharmacokinetics and pharmacodynamics of glipizide.* Clin Pharmacol Ther 2001, 69(2): Abst PIII-12.

11. Keung, A.C.F., Kosoglou, T., Statkevich, P., Anderson, L., Boutros, T., Cutler, D.L., Batra, V., Sellers, E.M. *Ezetimibe does not affect the pharmacokinetics of oral contraceptives.* Clin Pharmacol Ther 2001, 69(2): Abst PII-89.

12. Bauer, K.S., Kosoglou, T., Statkevich, P., Calzetta, A., Maxwell, S.E., Patrick, J.E., Batra, V. *Ezetimide does not affect the pharmacokinetics or pharmacodynamics of warfarin*. Clin Pharmacol Ther 2001, 69(2): Abst PI-15.

13. Reyderman, L., Kosoglou, T., Statkevich, P., Pember, L., Boutros, T., Maxwell, S., Batra, V., Affrime, M. *Assessment of a multiple-dose drug interaction between ezetimibe and gemfibrozil.* 14th Int Symp Drugs Affect Lipid Metab (Sept 9-12, New York) 2001, 92.

14. Knopp, R.H., Bays, H., Manion, C.V., Lipka, L.J., Melani, L., LeBeaut, A.P., Suresh, R., Veltri, E.P. *Effect of ezetimibe on serum concentrations of lipid-soluble vitamins*. Atherosclerosis Suppl 2001, 2(2): Abst P175.

15. Ezzet, F., Wexler, D., Statkevich, P., Kosoglou, T., Patrick, J., Lipka, L., Mellars, L., Veltri, E., Batra, V. *The plasma concentration and LDL-C relationship in patients receiving ezetimibe.* J Clin Pharmacol 2001, 41(9): 943.

16. Knopp, R.H., Gitter, H., Truitt, T., Lipka, L.J., LeBeaut, A.P., Suresh, R., Veltri, E.P. *Ezetimibe reduces low-density lipoprotein cholesterol: Results of a phase III, randomized, double-blind, placebo-controlled trial.* Atherosclerosis Suppl 2001, 2(2): Abst W6.2.

17. Lipka, L.J., Knopp, R.H., Gitter, H., Truitt, T., LeBeaut, A.P., Veltri, E.P., Suresh, R. *Ezetimibe significantly lowers low-density lipoprotein cholesterol in subjects with primary hypercholesterolaemia.* Eur Heart J 2001, 22(Suppl.): Abst 1405.

18. Bays, H.E., Moore, P.B., Drehobl, M.A. et al. *Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: Pooled analysis of two phase II studies.* Clin Ther 2001, 23(8): 1209.

19. Kosoglou, T., Meyer, I., Musio, B., Anderson, L., Reyderman, L., Statkevich, P., Cutler, D.L., Veltri, E.P., Affrime, M.B. *Pharmacodynamic interaction between fluvastatin and ezetimibe has favorable clinical implications*. Atherosclerosis Suppl 2001, 2(2): Abst P171.

20. Kosoglou, T., Guillaume, M., Sun, S., Pember, L.J.C., Reyderman, L., Statkevich, P., Cutler, D.L., Veltri, E.P., Affrime, M.B. *Pharmacodynamic interaction between fenofibrate and the cholesterol absorption inhibitor ezetimibe*. Atherosclerosis Suppl 2001, 2(2): Abst W6.1.

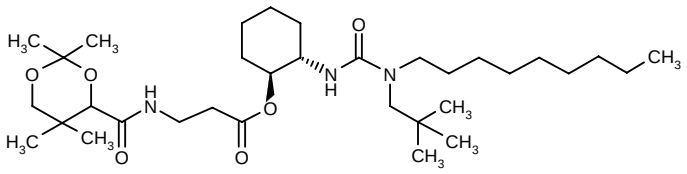
21. Kosoglou, T., Fruchart, J.-C., Guillaume, M., Pember, L.J.C., Sun, S., Picard, G., Affrime, M.B., Veltri, E.P. *Coadministration of ezetimibe and fenofibrate leads to favorable effects on Apo CIII and LDL subfractions.* Atherosclerosis Suppl 2001, 2(2): Abst P172.

22. Kosoglou, T., Seiberling, M., Statkevich, P., Reyderman, L., Anderson, L., Sun, S., Maxwell, S.E., Affrime, M.B., Veltri, E.P. *Pharmacodynamic interaction between cerivastatin and the selective cholesterol absorption inhibitor ezetimibe.* Eur Heart J 2001, 22(Suppl.): Abst 1406.

23. Kosoglou, T., Seiberling, M., Statlkevich, P., Cutler, D.L., Yang, B., Anderson, L., Maxwell, S.E., Affrime, M.B. *Pharmacodynamic interaction between the new selective cholesterol absorption inhibitor ezetimibe and atorvastatin.* J Am Coll Cardiol 2001, 37(2, Suppl. A): 229A.

Original monograph - Drugs Fut 2000, 25(7): 679.

F-1394



Cholesterol esterification via the ACAT enzyme in macrophages is thought to be a major step in foam cell formation and the subsequent progression of atherosclerosis. The antiatherosclerotic effect of orally administered F-1394 (UCB Japan), an ACAT inhibitor in phase II trials for the treatment of atherosclerosis, has been examined in the apolipoprotein E and LDL receptor double knockout (apoE/LDLr-DKO) mouse, an animal model that develops severe hyperlipidemia and atherosclerosis. ACAT inhibition by F-1394 diminished both lipid deposition and lesion size without affecting serum cholesterol levels, indicating the involvement of ACAT in foam cell formation and lesion development (1).

A study in rabbits fed a high-cholesterol or a regular diet for 4 weeks and subjected to denuding of the left common carotid arteries to induce arterial hyperplasia examined the effects of F-1394 on the atherosclerotic process. Hypercholesterolemia induced macrophage-derived foam cell accumulation in lesions, an effect enhanced by the presence of macrophages. Orally administered F-1394 significantly decreased neointimal thickening and the number of macrophages in lesions as compared to controls, while having no effect on serum cholesterol. Results suggest that F-1394 may be effective in the treatment of restenosis following PTCA in hyperlipidemic patients (2).

Treatment of cholesterol-fed rabbits with 100 or 200 mg/kg F-1394 significantly reduced the extent of atherosclerotic lesions and accelerated the regression of atherosclerosis without affecting serum triglyceride levels, suggesting that the drug acts directly on the arterial wall (3).

Combinations of an HMG-CoA reductase inhibitor and an ACAT inhibitor such as F-1394 have been claimed to have a synergistic effect in lowering plasma cholesterol and triglyceride levels (4).

1. Chiwata, T., Aragane, K., Fujinami, K., Kojima, K., Ishibashi, S., Yamada, N., Kusunoki, J. *Direct effect of an acyl-CoA:cholesterol acyltransferase inhibitor, F-1394, on atherosclerosis in apolipoprotein E and low density lipoprotein receptor double knockout mice.* Br J Pharmacol 2001, 133(7): 1005.

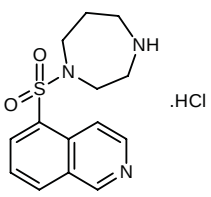
2. Aragane, K., Fujinami, K., Kojima, K., Kusonoki, J. *ACAT inhibitor F-1394 prevents intimal hyperplasia induced by balloon injury in rabbits.* J Lipid Res 2001, 42(4): 480.

3. Aragane, K., Kojima, K., Fujinami, K., Kamei, J., Kusunoki, J. *Effect of F-1394, an acyl-CoA:cholesterol acyltransferase inhibitor, on atherosclerosis induced by high cholesterol diet in rabbits.* Atherosclerosis 2001, 158(1): 139.

4. Chao, Y.-S. (Merck & Co., Inc.). *Anti-hypercholesterolemic drug combination.* WO 0122962.

Original monograph - Drugs Fut 1998, 23(7): 712.

Fasudil Hydrochloride

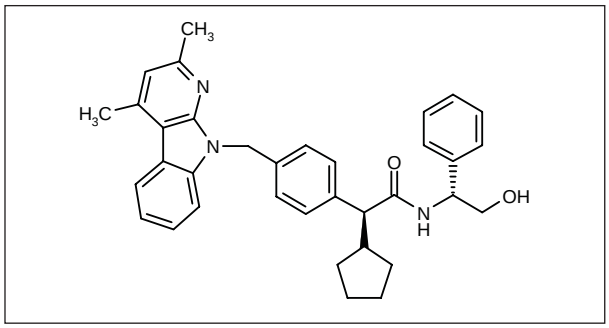


Schering AG has in-licensed fasudil, an innovative cardiovascular product, from the Japanese pharmaceutical company Asahi Kasei. The intravenous formulation of fasudil is available in Japan for the treatment of cerebral vasospasm/ischemia. An oral formulation will be jointly developed by the two companies for the treatment of angina pectoris. Schering's licensing rights include the marketing and sales of fasudil in the U.S. and Europe (1).

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

Original monograph - Drugs Fut 1989, 14(12): 1159.

Implitapide



Implitapide (Bay-13-9952) is an inhibitor of microsomal triglyceride transfer protein (MTP) developed at Bayer.

A randomized, double-blind, placebo-controlled trial tested the efficacy and safety of implitapide 20, 40, 80 and 160 mg/day and cerivastatin 0.3 mg/day over 4 weeks in 309 patients with primary hypercholesterolemia. Implitapide brought about dose-dependent decreases in LDL cholesterol, total cholesterol, apolipoprotein B (apo B), HDL cholesterol and triglycerides. A high incidence of digestive adverse events was observed with doses of 80 and 160 mg. No significant changes in vitamin A I levels, vitamin E/LDL cholesterol or vitamin E/apo A1 ratios were seen with implitapide treatment (1, 2) (Table VII).

1. Farnier, M., Stein, E., Megnien, S., Ose, L., Van Gaal, L., Kastelein, J., Rubinstein, A., Vermaak, W., Ros, E., Cruikshank, M., Ziegler, R. *Effect of implitapide, a microsomal triglyceride transfer protein inhibitor on serum concentrations of lipid-soluble vitamins.* 14th Int Symp Drugs Affect Lipid Metab (Sept 9-12, New York) 2001, 114.

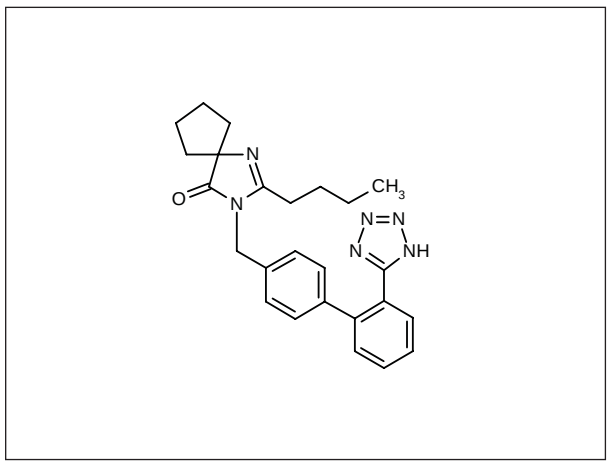
2. Farnier, M., Stein, E., Megnien, S., Ose, L., Van Mieghem, W., Kastelein, J., Rubinstein, A., Vermaak, W., Ros, E., Cruikshank, M., Ziegler, R. *Efficacy and safety of implitapide, a microsomal triglyceride transfer protein inhibitor in patients with primary hypercholesterolemia.* 14th Int Symp Drugs Affect Lipid Metab (Sept 9-12, New York) 2001, 46.

Original monograph - Drugs Fut 2000, 25(11): 1138.

Table VII: Clinical study of implitapide.

Indication	Design	Treatments	N	Conclusions	Ref.
Hypercholesterolemia	Randomized, double-blind,	Implitapide, 20 mg/d x 4 wks (n = 51 Implitapide, 40 mg/d x 4 wks (n = 53) Implitapide, 80 mg/d x 4 wks (n = 46) Implitapide, 160 mg/d x 4 wks (n = 38) Cerivastatin, 0.3 mg/d x 4 wks (n = 44) Placebo (n = 51)	309	Implitapide reduced total, HDL- and LDL-cholesterol, apolipoprotein A1, triglyceride and vitamin E levels but did not significantly change the vitamin A: LDL-cholesterol, vitamin E: LDL-cholesterol or vitamin E: apolipoprotein A1 ratios in primary hypercholesterolemia. The transaminase increases and significant incidence of gastrointestinal adverse events could limit the therapeutic use to 80 mg	1, 2

Irbesartan



The angiotensin II receptor antagonist irbesartan has been on the market since 1997 for the treatment of hypertension. It is sold worldwide by Bristol-Myers Squibb and Sanofi-Synthélabo as Avapro®, Aprovel™ and Karvea™. Clinical evaluation in heart failure is also in progress. The companies submitted a Type II variation with the EMEA and a supplemental NDA with the FDA last summer seeking approval for its use to protect hypertensive patients with type 2 diabetes against the progression of kidney disease. The submissions were based on data from the IRMA-2 (Irbesartan Micro-Albuminuria type 2) trial (see below) and the IDNT (Irbesartan Diabetic Nephropathy Trial) study, a double-blind, placebo-controlled trial in 1715 hypertensive patients with type 2 diabetes and late-stage kidney disease (1).

Table VIII: Clinical study of irbesartan.

Indication	Design	Treatments	N	Conclusions	Ref.
Hypertension	Randomized, double-blind, multicenter	Irbesartan, 150 mg/d po x 2 y (n = 195) Irbesartan, 300 mg/d po x 2 y (n = 194) Placebo (n = 201)	590	Irbesartan had a renoprotective effect independent of its blood pressure-lowering effect in patients with type 2 diabetes, hypertension and microalbuminuria	2

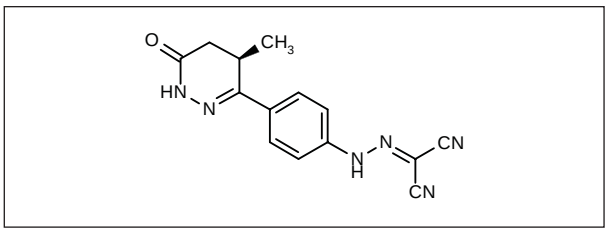
European researchers from the IRMA-2 study found that patients with type 2 diabetes and hypertension who received irbesartan had a reduced rate of progression to clinical albuminuria, indicating overt nephropathy, compared with those who received placebo, and that the effect appeared to be independent of an effect on blood pressure or glycemia. The 2-year study involved 590 patients at 96 centers around the world. Patients were randomized to receive either irbesartan 300 mg once daily, irbesartan 150 mg once daily or matching placebo. Nephropathy developed in significantly fewer patients taking irbesartan 300 mg compared to those taking placebo (10 *vs.* 30 patients) and the hazard ratio (adjusted for baseline blood pressure and level of microalbuminuria) for diabetic nephropathy in those in the high-dose group compared with placebo was 0.32. There was a higher incidence of serious adverse events in the placebo group than in the combined irbesartan groups (22.8% *vs.* 15.4%) (2) (Table VIII).

1. *New applications for irbesartan submitted in Europe and the U.S.* DailyDrugNews.com (Daily Essentials) Aug 21, 2001.

2. Parving, H.-H., Lehnert, H., Bröchner-Mortensen, J., Gomis, R., Andersen, S., Amer, P. *The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes.* New Engl J Med 2001, 345(12): 870.

Original monograph - Drugs Fut 1997, 22(5): 481.

Levosimendan



During the first part of last year, Orion received favorable mutual recognition decisions for levosimendan (Simdax®), a calcium sensitizer indicated for the short-term treatment of acutely decompensated severe chronic heart failure when conventional heart failure medications alone are not sufficient, in several European countries, including Finland, Spain, Italy, Iceland, Greece, Luxembourg, Norway and Portugal. Levosimendan was approved in Sweden in 2000 and launched there in October of the same year. In addition to Sweden, Orion will market the drug in Finland, Iceland and Norway, while marketing partner Abbott will lead product introduction in Italy, Spain, Greece, Luxembourg and Portugal (1). In order to support the filing of an NDA with the FDA, an additional phase III program was expected to begin last year with a scheduled 2-year time frame. A comprehensive and long-term phase III clinical trial program is being designed for the evaluation of an oral formulation of levosimendan in patients with milder stages of heart failure (2).

An open, randomized trial conducted in 10 healthy subjects showed that concomitant levosimendan administration (0.5 mg q.i.d. p.o. for 9 days) did not influence the pharmacodynamics of warfarin (25 mg p.o. on day 4). Although the volume of distribution of warfarin was higher and the elimination half-life was shorter with levosimendan treatment, the latter agent did not enhance the anticoagulant effects of warfarin. In addition, levosimendan administered alone was found to have no effect on blood coagulation. Headache was reported with continuous levosimendan dosing, possibly due to cerebral vasodilatation (3).

Levosimendan was reported in a recent patent to be useful for the treatment or prevention of coronary graft vasospasm after coronary artery bypass surgery. Preferably, levosimendan is administered intravenously, starting after the coronary bypass is completed and continuing throughout the early recovery period (4).

1. *Orion's Simdax receives favorable opinion in several E.U. countries.* DailyDrugNews.com (Daily Essentials) April 12, 2001.

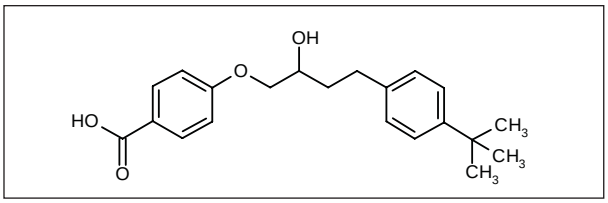
2. *Orion product update reported.* DailyDrugNews.com (Daily Essentials) March 21, 2001.

3. Antila, S., Jarvinen, A., Honkanen, T., Lehtonen, L. *Pharmacokinetic and pharmacodynamic interactions between the novel calcium sensitiser levosimendan and warfarin.* Eur J Clin Pharmacol 2000, 56(9-10): 705.

4. Lehtonen, L. et al. (Orion Corporation). *A method for the treatment of prevention of coronary graft vasospasm.* WO 0100211.

Original monograph - Drugs Fut 2000, 25(6): 563.

Lifibrol



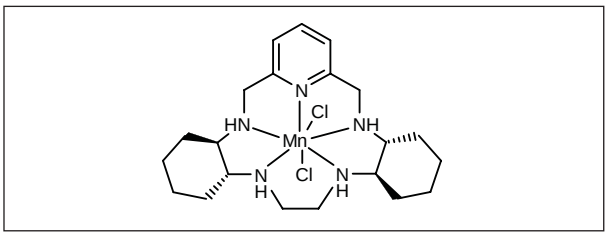
Lifibrol is a cholesterol-lowering agent from Klinge (now Fujisawa Deutschland) and Merckle which is undergoing phase II evaluation.

Kinetic studies in 5 hypercholesterolemic patients before and during treatment with lifibrol 450 mg/day for 4 weeks and in 5 patients with mixed hyperlipidemia before and during lifibrol treatment for 12 weeks indicated that the drug does not alter steady-state HDL concentrations but does enhance HDL apolipoprotein A-1 turnover (1).

1. Winkler, K., Schaefer, J.R., Klima, B. et al. *HDL steady state levels are not affected, but HDL apoA-I turnover is enhanced by lifibrol in patients with hypercholesterolemia and mixed hyperlipidemia.* Atherosclerosis 2000, 150(1): 113.

Original monograph - Drugs Fut 1995, 20(4): 352.

M-40403



MetaPhore's first candidate from its proprietary family of free radical-fighting superoxide dismutase (SOD) mimetics, M-40403, was safe and well tolerated in a phase I trial. This study was the first time that a small-molecule enzyme mimetic was tested in clinical trials. The double-blind, placebo-controlled clinical trial involved intravenous administration of single escalating doses of M-40403 in a total of 36 healthy volunteers. No dose-limiting adverse effects were observed (1).

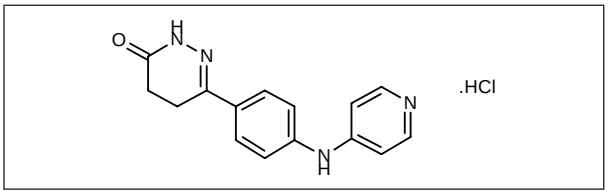
M-40403 was found to improve heart function in rat models of heart attack by removing free radicals from injured heart tissues. Administered prior to reopening the blood vessels in the heart in animal models of heart attack, the compound appears to protect the heart cells from further damage. M-40403 is much smaller than the enzyme which it mimics, allowing the drug to penetrate into tissues such as the brain and the heart that larger synthetic drugs and proteins cannot easily penetrate. Additional studies are needed to evaluate the efficacy of the drug administered after rather than prior to the opening of the blood vessels (2).

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

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

Original monograph - Drugs Fut 2000, 25(10): 1027.

MCI-154



The calcium sensitizer MCI-154 (Mitsubishi Pharma), currently in clinical evaluation for the treatment of heart failure, has been evaluated in several experiments in endotoxemic animals.

The effects of MCI-154 (0.1 mg/kg i.v.) on cardiac function were investigated in rabbits 10 h after administration of endotoxin. MCI-154 treatment markedly reversed the decline in left ventricular systolic pressure, isovolumetric pressure and myocardial contractility. Heart rate was not affected while left ventricular end-diastolic pressure was markedly reduced by MCI-154 (1).

Studies in rats subjected to endotoxic shock showed that the Ca^{2+} sensitivity of myocardial fibers is decreased in these animals. MCI-154 was found to significantly reverse this condition and increase the maximal Ca^{2+}-activated tension of myocardial muscles (2, 3).

The Ca^{2+} sensitizers MCI-154, EMD-57033 and EGIS-9377 were investigated in cardiac preparations from diabetic and nondiabetic rats and were found to increase the force of contraction to the same extent in both preparations (4).

1. Mei, J.-M., Hu, D.Y., Chen, H.S., Liu, L.M., Xiao, N., Chen, H.H., Lu, R.Q. *Effects of MCI-154, a calcium sensitizer, on cardiac function in endotoxemic rabbits.* Acta Pharmacol Sin 2000, 21(9): 824.

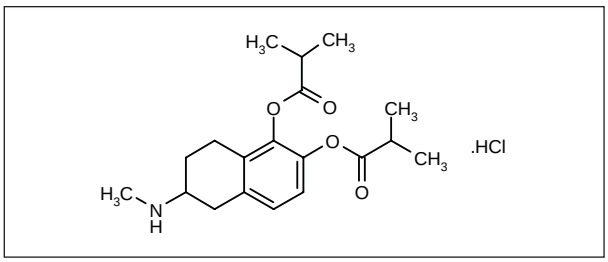
2. Mei, J.-M., Hu, D.Y., Chen, H.S., Liu, L.M., Xiao, N., Chen, H.H., Lu, R.Q. *Effect of MCI-154, a calcium sensitizer, on calcium sensitivity of myocardial contractile system in endotoxemic rats.* Acta Pharmacol Sin 2000, 21(9): 830.

3. Ming, M.J., Hu, D., Chen, H.S., Liu, L.M., Nan, X., Hua, C.H., Lu, R.Q. *Effect of MCI-154, a calcium sensitizer, on calcium sensitivity of myocardial fibers in endotoxic shock rats.* Shock 2000, 14(6): 652.

4. Ishitani, T., Hattori, Y., Sakuraya, F., Onozuka, H., Makino, T., Matsuda, N., Gando, S., Kemmotsu, O, *Effects of Ca^{2+} sensitizers on contraction, $[Ca^{2+}]_i$ transient and myofilament Ca^{2+} sensitivity in diabetic rat myocardium: Potential usefulness as inotropic agents.* J Pharmacol Exp Ther 2001, 298(2): 613.

Original monograph - Drugs Fut 1987, 12(9): 856.

Nolomirole Hydrochloride



Nolomirole hydrochloride (CHF-1035) is a non-selective dopaminergic agent in phase III evaluation for heart failure at Chiesi.

Nolomirole was tested for its efficacy and safety as add-on therapy in patients with NYHA class II-III congestive heart failure not controlled following 1 month of therapy with a diuretic or a diuretic plus an angiotensin-converting enzyme (ACE) inhibitor. Sixty-four patients were randomized to receive double-blind treatment with placebo or CHF-1035 2.5, 5 or 10 mg b.i.d. in addition to their existing therapy. Clinical indicators of heart failure showed improvement on 10 mg/day compared to placebo, and certain variables also improved on the highest dose of CHF-1035. Adverse events were reported more frequently on the 20 mg/day dose (1) (Table IX).

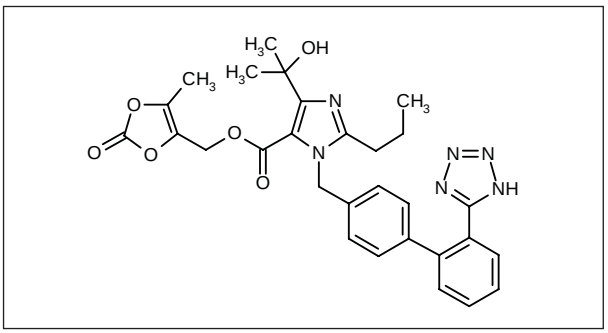
1. Crippa, G., Reyes, A.J., Giogi-Pierfranceschi, M., Meny, M.G., Sverzellati, E. *Pilot clinical study of a new dopaminergic in heart failure.* Eur Heart J 2001, 22(Suppl.): Abst 2745.

Original monograph - Drugs Fut 2001, 26(11): 1046.

Table IX: Clinical study of nolomirole.

Indication	Design	Treatments	N	Conclusions	Ref.
Congestive heart failure	Randomized, double-blind	Nolomirole, 2.5 mg (5/d group) bid x 4 wks Nolomirole, 5 mg (10/d group) bid x 4 wks Nolomirole, 10 mg (20/d group) bid x 4 wks Placebo	64	Clinical indicators of heart failure improved in response to add-on therapy with nolomirole at doses up to 10 mg bid	1

Olmesartan Medoxomil



Before the end of last year, Sankyo and Forest entered into a long-term agreement for the copromotion in the U.S. of olmesartan medoxomil (CS-866, Benicar™), an angiotensin receptor blocker (ARB), for the treatment of hypertension. An NDA is currently under review at the FDA, and subject to approval, the product is scheduled for launch during the first half of 2002. In Europe, the drug will be comarketed by Sankyo's European subsidiary and Menarini. It is undergoing review by the German authorities (1).

In phase III trials, olmesartan medoxomil, when given alone, reduced blood pressure in comparison to placebo in hypertensive patients, and showed a favorable safety profile. A recently completed comparative trial of olmesartan medoxomil *versus* currently available ARBs indicated that olmesartan is better at reducing blood pressure when administered at the respective starting doses. In another comparative trial with the standard angiotensin-converting enzyme (ACE) inhibitor captopril, it displayed statistically greater efficacy and improved tolerability. In particular, the dry cough observed during captopril treatment did not occur with olmesartan medoxomil (2).

Olmesartan exhibited selectivity for the angiotensin II AT_1 receptor binding site in *in vitro* pharmacological models and potent, long-lasting and dose-dependent antihypertensive activity in a variety of rat and dog models of hypertension (3).

An *in vitro* study using microdialysis combined with tandem mass spectrometry examined the hydrolysis of olmesartan in human and rat plasma and hepatic and intestinal microsome preparations. A linear calibration curve was obtained for olmesartan at concentrations ranging from 0.2-20 μM; intraassay precision was 15% or less. Rapid hydrolysis of olmesartan to RNH-6270, the active metabolite, was observed in rat plasma and liver microsomes. Hydrolysis was also rapid in human plasma (complete within 10 min) with a $t_{1/2}$ value of approximately 2 s calculated for undiluted plasma. This was about 20 times more rapid than hydrolysis seen in human liver and intestinal microsomes (4).

An *in vivo* study in nephrectomized spontaneously hypertensive rats with chronic renal failure examined the antihypertensive and renoprotective effects of olmesartan alone or in combination with temocapril. Analysis after 8 weeks of treatment indicated that the organ protective effects of olmesartan, temocapril and combination therapy were related to the magnitude of their respective hypotensive effects (5).

In a rat model of insulin-resistant hypertension, 2 weeks of treatment with olmesartan and cilnidipine equally improved insulin resistance and hypertension (6).

A series of studies conducted to assess the metabolic, pharmacokinetic/pharmacodynamic and safety properties of olmesartan found no clinically significant steady-state pharmacokinetic interactions after coadministration of the drug with digoxin, warfarin or aluminium magnesium hydroxide (7-10). Furthermore, the authors of an open phase I study comparing olmesartan 10 mg/day in 26 patients with varying degrees of renal impairment and 8 healthy volunteers concluded that dose adjustments were unnecessary in patients with mild to moderate renal dysfunction. The drug was well tolerated in all groups (11). Though increased plasma concentrations of olmesartan were found in elderly patients and those with mild and moderate renal and hepatic impairment, dose adjustment for these patients is not considered necessary. Dose adjustments are recommended, however, for patients with severe renal impairment (12). The combined results of two trials indicate that olmesartan is well tolerated in young and elderly hypertensive patients and that dose adjustments in the elderly will probably not be necessary (13).

The safety, tolerability and pharmacokinetics of single and multiple oral doses of olmesartan (10, 20, 40, 80 or 160 mg once daily for 10 days) were determined in 2 double-blind, randomized, placebo-controlled, ascending-dose studies conducted in a total of 70 healthy adult males. In addition, the safety, tolerability and pharmacokinetics of single i.v. doses of RNH-6270 (1, 2, 4, 8, 16 and 22 mg), the active metabolite of olmesartan, were also examined in an open-label, ascending-dose study conducted in 34 healthy male volunteers. Oral olmesartan was safe and well tolerated at doses up to 160 mg/day. Linear pharmacokinetics were obtained following i.v. administration of 1-32 mg RNH-6270 and oral administration of 10-160 mg olmesartan. No drug accumulation was observed with multiple doses (14).

Patients with mild to moderate hypertension were randomized to olmesartan 10 mg once daily (n = 165) or atenolol 50 mg once daily (n = 161) in a double-blind study. Doses could be doubled after 4 weeks if diastolic blood pressure was 90 mmHg or more and/or if it had decreased by < 10 mmHg. After 12 weeks, the treatments were found to be equieffective in lowering diastolic blood pressure, although olmesartan was better than atenolol in reducing systolic blood pressure (15).

During a 12-week, double-blind, randomized trial, 328 patients with moderate to severe hypertension received once-daily olmesartan (10 mg) or atenolol (50 mg) after a run-in period of once-daily hydrochlorothiazide (25 mg). Treatment could be doubled at 4 weeks if blood pressure was not controlled. The treatments were similarly effective in reducing blood pressure and olmesartan was well tolerated in this population (16).

Meta-analysis of 7 double-blind, randomized, placebo-controlled, dose-finding trials of olmesartan (2.5-80 mg) found that the drug was safe and highly effective in lowering blood pressure in over 3000 patients with mild to moderate essential hypertension. Efficacy, but not safety, was dose-related. The agent retained most of its peak effect 24 h after treatment, making it suitable for once-daily dosing. Olmesartan was very well tolerated and had a side effect profile similar to placebo (17-19).

A study conducted in 26 hypertensive outpatients demonstrated the long-term effects of oral olmesartan (5-40 mg once daily for up to 1 year) on blood pressure and the renin-angiotensin-aldosterone system (20).

A multicenter, double-blind, randomized study conducted in 588 patients with essential hypertension compared the hypotensive efficacy of olmesartan (20 mg), losartan (50 mg), valsartan (80 mg) and irbesartan (150 mg) administered for 8 weeks. All treatments were well tolerated, with a similar overall incidence of adverse events in all groups. Olmesartan reduced sitting cuff diastolic blood pressure significantly more than losartan, valsartan and irbesartan; reductions in systolic blood pressure were similar for all treatments. Olmesartan also decreased mean 24-h ambulatory diastolic blood pres-

Table X: Clinical studies of olmesartan medoxomil.

Indication	Design	Treatments	N	Conclusions	Ref.
Healthy Volunteers	Randomized, double-blind, crossover	Digoxin, 0.375 mg po od x 10 d → 0.375 mg po od + olmesartan, 20 mg po od x 7 d Digoxin, 0.375 mg po od x 10 d → 0.375 mg po od + placebo x 7 d	24	The coadministration of olmesartan and digoxin was safe	9
Healthy Volunteers	Randomized, double-blind, crossover	Warfarin, dose adjusted to a Quick test value 1.4-1.8 x 13 d → Olmesartan, 40 mg po od x 7 d Warfarin, dose adjusted to a Quick test value 1.4-1.8 x 13 d → Placebo x 7 d	24	The coadministration of olmesartan and warfarin did not alter coagulation factors and was well tolerated	10
Essential hypertension	Randomized, double-blind, multicenter	Olmesartan, 10-20 mg po od x 12 wks (n = 165) Atenolol, 50-100 mg po od x 12 wks (n = 161)	326	Olmesartan and atenolol showed the same efficacy in reducing diastolic blood pressure but olmesartan was more effective than atenolol in reducing systolic blood pressure in patients with mild to moderate hypertension	15
Essential hypetension	Randomized, double-blind, multicenter	Olmesartan, 10-20 mg po od + Hydrochlorothiazide, 25 mg po od x 12 wks (n = 164) Atenolol, 50-100 mg po od + Hydrochlorothiazide, 25 mg po od x 12 wks (n = 164)	328	Olmesartan and atenolol were equally effective, when added to hydrochlorothiazide, for the treatment of moderate to severe hypertension	16
Essential hypertension	Open	Olmesartan, 5-40 mg po od x 52 wks	26	Olmesartan was safe and effective in the long-term treatment of hypertension by decreasing angiotensin I and II levels	20
Essential hypertension	Randomized, double-blind, multicenter	Olmesartan, 10-20 mg po od x 24 wks + Hydrochlorothiazide (optional), 12.5-25 mg po od (n = 160) Losartan, 50-100 mg po od x 24 wks + Hydrochlorothiazide (optional), 12.5-25 mg po od (n = 156)	316	Olmesartan showed a blood pressure-lowering effect superior to losartan in patients with mild to moderate hypertension	23
Essential hypertension	Randomized double-blind, multicenter	Olmesartan, 5-20 mg po od x 12 wks (n = 148) Captopril, 12.5-50 mg po od x 12 wks (n = 143)	291	Olmesartan showed a superior blood pressure-lowering effect than captopril in patients with mild to moderate hypetension	24

sure significantly more than losartan and valsartan and was slightly more effective than irbesartan. Similarly, olmesartan was significantly more potent in reducing 24-h systolic blood pressure than losartan and valsartan but was equipotent to irbesartan (21).

Three multicenter, double-blind, randomized phase III trials compared several antihypertensive agents in patients with mild to severe hypertension. Olmesartan (5 or 10 mg once daily) reduced blood pressure significantly more effectively than losartan (50 mg once daily) and captopril (12.5 mg b.i.d.), and as effectively as atenolol (50 mg once daily) (22).

Patients with mild to moderate hypertension (n = 316) received olmesartan 10 mg or losartan 50 mg, both once daily, for up to 12 weeks in a multicenter, double-blind, randomized phase III trial. Doses could be doubled if diastolic blood pressure was not controlled and hydrochlorothiazide could be added to the regimen at 12 weeks. Although both agents lowered diastolic blood pressure, the effect of olmesartan was superior (23).

Olmesartan 5 mg once daily and captopril 12.5 mg twice daily were administered to 291 patients with mild to moderate hypertension in a multicenter, double-blind, randomized phase III study. The doses could be doubled at 4 and 8 weeks if diastolic blood pressure was not controlled. After 12 weeks, olmesartan was found to have a greater diastolic blood pressure-lowering effect at trough than captopril (24).

Results of some of the clinical studies discussed above are summarized in Table X.

1. *Sankyo and Menarini to market olmesartan medoxomil for treatment of hypertension in Europe.* DailyDrugNews.com (Daily Essentials) March 27, 2001.

2. *Sankyo and Forest to copromote Benicar in U.S. for treatment of hypertension.* DailyDrugNews.com (Daily Essentials) Dec 14, 2001.

3. Koike, H., Sada, T., Mizuno, M. *In vitro and in vivo pharmacology of olmesartan medoxomil, an angiotensin II type AT_1 receptor antagonist.* J Hypertens 2001, 19(Suppl. 1): S3.

4. Kobayashi, N., Fujimori, I., Watanabe, M., Ikeda, T. *Real-time monitoring of metabolic reactions by microdialysis in combination with tandem mass spectrometry: Hydrolysis of CS-866 in vitro in human and rat plasma, livers, and small intestines.* Anal Biochem 2000, 287(2): 272.

5. Xu, H.L., Yoshida, K., Wu, X.-M., Kohzuki, M. *Effects of CS-866, an angiotensin II receptor antagonist, in 5/6 nephrectomized spontaneously hypertensive rats.* Jpn J Nephrol 2001, 43(7): 580.

6. Hagiwara, M., Takizawa, H., Ura, N., Higashiura, K., Togashi, N., Yamaguchi, K., Shimamoto, K. *Effects of calcium channel blocker and angiotensin receptor blocker on lipid profile and insulin sensitivity in fructose-fed rats.* J Hypertens 2000, 18(Suppl. 4): Abst P13.27.

7. Laeis, P., Püchler, K, Kirch, W. *The pharmacokinetic and metabolic profile of olmesartan medoxomil limits the risk of clinically relevant drug interaction.* J Hypertens 2001, 19(Suppl. 1): S21.

8. Laeis, P., Püchler, K., von Bergmann, K. *The effect of aluminium magnesium hydroxide on the pharmacokinetics of the oral angiotensin II-antagonist olmesartan medoxomil in healthy male volunteers.* J Hypertens 2001, 19(Suppl. 2): Abst P2.177.

9. Laeis, P., Püchler, K., Kirch, W. *The effect of the oral angiotensin II-antagonist olmesartan medoxomil on the safety, tolerability and pharmacokinetics of digoxin in healthy, male subjects.* J Hypertens 2001, 19(Suppl. 2): Abst P2.179.

10. Püchler, K., Laeis, P., Kirch, W. *The effect of the oral angiotensin II antagonist olmesartan medoxomil on the pharmacodynamics, pharmacokinetics and safety of warfarin in healthy, male subjects.* J Hypertens 2001, 19(Suppl. 2): Abst P2.178.

11. Laeis, P., Püchler, K., von Bergmann, K. *A comparative pharmacokinetic, safety and tolerability trial of the oral angiotensin II-antagonist olmesartan medoxomil in subjects with varying degrees of renal impairment and in healthy volunteers.* J Hypertens 2001, 19(Suppl. 2): Abst P2.147.

12. von Bergmann, K., Laeis, P., Püchler, K., Sudhop, T., Schwocho, L.R., Gonzalez, L. *Olmesartan medoxomil: Influence of agent, renal and hepatic function on the pharmacokinetics of olmesartan medoxomil.* J Hypertens 2001, 19(Suppl. 1): S33.

13. Püchler, K., Nussberger, J., Witte, P.U., Laeis, P., Brunner, H.R. *Pharmacokinetic, safety and tolerability studies of the oral angiotensin II-antagonist olmesartan medoxomil in young, elderly and very elderly patients with hypertension.* J Hypertens 2001, 19(Suppl. 2): Abst P2.180.

14. Schwocho, L.R., Masonson, H.N. *Pharmacokinetics of CS-866, a new angiotensin II receptor blocker, in healthy subjects.* J Clin Pharmacol 2001, 41(5): 515.

15. Van Mieghem, W. *A multi-centre, double-blind, efficacy, tolerability and safety study of the oral angiotensin II-antagonist olmesartan medoxomil versus atenolol in patients with mild to moderate essential hypertension.* J Hypertens 2001, 19(Suppl. 2): Abst P2.174.

16. Püchler, K., Laeis, P., Stumpe, K.O. *A comparison of the efficacy and safety of the oral angiotensin II-antagonist olmesartan medoxomil with those of atenolol in patients with moderate to severe hypertension under continuous treatment with hydrochlorothiazide.* J Hypertens 2001, 19(Suppl. 2): Abst P2.175.

17. Püchler, K., Laeis, P., Stumpe, K.O. *Blood pressure response, but not adverse event incidence, correlates with dose of angiotensin II antagonist.* J Hypertens 2001, 19(Suppl. 1): S41.

18. Neutel, J.M. *Clinical studies of CS-866, the newest angiotensin II receptor antagonist.* Am J Cardiol 2001, 87(8A): 37C.

19. Püchler, K., Laeis, P., Stumpe, K.O. *Dose related differences in blood pressure response are not related to adverse event incidence.* J Hypertens 2001, 19(Suppl. 2): Abst P1.191.

20. Ichikawa, S., Takayama, Y. *Long-term effects of olmesartan, an Ang II receptor antagonist, on blood pressure and the renin-angiotensin aldosterone system in hypertensive patients.* Hypertens Res 2001, 24(6): 641.

21. Oparil, S., Williams, D., Chrysant, S.G., Marbury, T.C., Neutel, J. *Comparative efficacy of olmesartan, losartan, valsartan, and irbesartan in the control of essential hypertension.* J Clin Hypertens (Greenwich) 2001, 3(5): 283.

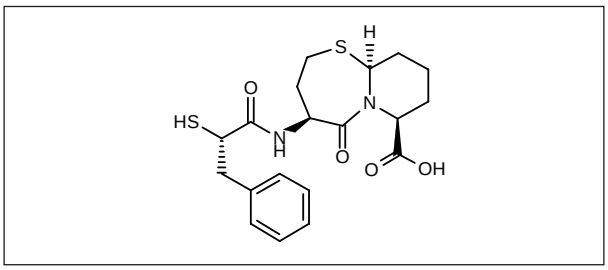
22. Ball, K.J., Williams, P.A., Stumpe, K.O. *Relative efficacy of an angiotensin II antagonist compared with other antihypertensive agents. Olmesartan medoxomil versus antihypertensives.* J Hypertens 2001, 19(Suppl. 1): S49.

23. Ball, K. *A multi-centre, double-blind, efficacy, tolerability and safety study of the oral angiotensin II-antagonist olmesartan medoxomil versus losartan in patients with mild to moderate essential hypertension.* J Hypertens 2001, 19(Suppl. 2): Abst P2.176.

24. Williams, P.A. *A multi-centre, double-blind, efficacy, tolerability and safety study of the oral angiotensin II-antagonist olmesartan medoxomil versus captopril in patients with mild to moderate essential hypertension.* J Hypertens 2001, 19(Suppl. 2): Abst 207.

Original monograph - Drugs Fut 1997, 22(11): 1205.

Omapatrilat



The novel vasopeptidase inhibitor (dual inhibitor of angiotensin-converting enzyme [ACE] and neutral endopeptidase [NEP]) omapatrilat (Vanlev™) from Bristol-Myers Squibb was refiled for approval with the FDA late last year for the treatment of hypertension. The NDA was supported by data from the large OCTAVE (Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril) study in which omapatrilat was compared to the ACE inhibitor enalapril (1-3).

Omapatrilat is also being evaluated for the treatment of heart failure in the OVERTURE (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events) study and for the treatment of isolated systolic hypertension in the OPERA (Omapatrilat in Persons with Enhanced Risk of Atherosclerotic events) study (4). The use of vasopeptidase inhibitors, particularly omapatrilat, for the treatment of systolic hypertension has been claimed in patent literature (5).

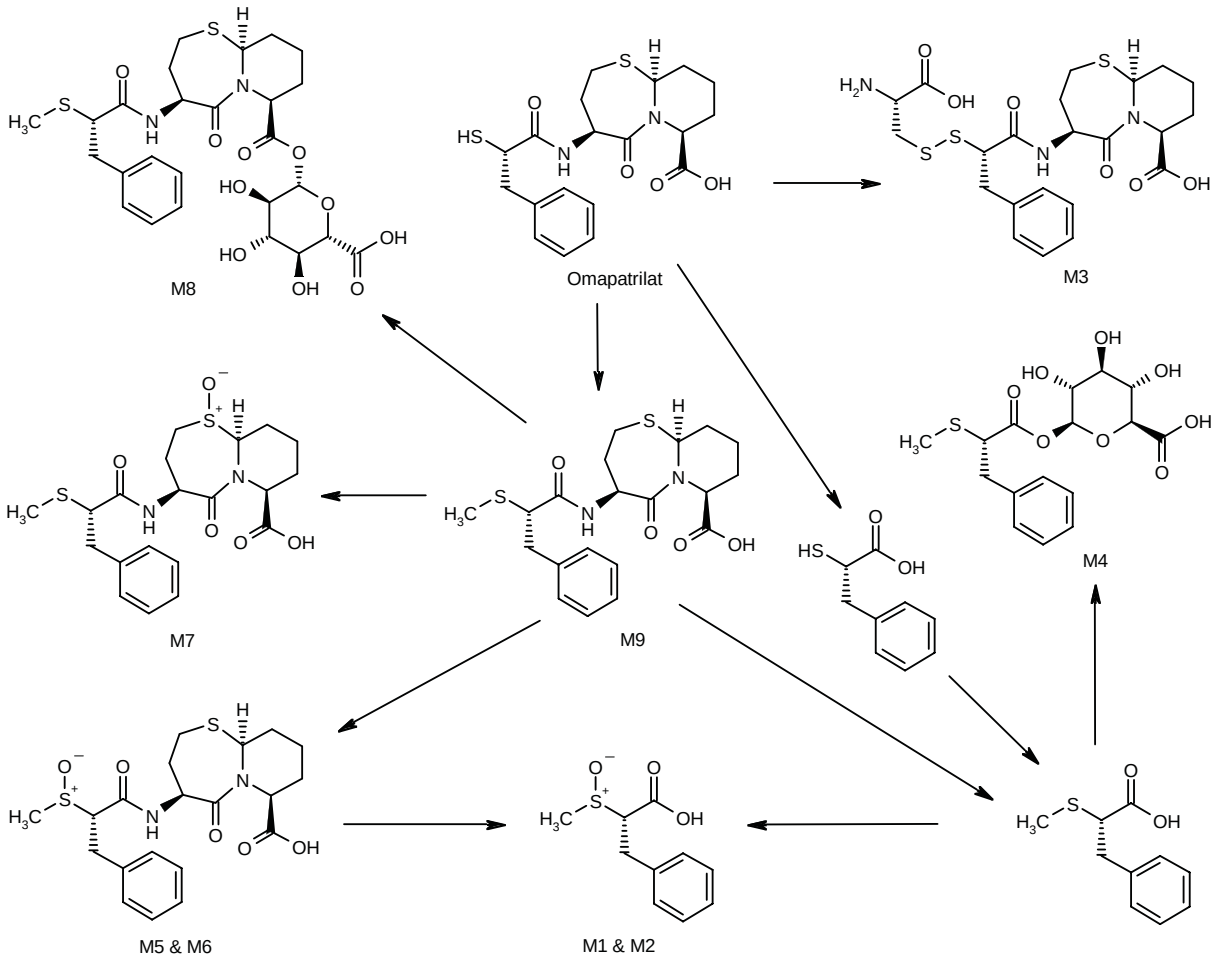
Numerous preclinical studies investigating the effects of omapatrilat in models of heart failure and hypertension have been reported over the last year or so. In rats with coronary heart failure induced by coronary ligation, treatment with the vasopeptidase inhibitor omapatrilat for 3 months was superior to the ACE inhibitor captopril in lowering cardiac preload and afterload, preventing left ventricular remodeling and improving left ventricular function (6). The cardiorenal and humoral effects of omapatrilat were compared to those of fosinopril in a pacing-induced canine model of severe congestive heart failure.

Compared to fosinopril, omapatrilat lowered cardiac filling pressures and inhibited aldosterone activation while maintaining cardiac output and natriuresis. Plasma ANP and BNP were similarly increased in both treatment groups, and plasma cGMP concentrations were higher following omapatrilat administration (7). Treatment of dogs with congestive heart failure with furosemide plus omapatrilat was compared to furosemide plus fosinoprilat. Despite less natriuresis, the therapy with omapatrilat was found to be superior, resulting in lower cardiac filling pressures, maintenance of cardiac output, peripheral vasodilatation, preservation of glomerular filtration rate and delayed activation of aldosterone (8). Omapatrilat was found to enhance left ventricular positive inotropic and lusitropic responses to dobutamine in conscious dogs after pacing-induced heart failure. According to this study, combination of the treatments for heart failure may have additive effects in enhancing left ventricular relaxation and contractile performance (9). In a canine model of mild heart failure, omapatrilat induced a greater natriuretic response than fosinoprilat, while plasma renin activity was increased only in those animals given fosinoprilat. The renal activity of omapatrilat appeared to involve the natriuretic peptide system (10).

Different animal models have been used to investigate the antihypertensive effect of omapatrilat. When administered over 8 weeks, the drug more effectively decreased systolic arterial pressure in spontaneously hypertensive rats (SHR) than in Dahl salt-sensitive rats (11). In another study in Dahl salt-sensitive rats given normal or salt-enriched chow, omapatrilat for 8 weeks restored endothelium-dependent responses to ET-1 and prevented vascular hypertrophy in salt-induced hypertension (12). Both omapatrilat and captopril similarly controlled systolic blood pressure in Dahl salt-sensitive rats, but omapatrilat was superior to captopril in improving endothelium-dependent relaxation (13). The long-term effects of omapatrilat by daily gavage on blood pressure and cardiac function were explored in SHR and compared to fosinopril. The effects of omapatrilat were superior to those of fosinopril and included potent and stable antihypertensive activity, reduction of left ventricular mass and improved cardiac function (14). The effects of omapatrilat on resistance artery structure and function were examined in DOCA/salt hypertensive rats and compared to enalapril for 3 weeks. The ACE inhibitor enalapril was ineffective, indicating that NEP inhibition contributed significantly to omapatrilat's potent antihypertensive activity, improvement of endothelial function and reduction of the media/lumen ratio of resistance arteries. Such effects may protect against the end-organ damage associated with severe hypertension (15). Stroke-prone SHR were treated with omapatrilat or vehicle for 8 weeks and the effects on blood pressure, endothelial function and cardiac hypertrophy were determined. Endothelial function in carotid arteries, but not in mesenteric arteries, was significantly improved by omapatrilat. Omapatrilat produced a significant reduction in systolic blood pressure and in the development of cardiac hypertrophy (16). The effects on the coronary microvasculature of SHR were compared after 10 weeks of treatment with omapatrilat, irbesartan or fosinopril. While omapatrilat significantly decreased cardiac arteriolar growth and capillary rarefaction in the left ventricle, the other treatments affected only arteriolar growth. Omapatrilat also brought about greater improvement in microvascular remodeling (17). In SHR with normal and elevated sodium intake, 15 days of oral omapatrilat normalized blood pressure without affecting the renal capacity to manage excess sodium (18). In salt-sensitive rats on a high-salt diet, omapatrilat and captopril lowered systolic blood pressure to a similar degree, but omapatrilat was superior in normalizing endothelium-dependent relaxation in the mesenteric arteries (19). The effects of omapatrilat and captopril on ET-1-mediated vascular function were investigated in salt-induced hypertensive rats. Omapatrilat appeared to normalize cardiovascular control systems, restoring renovascular endothelin-converting enzyme (ECE) activity and endothelin levels (20). Calcitonin gene-related peptide (CGRP) did not appear to contribute to the antihypertensive activity of omapatrilat in nephrectomy/salt-induced hypertensive rats. Omapatrilat not only reduced blood pressure in this model of hypertension, but also appeared to prevent stimulation of the efferent vasodilator function of perivascular sensory nerves (21). *In vitro*, omapatrilat exhibited a potent vasorelaxant effect through a nitric oxide (NO)-dependent pathway in aortic rings isolated from SHR (22).

In a study in rats with coronary ligation-induced myocardial infarction (MI), both omapatrilat and captopril were shown to markedly improve post-MI survival, cardiac function and cardiac remodeling. Furthermore, although the two classes of drugs had some different activities, the addition of NEP inhibition to ACE inhibition did not appear to enhance the cardioprotective effect of omapatrilat in this model (23). Cardioprotection with omapatrilat was superior to with ramipril in rat hearts following total ischemia. The effects of omapatrilat appeared to be mediated by endgenous cardiac bradykinin and endogenous natriuretic peptides (24). Omapatrilat also provided cardioprotection in rat hearts via augmentation of a subthreshold ischemic preconditioning stimulus through a bradykinin-mediated mechanism (25). In another study in wild-type and B_2 kinin receptor knockout mice subjected to MI, results indicated that kinins are involved in the cardioprotective effects and indicated that omapatrilat was not superior to ramipril (26). In an *in vitro* study using ventricular membranes prepared from hearts from normal donors and patients with ischemic or dilated cardiomyopathy, omapatrilat was significantly more effective in increasing the half-life of bradykinin in cardiomyopathic tissue compared to normal tissue, in contrast to ramiprilat (27). In rabbits fed a 1% cholesterol diet, omapatrilat was found to inhibit atheroma formation and to selectively enhance ANP-mediated but not C-type natriurietic peptide-mediated vasorelaxation (28). In apolipoprotein E-deficient mice, omapatrilat, unlike candoxatril, dose-dependently protected the mice from fatty streak deposit

Scheme 1: Metabolism of Omapatrilat



(29). Using a rat model of MI, omapatrilat, but not captopril or SQ-28603, significantly reduced left ventricular BNP mRNA levels. Omapatrilat was also more effective in preventing activation of cardiomyocyte apoptosis and it was more effective than captopril in preventing myocardial hypertrophy (30). Omapatrilat was tested in a rabbit model of atherosclerosis and was found to reduce atherosclerotic plaque surface area in the aorta and to enhance vasorelaxation to ANP in isolated thoracic aorta rings. Vasorelaxation to CNP in the aortic rings was not enhanced (31).

Extensive metabolism of the drug was seen in a study conducted in 12 subjects administered a single dose of [^{14}C]-omapatrilat of 50 mg p.o. (2 μCi/ml). The major metabolites detected in plasma were *S*-methyl-omapatrilat and its acyl glucuronide and (*S*)-2-(methylthio)-3-phenylpropionic acid, with omapatrilat accounting for < 3% of plasma radioactivity. No unchanged drug was found in urine, over half of the radioactivity being in the form of the diastereomers and the acyl glucuronide of (*S*)-2-(methylthio)-3-phenylpropionic acid (32). Scheme 1.

In a randomized, crossover study of i.v. (20 mg) and oral (50 mg) omapatrilat in 12 healthy volunteers, the absolute oral bioavailability of the drug was, on average, 31%. Oral omapatrilat was again found to undergo substantial first-pass metabolism and its metabolites were primarily eliminated in the urine (33).

The hemodynamics and safety of single oral doses of omapatrilat (1, 2.5, 5, 10, 25 and 50 mg) were evaluated in a randomized, double-blind, placebo-controlled study in patients with heart failure. The drug was well tolerated and produced dose-related reductions in pulmonary capillary wedge pressure, mean arterial pressure and systemic vascular resistance. Small increases in cardiac index and stroke volume index were also noted (34).

Patients (n = 348) with stable effort-induced angina pectoris participating in a multicenter, randomized, double-blind trial of omapatrilat received 10 mg of the study

Table XI: Clinical studies of omapatrilat.

Indication	Design	Treatments	N	Conclusions	Ref.
Chronic heart failure	Randomized, double-blind, multicenter	Omapatrilat, 1 mg po (n = 11) Omapatrilat, 2.5 mg po (n = 13) Omapatrilat, 5 mg po (n = 12) Omapatrilat, 10 mg po (n = 15) Omapatrilat, 25 mg po (n = 15) Omapatrilat, 50 mg po (n = 14) Placebo (n = 33)	151	Omapatrilat induced dose-related improvements in hemodynamic parameters in patients with heart failure. It induced dose-related reductions in pulmonary capillary wedge pressure, mean arterial pressure and systemic vascular resistance and increases in atrial natriuretic peptide and cGMP levels	37
Hypertension	Randomized, double-blind, multicenter	Hydrochlorothiazide, 25 mg po od x 4 wks → Hydrochlorothiazide, 25 mg po od + Omapatrilat, 10-20 mg x 8 wks (n = 93) Hydrochlorothiazide, 25 mg po od x 4 wks → Hydrochlorothiazide, 25 mg po od + Omapatrilat, 20-40 mg x 8 wks (n = 90) Hydrochlorothiazide, 25 mg po od x 4 wks → Hydrochlorothiazide, 25 mg po od + Placebo x 8 wks (n = 91)	657	Omapatrilat plus hydrochlorothiazide combination was well tolerated and effective in hypertensive patients	38
Angina pectoris	Randomized double-blind, multicenter	Omapatrilat, 10-80 mg x 3 wks Placebo	348	Omapatrilat was effective as antiischemic and antianginal treatment in stable effort-induced angina pectoris	39

drug before titration (as tolerated) to 40 and 80 mg at 1-week intervals. Exercise treadmill tests were performed at baseline and after 2 weeks on the maximum drug dose and significant antiischemic and antianginal activity was noted (35).

A randomized, placebo-controlled study evaluated the combined treatment of omapatrilat plus hydrochlorothiazide in 274 patients with severe hypertension not controlled by hydrochlorothiazide alone. Statistically significant reductions in trough diastolic and systolic blood pressures were seen, laboratory parameters did not change significantly and the treatment had an adverse event profile similar to placebo (36).

Another clinical study examined the safety and efficacy of omapatrilat (10-40 mg) combined with hydrochlorothiazide (25 mg) in 657 patients with mild to severe hypertension not responding to hydrochlorothiazide alone. The combination proved effective and well tolerated (37) (Table XI).

The effects of omapatrilat 40 and 20 mg were assessed in a double-blind, randomized, placebo-controlled study in 723 coronary heart disease patients. Both omapatrilat doses had similar effects in lowering systolic blood pressure. The drug also reduced ACE levels and increased plasma renin activity, atrial natriuretic peptide, endothelin and homocysteine levels (38) (Table XI).

A neurohormone substudy of the IMPRESS trial examined omapatrilat treatment in 120 patients with chronic stable heart failure. Analysis revealed that the drug was associated with higher levels of C-terminal atrial natriuretic peptide (C-ANP) when compared with patients administered lisinopril; C-ANP was the most powerful of the neurohormones studied in predicting clinical outcome (39) (Table XI).

A randomized, dose-ranging (2.5, 5, 10, 20 or 40 mg for 12 weeks) study conducted in 48 patients with chronic heart failure (NYHA class II/III; left ventricular ejection fraction = 40% or less) showed the efficacy of the higher doses of omapatrilat in improving ventricular-vascular coupling and arterial function. Higher doses resulted in significant reductions in systolic and mean arterial pressures and dose-dependent improvements in ventricular-arterial coupling were seen. Treatment with the higher doses also increased the maximum forearm vasodilator response during reactive hyperemia and ANP levels (40).

1. *BMS submits NDA for Vanlev for the treatment of hypertension.* DailyDrugNews.com (Daily Essentials) Dec 20, 2001.

2. *Bristol-Myers Squibb highlights significant developments during 2000.* DailyDrugNews.com (Daily Essentials) Jan 30, 2001.

3. *Patient enrollment in OCTAVE hypertension trial nears completion.* DailyDrugNews.com (Daily Essentials) Jan 19, 2001.

4. McClean, D.R., Ikram, H., Garlick, A.H., Crozier, I.G. *Effects of omapatrilat on systemic arterial function in patients with chronic heart failure.* Am J Cardiol 2001, 87(5): 565.

5. Reeves, R.A. et al. (Bristol-Myers Squibb Co.). *Vasopeptidase inhibitors to treat isolated systolic hypertension.* WO 0174348.

6. Mulder, P., Viguier, D., Richard, V., Henry, J.-P., Renet, S., Moran, S., Thuillez, C. *Synergy between ACE and NEP inhibition by omapatrilat in terms of hemodynamics, cardiac remodeling and function in rats with chronic heart failure.* Circulation 2001, 104(17, Suppl. 2): Abst 2076.

7. Lee, S., Cataliotti, A., Llarsen, A., Christiansen, D., Reed, C., Harty, G., Burnett, J. *Cardiorenal and humoral actions of chronic vasopeptidase vs.*

angiotensin converting enzyme inhibition in experimental severe heart failure. Eur J Heart Fail 2001, 3(Suppl. 1): S19.

8. Cataliotti, A., Chen, H.H., Boerrigter, G., Reed, C.L., Costello, L.C. *Acute diuretic therapy with vasopeptidase inhibition is superior to diuretic with ACE inhibition in preserving cardiorenal function in experimental CHF.* Circulation 2001, 104(17, Suppl. 2): Abst 957.

9. Hasegawa, H., Cheng, H.-J., Zhang, Z.-S., Morimoto, A., Wannenburg, T., Little, W.C., Cheng, C.-P. *Omapatrilat enhances cardiac positive inotropic and lusitropic responses to dobutamine in heart failure: Assessment by pressure-volume analysis.* Circulation 2001, 104(17, Suppl. 2): Abst 2696.

10. Chen, H.H., Lainchbury, J.G., Matsuda, Y., Harty, G.J., Burnett, J.C. Jr. *Endogenous natriuretic peptides participate in renal and humoral actions of acute vasopeptidase inhibition in experimental mild heart failure.* Hypertension 2001, 38(2): 187.

11. de las Heras, N., Vázquez-Pérez, S., Cediel, E., Sanz-Rosa, D., Navarro-Cid, J., Vázquez-Cruz, B., Ruliope, L.M., Cachofeiro, V., Lahera, V. *Effects of omapatrilat treatment on endothelila dysfunction in spontaneously hypertensive (SHR) and Dahl salt sensitive (DSS) rats.* J Hypertens 2001, 19(Suppl. 2): Abst P3.64.

12. Quaschning, T., d'Uscio, L.V., Shaw, S., Shaw, S.H.J., Ruschitzka, F., Luscher, T.F. *Vasopeptidase inhibition restores renovascular endothelial dysfunction in salt-induced hypertension.* J Am Soc Nephrol 2001, 12(11): 2280.

13. Quaschning, T., d'Uscio, L.V., Shaw, S., Luscher, T.F. *Vasopeptidase inhibition exhibits endothelial protection in salt-induced hypertension.* Hypertension 2001, 37(4): 1108.

14. Wei, C., Dong, Y., Shaffer, E., Liao, W.C. *The cardiovascular actions of omapatrilat in spontaneously hypertensive rats.* J Hypertens 2001, 19(Suppl. 2): Abst P1.34.

15. Pu, Q., Schiffrin, E.L. *Effect of dual inhibition of angiotensin converting enzyme and neutral endopeptidase on blood pressure and resistance arteries of deoxycorticosterone acetate-salt hypertensive rats.* J Hypertens 2001, 19(Suppl. 2): Abst P3.57.

16. Graham, D., Hamilton, C., Beattie, E., Spiers, A., Dominiczak, A.F. *Effects of the vasopeptidase inhibitor, omapatrilat, on endothelial function and cardiac hypertrophy in the stroke-prone spontaneously hypertensive rat.* J Hypertens 2001, 19(Suppl. 2): Abst 2A.5.

17. Pu, Q., Larouche, I., Schiffrin, E.L. *Effect of dual inhibition of angiotensin converting enzyme (ACE) and neutral endopeptidase (NEP) on coronary microvasculature in SHR*. Circulation 2001, 104(17, Suppl. 2): Abst 102.

18. Morazo, P., Fortepiani, L.A., Clara Ortiz, M., Atucha, N.M., Garcia-Estan, J. *Omapatrilat normalizes renal function curve in spontaneously hypertensive rats.* BMC Pharmacol 2001, 1(1): 5.

19. d'Uscio, L.V., Quaschning, T., Burnett, J.C. Jr., Luscher, T.F. *Vasopeptidase inhibition prevents endothelial dysfunction of resistance arteries in salt-sensitive hypertension in comparison with single ACE inhibition.* Hypertension 2001, 37(1): 28.

20. Quaschning, T., d'Uscio, L.V., Shaw, S., Viswambharan, H., Ruschitzka, F.T., Luscher, T.F. *Chronic vasopeptidase inhibition restores endothelin-converting enzyme activity and normalizes endothelin levels in salt-induced hypertension.* Nephrol Dial Transplant 2001, 16(6): 1176.

21. Supowit, S.C., Zhao, H., Wang, D.H., DiPette, D.J. *Omapatrilat in subtotal nephrectomy-salt hypertension: Role of calcitonin gene-related peptide.* Hypertension 2001, 38(3, Part 2): 697.

22. Jemal, M., Khan, S., Teitz, D.S., McCafferty, J.A., Hawthorne, D.J. *LC/MS/MS determination of omapatrilat, a sulfhydryl-containing vasopeptidase inhibitor, and its sulfhydryl- and thioether-containing metabolites in human plasma.* Anal Chem 2001, 73(22): 5450.

23. Lapointe, N., Blais, C. Jr., Adam, A., Sirois, M., Clement, R., Gosselin, H., Rouleau, J.L. *Cardioprotective effect of vasopeptidase inhibitors in the infarcted and remodeling rat heart.* J Am Coll Cardiol 2001, 37(2, Suppl. A): 317A.

24. Dumoulin, M.J., Lamontagne, D., Burnett, J., Heubein, D., Yamaguchi, N., Adam, A. *Respective role of endogenous kinins and natriuretic peptides in the cardioprotective effect of omapatrilat following total heart ischaemia.* Eur Heart J 2001, 22(Suppl.): Abst P394.

25. Baxter, G.F., Ebrahim, Z., Yellon, D.M. *Omapatrilat, a vasopeptidase inhibitor, lowers the threshold for induction of ischaemic preconditioning through a bradykinin-mediated mechanism.* Eur Heart J 2001, 22(Suppl.): Abst 349.

26. Xu, J., Carretero, O.A., Liu, Y.-H., Shesely, E.G., Yang, F., Yang, X.-P. *Role of kinins and natriuretic peptides in the cardioprotective effect of omapatrilat in mice with MI.* Circulation 2001, 104(17, Suppl. 2): Abst 1347.

27. Blais, C. Jr., Fortin, D., Rouleau, J.-L., Molinaro, G., Adam, A. *Protective effect of omapatrilat, a vasopeptidase inhibitor, on the metabolism of bradykinin in normal and failing human hearts.* J Pharmacol Exp Ther 2000, 295(2): 621.

28. Cataliotti, A., Leskinen, H., Jougasaki, M., Sandberg, S.M., Larsen, A., Malatino, L.S., Burnett, J.C. Jr. *Omapatrilat reduces atheroma formation and enhances ANP mediated vasorelaxations in an experimental model of atherosclerosis.* J Hypertens 2001, 19(Suppl. 2): Abst P2.46.

29. Arnal, J.F., Castano, C., Maupas, E., Mugniot, A-, Darblade, B., Gourdy, P., Michel, J.B., Bayard, F. *Omapatrilat, a dual angiotensin-converting enzyme and neutral endopeptidase inhibitor, prevents fatty streak deposit in apolipoprotein E-deficient mice.* Atherosclerosis 2001, 155(2): 291.

30. Backlund, T., Eriksson, A., Vuolteenaho, O., Nieminen, M.S., Voipio-Pukki, L.-M., Laine, M., Tikkanen, I., Grönholm, T., Saraste, A., Palojoki, E. *Dual NEP/ACE inhibition is superior to selective ACE inhibition in preventing myocardial hypertrophy after experimental myocardial infarction in rat.* Eur Heart J 2001, 22(Suppl.): Abst 902.

31. Cataliotti, A., Leskinen, H., Jougasaki, M., Sandberg, S.M., Heublein, D.M., Malatino, L.S., Harty, G.J., Lee, S.C., Burnett, J.C. *Vasopeptidase inhibition with omapatrilat reduces atheroma formation and enhances ANP mediated vasorelaxations in an experimental model of atherosclerosis independent of cholesterol lowering.* Eur J Heart Fail 2001, 3(Suppl. 1): S9.

32. Iyer, R.A., Mitroka, J., Malhotra, B., Bonacorsi, S., Waller, S.C., Rinehart, J.K., Roongta, V.A., Kripalani, K. *Metabolism of [^{14}C]-omapatrilat, a sulfhydryl-containing vasopeptidase inhibitor in humans.* Drug Metab Dispos 2001, 29(1): 60.

33. Wei, C., Lin, R., Chen, L., Dong, Y., McLaughlin, J.S. *Omapatrilat is a potent vasodilator in hypertensive rats through nitric oxide pathway.* J Hypertens 2001, 19(Suppl. 2): Abst P3.48.

34. Malhotra, B.K., iyer, R.A., Soucek, K.M., Behr, D., Liao, W., Mitroka, J.G., Kaul, S., Cohen, M.B., Knupp, C.A. *Oral bioavailability and disposition of [^{14}C]-omapatrilat in healthy subjects.* J Clin Pharmacol 2001, 41(8): 833.

35. Ferdinand, K.C. *Advances in hypertensive combination therapy: Benefits of low-dose thiazide diuretics in conjunction with omapatrilat, a vasopeptidase inhibitor.* J Clin Hypertens (Greenwich) 2001, 3(5): 307.

36. McMahon, S., Tonkin, A., Neal, B., Richards, M., Simes, J., Wicken, D., Murphy, J. *Effects of omapatrilat on blood pressure and neurohormone levels among 723 individuals with coronary heart disease – The PACIFIC study.* Circulation 2001, 104(17, Suppl. 2): Abst 2845.

37. Klapholz, M., Thomas, I., Eng, C., Iteld, B.J., Ponce, G.A., Niederman, A.L., Bilsker, M., Heywood, J.T., Synhorst, D. *Effects of omapatrilat on hemodynamics and safety in patients with heart failure.* Am J Cardiol 2001, 88(6): 657.

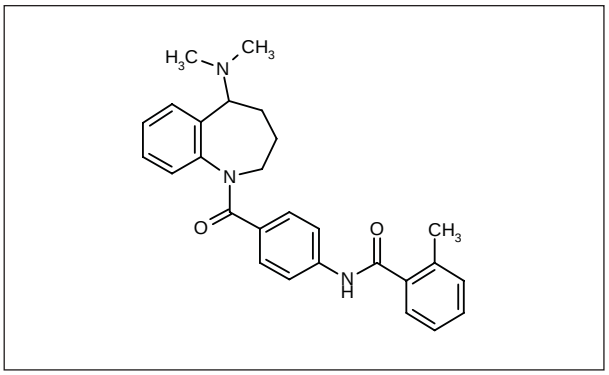
38. Ferdinand, K., Saini, R., Lewin, A., Yellen, L., Barbosa, J.A., Kushnir, E. *Efficacy and safety of omapatrilat with hydrochlorothiazide for the treatment of hypertension in subjects nonresponsive to hydrochlorothiazide alone.* Am J Hypertens 2001, 14(8, Part 1): 788.

39. Lawrence, J.H., Ivleva, A.I., Chaitman, B.R., Shyyakhto, E., Ujda, M., Lenis, J., Toth, C., Stieber, D., Reisin, L., Pangerl, A. *Omapatrilat: Novel vasopeptidase inhibitor with anti-ischaemia and anti-anginal activity in a placebo-controlled trial in stable, effort-induced angina pectoris.* Eur Heart J 2001, 22(Suppl.): Abst P1608.

40. Sheth, T., Parker, T., Block, A., Wian, C., Rouleau, J. *Natriuretic peptides in chronic stable heart failure patients treated with omapatrilat, a vasopeptidase inhibitor: The IMPRESS neurohormone substudy.* Circulation 2001, 104(17, Suppl. 2): Abst 3589.

Original monograph - Drugs Fut 1999, 24(3): 269.

OPC-31260

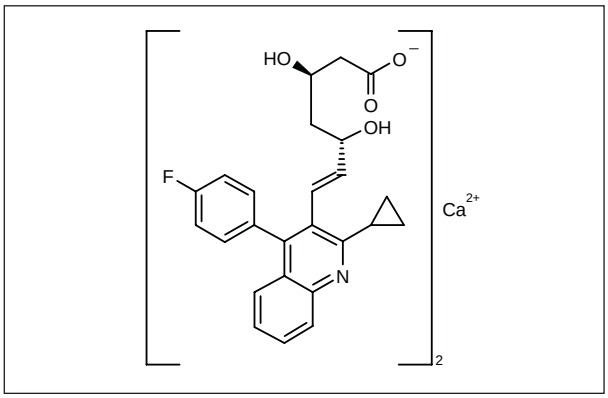


Otsuka's OPC-31260, a nonpeptide vasopressin V_2 receptor antagonist with diuretic properties currently in phase II trials for the treatment of heart failure, has been designated an orphan drug by the Japanese regulatory authorities for improving hyponatremia in the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) (1).

1. *Compound for SIADH designated an orphan drug in Japan.* DailyDrugNews.com (Daily Essentials) Oct 25, 2001.

Original monograph - Drugs Fut 1993, 18(9): 802.

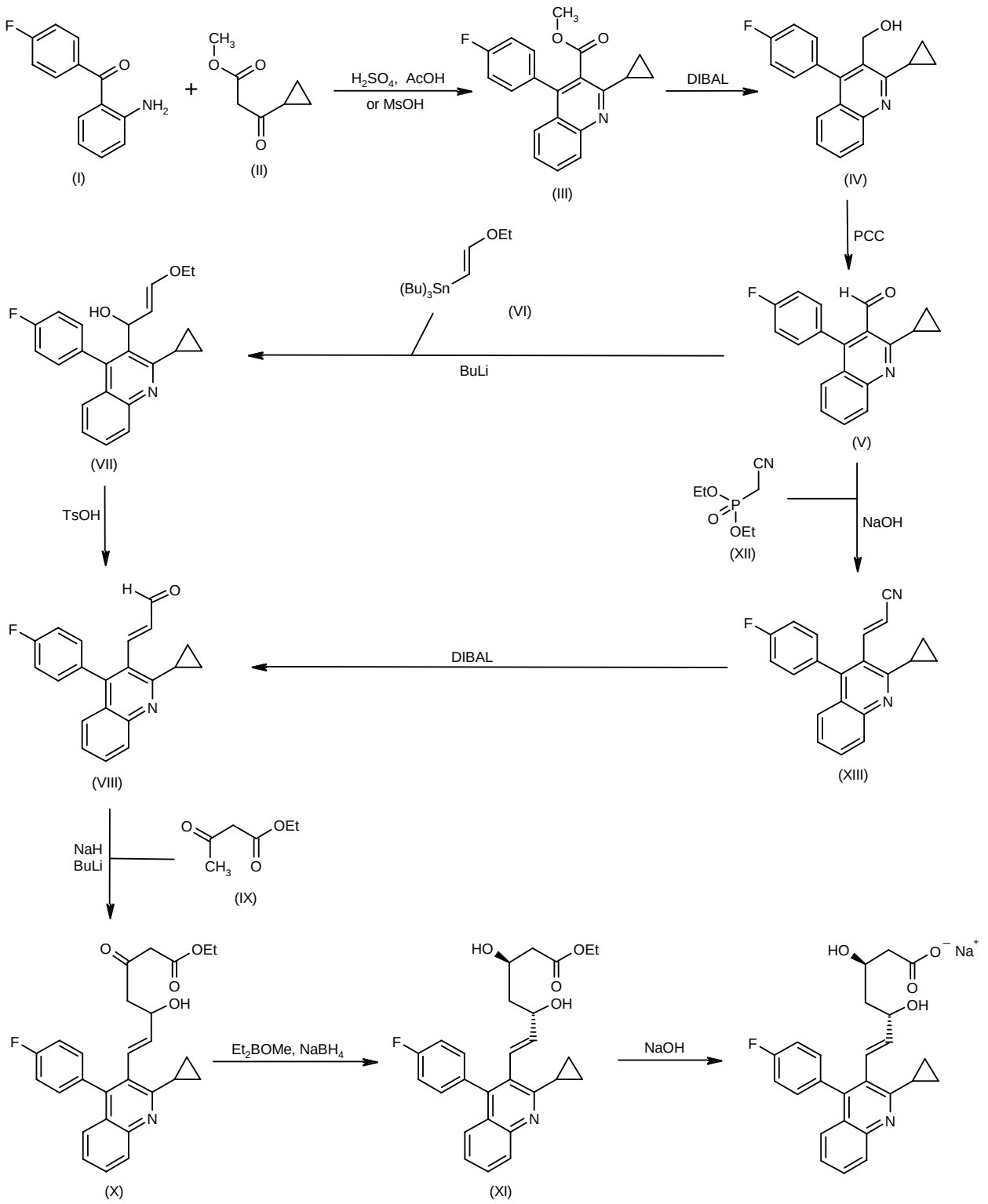
Pitavastatin Calcium



Pitavastatin (itavastatin, NK-104) is a new lipid-lowering statin from Kowa. SkyePharma has signed a contract with Kowa for the scale-up and manufacturing of phase III clinical batches of the drug. A marketing application for the drug has been filed in Japan. Once approved, the product will be copromoted by Sankyo in the U.S. and in Europe by a Kowa affiliate and Negma (1).

A synthesis of pitavastatin has been reported: Cyclization of 2-amino-4'-fluorobenzophenone (I) with 3-cyclopropyl-3-oxopropionic acid methyl ester (II) by means of H_2SO_4 in refluxing acetic acid or methanesulfonic acid in refluxing benzene gives 2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-carboxylic acid methyl ester (III), which is reduced with DIBAL in toluene to yield the carbinol (IV). Oxidation of compound (IV) with PCC and AcONa in dichloromethane affords carbaldehyde (V), which is condensed with tributylstannane (VI) by means of BuLi in THF to provide the enol ether (VII). Hydrolysis of (VII) by means of TsOH in THF/water gives the unsaturated carbaldehyde (VIII), which is condensed with acetoacetic ester (IX) by means of NaH and BuLi in THF to yield the 5-hydroxy-3-oxoheptenoic ester derivative (X). Stereoselective reduction of the oxo group of (X) by means of diethylmethoxyborane and $NaBH_4$ in THF/methanol gives the racemic *syn*-dihydroxy compound (XI) in a *syn/anti* ratio of 98:2. Finally, compound (XI) is hydrolyzed with NaOH in aqueous ethanol to yield racemic pitavastatin sodium. Alternatively, the unsaturated carbaldehyde (VIII) can also be obtained by reaction of carbaldehyde (V) with phosphonate (XII) by means of

Scheme 2: Synthesis of Pitavastatin Sodium



NaOH in toluene/water to give the unsaturated nitrile (XIII), which is finally reduced with DIBAL in toluene to afford the target carbaldehyde (VIII) (2). Scheme 2.

Experiments in monocytic THP-1 cells incubated in the presence of pitavastatin demonstrated that the drug modulates the MCP-1-induced phenotypic change in the monocyte-endothelium interaction, possibly accounting for the antiinflammatory effects of statins (3).

Pitavastatin was found to inhibit cholesterol synthesis in HepG2 cells, which appeared to be correlated with increased LDL receptor number (4).

Experimental evaluation of the inhibition of hepatic sterol synthesis by pitavastatin *in vitro* determined that this activity results from selective inhibition of HMG-CoA reductase in the liver (5).

In a study of the mechanisms by which pitavastatin may reduce cardiovascular events, investigators found that the drug reduced VCAM-1 expression in endothelial cells, and in macrophages it decreased CD36 mRNA in cells incubated with oxidized LDL, reduced basal and lipopolysaccharide (LPS)-induced tissue factor activity and inhibited basal and LPS-induced metalloproteinase-9 expression (6).

A study in guinea pigs compared the hypolipidemic effects of pitavastatin with simvastatin, pravastatin, fluvastatin, cerivastatin and atorvastatin following 2 weeks of oral treatment. Although all statins dose-dependently reduced total cholesterol, title compound produced the most marked effect. Significant decreases in triglycerides and liver cholesterol content were only observed with pitavastatin and atorvastatin. Simvastatin and pravastatin significantly increased liver triglyceride content. Simvastatin increased triglyceride content in liver endoplasmic reticulum while pitavastatin had only slight effects. Although simvastatin increased activity of microsomal triglyceride transfer protein (MTP), pitavastatin had no effect (7).

It was concluded from a series of studies in rats that the triglyceride-lowering effects of pitavastatin after a meal are due to suppression of chylomicron triglyceride secretion via a reduction in intestinal MTP activity (8).

In guinea pigs given pitavastatin 3 mg/kg p.o. daily for 2 weeks followed by overnight fasting and fresh cream, postprandial triglyceride levels were lowered by acceleration of remnant clearance and not via suppression of chylomicron-triglyceride secretion as had been shown in rats (9).

The hypocholesterolemic effects of pitavastatin (0.1, 0.3 and 1 mg/kg p.o. for 2 weeks starting at week 4) were studied in guinea pigs fed a high-fat diet for 6 weeks. Treatment resulted in decreases in LDL cholesterol of 11%, 27% and 32% for the respective doses. In comparison, atorvastatin at doses 10 times higher (3 and 10 mg/kg) decreased these levels by 25% and 39%, respectively. LDL clearance was also improved on pitavastatin (24% at 1 mg/kg *vs*. 47% at 10 mg/kg atorvastatin), as was LDL composition (10).

Researchers evaluated the effects of pitavastatin on the expression of osteopontin in cultured rat aortic smooth muscle cells and in the aorta and kidneys of diabetic rats treated at a dose of 3 mg/kg/day for 7 days. Pitavastatin was found to reduce osteopontin mRNA and protein expression *in vitro* and *in vivo*, suggesting the possibility of its use in diabetic patients with hypercholesterolemia (11, 12).

In vitro studies revealed that glucuronidation through UGT is the principal means by which pitavastatin lactone is formed from pitavastatin and that pitavastatin lactone is unlikely to cause drug-drug interactions. Possibly due to lower bioavailability in monkeys, pitavastatin metabolism was found to differ between monkeys and humans (13, 14).

Extensive pharmacological studies of pitavastatin in mice, rats, guinea pigs and dogs demonstrated that the agent does not cause any serious acute adverse events (15).

Combinations of an HMG-CoA reductase inhibitor such as pitavastatin and an ACAT inhibitor demonstrated a synergistic effect in lowering plasma cholesterol and triglyceride levels according to recent patent literature (16).

1. *SkyePharma to manufacture NK-104 for Kowa*. DailyDrugNews.com (Daily Essentials) Feb 13, 2001.

2. Suzuki, M., Iwasaki, H., Fujikawa, Y., Kitahara, M., Sakashita, M., Sakoda, R. *Synthesis and biological evaluations of quinolone-based HMG-CoA reductase inhibitors.* Bioorg Med Chem 2001, 9(10): 2727.

3. Yoshida, M., Nakamura, Y., Kawakami, A., Yasukochi, Y. *A novel HMG CoA reductase inhibitor, NK-104, inhibits MCP-1 induced THP-1 transition from rolling to stable adhesion under physiological flow conditions.* Circulation 2001, 104(17, Suppl. 2): Abst 253.

4. Nakagawa, S., Tanabe, S., Tamaki, T., Wada, Y., Yokoo, N., Sato, F. *Effect of NK-104, an HMG-CoA reductase inhibitor on lipid metabolism in HepG2 cells.* Jpn Pharmacol Ther 2001, 29(1): 51.

5. Kohima, J., Oshima, T., Yoneda, M., Sawada, H., Kawagoe, J. *Effect of biliary excretion on the pharmacokinetics of pitavastatin (NK-104) in the dog.* 14th Int Symp Drugs Affect Lipid Metab (Sept 9-12, New York) 2001, 121.

6. Haijar, D.P., Nicholson, A.C., Han, J., Summers, B., Feirt, N., Gotto, A.C. Jr. *NK-104 inhibits expression of VCAM-1 by endothelial cells and CD36, tissue factor and MMP-9 by macrophages.* 14th Int Symp Drugs Affect Lipid Metab (Sept 9-12, New York) 2001, 104.

7. Suzuki, H., Yamazaki, H., Aoki, T., Tamaki, T., Sato, F., Kitahara, M., Saito, Y. *Hypolipidemic effect of NK-104 and other 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in guinea pigs.* Arzneim-Forsch Drug Res 2001, 51(1): 38.

8. Tamaki, T., Aoki, T., Yoshinaka, Y., Suzuki, H., Sato, F., Kitahara, M., Saito, Y. *Effects of NK-104 in rat model of postprandial lipaemia.* Arterioscler Thromb Vasc Biol 2001, 21(4): Abst 68.

9. Fujino, H., Yamada, I., Shimada, S., Yoneda, M. *Studies on metabolic fate of pitavastatin (NK-104), a new inhibitor of HMG-CoA reductase – Does glucuronidation mediate the lactonization of pitavastatin?* 14th Int Symp Drugs Affect Lipid Metab (Sept 9-12) 2001, 120.

10. Aoki, T., Yamazaki, H., Suzuki, H., Tamaki, T., Sato, F., Kitahara, M., Saito, Y. *Cholesterol-lowering effect of NK-104, a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor, in guinea pig model of hyperlipidemia.* Arzneim-Forsch Drug Res 2001, 51(3): 197.

11. Mori, S., Takemoto, M., Kitahara, M., Yokote, K., Asaumi, S., Take, A., Saito, Y. *NK-104, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, reduces osteopontin expression by rat aortic smooth muscle cells.* Circulation 2001, 104(17, Suppl. 2): Abst 1024.

12. Takemoto, M., Kitahara, M., Yokote, K., Asaumi, S., Take, A., Saito, Y., Mori, S. *NK-104, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, reduces osteopontin expression by rat aortic smooth muscle cells.* Br J Pharmacol 2001, 133(1): 83.

13. Fujino, H., Yamada, I., Shimada, S., Yoneda, M. *Studies on metabolic fate of pitavastatin (NK-104), a new inhibitor of HMG-CoA reductase – Does glucronidation mediate the lactonization of pitavastatin?* Xenobiotic Metab Dispos 2001, 16(Suppl.): Abst 19B09-4.

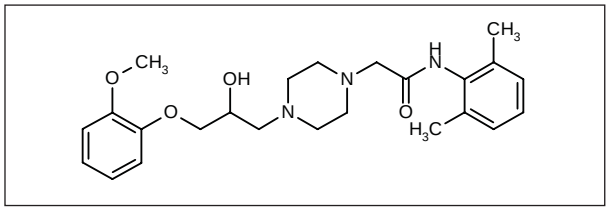
14. Yamada, I., Fujino, H., Shimada, S., Yoneda, M. *Studies on metabolic fate of pitavastatin (NK-104), a new inhibitor of HMG-CoA reductase – Is the metabolism of pitavastatin in monkey similar to that in human?* Xenobiotic Metab Dispos 2001, 16(Suppl.): Abst 18PE-15.

15. Yoshinaka, Y., Suzuki, H., Tamaki, T., Sato, F., Wada, Y. *General pharmacological study of an anti-hyperlipidemic agent, NK-104.* Jpn Pharmacol Ther 2001, 29(1): 59.

16. Chao, Y.-S. (Merck & Co., Inc.). *Anti-hypercholesterolemic drug combination.* WO 0122962.

Original monograph - Drugs Fut 1998, 23(8): 847.

Ranolazine



CV Therapeutics' ranolazine is an investigational candidate from a class of drugs known as pFOX (partial fatty acid oxidation) inhibitors which have the potential to offer an entirely new way of managing heart failure and chronic angina in patients with a history of congestive heart failure (CHF).

pFOX inhibitors appear to work by altering the metabolism of the heart to make it use oxygen in a more efficient manner, thereby reducing oxygen requirements without reducing the work of the heart. This working hypothesis was supported by canine data. In this study, dogs with chronic left ventricular dysfunction and heart failure were given dobutamine or ranolazine. Both treatments produced a significant and similar increase in ejection fraction and stroke volume without effects on heart rate or systemic pressure. However, in contrast to dobutamine, ranolazine improved left ventricular function without increasing coronary blood flow or myocardial oxygen consumption, and it significantly increased left ventricular mechanical efficiency. Ranolazine thus appears to partly inhibit the use of fatty acids to generate energy to pump blood, switching back to the use of the more oxygen-efficient carbohydrates or sugars (1-4).

Results from the MARISA (Monotherapy Assessment of Ranolazine In Stable Angina) study demonstrated that patients with both chronic angina and a history of CHF tolerated and responded to ranolazine at least as well as angina patients without CHF. The phase III MARISA trial was a double-blind, placebo-controlled, crossover study of ranolazine in patients not receiving any other antianginal drugs who were treated with ranolazine at doses of 500, 1000 or 1500 mg b.i.d. and placebo for 1 week each. Exercise tests at the time of trough and peak drug levels were evaluated in 146 patients without a history of CHF and 29 with NYHA class I or II CHF. At trough plasma concentrations, ranolazine produced significant increases in exercise duration, time to angina and time to 1-mm S-T segment depression compared to placebo in both groups of patients. At peak plasma levels, patients with CHF had increases in exercise duration and time to 1-mm S-T segment depression compared to placebo which were significantly greater than those observed in the patients without CHF. Adverse event rates were generally not greater in the CHF subgroup than in those without CHF. No clinically relevant changes in resting or exercise heart rate or systolic blood pressure were seen in either group of patients, an important finding considering that many patients with chronic angina and CHF also have low heart rate and blood pressure. CV Therapeutics is conducting a second phase III trial with ranolazine known as CARISA, for Combination Assessment of Ranolazine In Stable Angina, examining the efficacy of the drug in combination with other antianginal medications in patients with chronic angina (5). CARISA is a randomized, double-blind, placebo-controlled, multinational trial comparing the safety and efficacy of two dose regimens of ranolazine (750 mg and 1000 mg b.i.d.) together with background antianginal medications in over 700 chronic angina patients (6).

Data from the MARISA trial were also analyzed to compare study patients with and without diabetes. At both peak and trough drug levels, ranolazine treatment prolonged exercise duration to a similar extent in patients with and those without diabetes. Tolerability was likewise similar between the study groups (7) (Table XII).

A randomized, double-blind, placebo-controlled trial was conducted in 191 patients with ischemic heart disease. As part of the crossover design, patients were given ranolazine (500, 1000 and 1500 mg b.i.d.) and placebo each for 1 week. Both trough and peak exercise times were significantly increased by ranolazine as compared to placebo. Analysis of patients with and without

Table XII: Clinical studies of ranolazine.

Indication	Design	Treatments	N	Conclusions	Ref.
Angina pectoris	Randomized, double-blind, crossover	Ranolazine 500 mg bid Ranolazine, 1000 mg bid Ranolazine, 1500 mg bid Placebo	175	Ranolazine was effective and well tolerated in diabetic and nondiabetic patients with chronic angina	7
Angina pectoris	Randomized, double-blind, crossover	Ranolazine, 500 mg bid x 7 d Ranolazine, 1000 mg bid x 7 d Ranolazine, 1500 mg bid x 7 d Placebo	191	Ranolazine could be useful in angina	8

CHF suggested that ranolazine may benefit a variety of angina patients (8) (Table XII).

CV Therapeutics is also conducting a phase II trial of ranolazine in patients with CHF. This multicenter, double-blind, randomized, placebo-controlled trial is evaluating the pharmacokinetics, safety and tolerability of orally administered ranolazine in patients with NYHA class III and IV CHF (9).

In a rat model of anterior descending coronary artery occlusion, ranolazine significantly reduced infarct size and cardiac troponin T release (10).

Sustained-release formulations of ranolazine have been claimed (11, 12), as has the use of pFOX inhibitors in the treatment of CHF (12).

1. Sabbah, H.N., Chandler, M.P., Suzuki, G., Morita, H., Nass, O., Blackburn, B., Wolff, A., Stanley, W.C. *Ranolazine improves left ventricular mechanical efficiency in dogs with heart failure: Comparison with dobutamine.* J Am Coll Cardiol 2001, 37(2, Suppl. A): 173A.

2. Sabbah, H.N., Stanley, W.C. *Partial fatty acid oxidation inhibition: A novel approach for the treatment of heart failure.* J Mol Cell Cardiol 2001, 33(6): A154.

3. Chandler, M.P., Stanley, W.C., Morita, H., Suzuki, G., Nass, O., Blackburn, B., Wolff, A., Sabbah, H.N. *Ranolazine, a partial fatty acid oxidation inhibitor, improves left ventricular function in dogs with heart failure through an increase in myocardial efficiency.* Eur J Heart Fail 2001, 3(Suppl. 1): S47.

4. Chandler, M.P., Stanley, W.C., Morita, H., Suzuki, G., Nass, O., Blackburn, B., Wolfe, A., Sabbah, H.N. *Ranolazine, a partial fatty acid oxidation inhibitor, improves left ventricular function in dogs with heart failure through an increase in myocardial efficiency.* J Mol Cell Cardiol 2001, 33(6): A164.

5. Chaitman, B.R., Skettino, S., DeQuattro, V., Hanley, P.C., Jansky, P., Kuch, J.K., Parker, J.O., Nelson, J.J., Hebert, D., Wolff, A.A. *Improved exercise performance on ranolazine in patients with chronic angina and a history of heart failure: The MARISA trial.* J Am Coll Cardiol 2001, 37(2, Suppl. A): 149A.

6. *Enrollment completed in second phase III trial of ranolazine for chronic angina.* DailyDrugNews.com (Daily Essentials) Aug 13, 2001.

7. DeQuattro, V., Skettino, S., Chaitman, B.R., Hanley, P.C., Jansky, P., Kuch, J.K., Parker, J.O., Nelson, J.J., Hebert, D., Wolff, A.A. *Comparative antianginal efficacy and tolerability of ranolazine in diabetic and nondiabetic patients: Results of the MARISA trial.* J Am Coll Cardiol 2001, 37(2, Suppl. A): 338A.

8. Wolff, A.A., Skertino, S.L., Wang, W. *Clinical experience with ranolazine, a partial fatty acid oxidation (pFOX) inhibitor, in ischemic heart disease.* J Mol Cell Cardiol 2001, 33(6): A151.

9. *Ranolazine enters phase II for CHF.* DailyDrugNews.com (Daily Essentials) Dec 22, 2000.

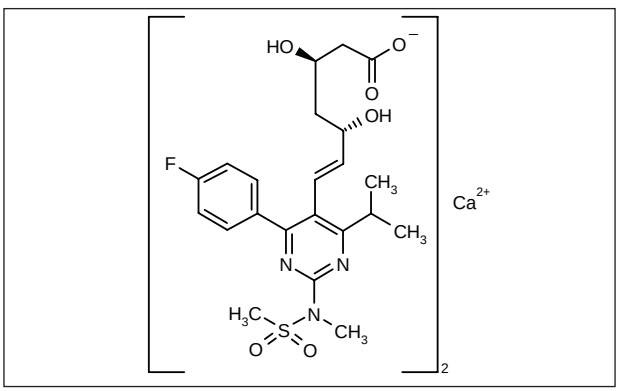
10. Zacharowski, K., Blackburn, B., Thiememann, C. *Ranolazine, a partial fatty acid oxidation inhibitor, reduces myocardial infarct size and cardiac troponin T release in the rat.* Eur J Pharmacol 2001, 418(1-2): 105.

11. Wolff, A.A. (CV Therapeutics, Inc.). *Sustained release ranolazine formulations.* WO 0166093.

12. Wolff, A.A., Blackburn, B. (CV Therapeutics, Inc.). *Partial fatty acid oxidation inhibitors in the treatment of congestive heart failure.* WO 0160348.

Original monograph - Drugs Fut 1988, 13(9): 837.

Rosuvastatin Calcium



AstraZeneca has submitted marketing applications in the U.S. and Europe for rosuvastatin calcium (Crestor™, ZD-4522) for the management of hypercholesterolemia, mixed dyslipidemia and isolated hypertriglyceridemia. The submissions are based on data from the clinical development program involving over 4000 patients and including head-to-head comparative studies, which demonstrated that rosuvastatin has a dramatic beneficial effect on lipid levels and can quickly get patients to the recommended U.S. and European cholesterol guidelines. AstraZeneca licensed worldwide rights to rosuvastatin from Shionogi in 1998 (1).

Rosuvastatin was found to act as a competitive inhibitor of HMG-CoA reductase with slow binding kinetics and high affinity (K_i ~ 0.1 nM). When compared to other statins for enzyme inhibition, 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) (2, 3).

In human monocyte-derived macrophages, rosuvastatin inhibited matrix metalloproteinase-7 and matrix metalloproteinase-9 secretion, effects which were reversed by exogenous mevalonate, farnesylpyrophosphate or geranylgeranylpyrophosphate (4).

Results from a study in rats examining the mechanisms of action of rosuvastatin showed that pretreatment with the agent attenuated thrombin-induced leukocyte rolling, adherence and transmigration in mesenteric microvasculature, which could be reversed by mevalonic acid. Rats treated with rosuvastatin displayed a significant 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 anti-inflammatory effects of the agent are mediated by inhibition of endothelial cell adhesion molecule expression and dependent on NO release (5-7).

The preclinical and clinical pharmacology of rosuvastatin has been 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. It was significantly more active in inhibiting cholesterol synthesis in rat hepatocytes as compared to several 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 cytochrome P450 3A4. 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 (8).

Healthy male volunteers (n = 37) were enrolled in 3 double-blind, randomized, placebo-controlled studies in which they received placebo or single doses of rosuvastatin 5, 10, 20 or 40 mg (trial 1), placebo or single doses of rosuvastatin 20 or 40 mg (trial 2), or placebo or single doses of rosuvastatin 80 mg (trial 3). The resulting pharmacokinetic and safety data indicated that rosuvastatin could be used in long-term trials in patients with hyperlipidemia (9).

An open pharmacokinetic trial in 32 healthy young and elderly volunteers of both sexes given a single oral dose of rosuvastatin 40 mg concluded that no dose adjustment for age or gender is necessary with the drug (10). In a randomized trial, healthy controls and subjects with alcohol-induced hepatic impairment received rosuvastatin 10 mg daily for 14 days. The pharmacokinetics of rosuvastatin were not significantly different in the groups and the treatment resulted in significant reductions in LDL cholesterol (11).

Rosuvastatin was administered to 10 subjects with hypertriglyceridemia and to 14 subjects with normal triglyceride levels in a double-blind study. The treatment decreased atherogenic apolipoprotein B (apo B)-containing lipoproteins, including remnants and small dense LDL. Particle composition was also normalized (12).

A multicenter, randomized, placebo-controlled, parallel-group study 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 and all doses of rosuvastatin significantly reduced LDL cholesterol in a dose-dependent manner (34-65%) and improved lipid ratios compared to placebo. No statistical comparison was made between rosuvastatin and atorvastatin, although it appeared that rosuvastatin produced greater improvements (13).

A study compared rosuvastatin with diet and maximal lipid therapy ("usual care") in patients with severe heterozygous familial hypercholesterolemia (HeFH) and baseline LDL cholesterol levels of over 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 or 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, and LDL cholesterol levels of < 160 mg/dl were achieved in 92% of patients on rosuvastatin therapy compared to 51% of patients receiving usual care. Rosuvastatin was well tolerated (14).

The lipid-lowering efficacies of rosuvastatin and atorvastatin were compared in patients with HeFH. This double-blind, randomized, parallel-group, forced-titration trial included 622 patients with HeFH. After a 6-week dietary run-in period, patients were randomized to rosuvastatin (435 patients) or atorvastatin (187 patients). Dosing began at 20 mg/day and was titrated to 40 mg/day and then 80 mg/day at 6-week intervals. The results at 18 weeks of treatment demonstrated that rosuvastatin led to a significantly greater reduction in LDL cholesterol, total cholesterol and apo B levels than atorvastatin. A significantly greater increase in HDL cholesterol and apo A1 was also observed with rosuvastatin therapy. Both drugs, however, yielded similar reductions in triglyceride levels. The improvement in LDL/HDL cholesterol ratio was 20% greater in patients receiving rosuvastatin as compared to

Table XIII: Clinical studies of rosuvastatin.

Indication	Design	Treatments	N	Conclusions	Ref.
Hypertriglyceridemia	Open	Rosuvastatin, 40 mg/d	32	Rosuvastatin decreased apolipoprotein B-containing lipoproteins, comprising small dense LDL and remnants, and normalized particle composition, enhancing its cardioprotective effects	12
Hypercholesterolemia	Randomized, double-blind, multicenter	Rosuvastatin, 1 mg po od x 6 wks → R 80 mg po od Rosuvastatin, 2.5 mg po od x 6 wks → R 80 mg po od Rosuvastatin, 5 mg po odx6 wks → R 80 mg po od Rosuvastatin, 10 mg po od x 6 wks → R 80 mg po od Rosuvastatin, 20 mg po od x 6 wks → R 80 mg po od Rosuvastatin, 40 mg po od x 6 wks → R 80 mg po od Rosuvastatin, 80 mg po od x 6 wks → R 80 mg po od Atorvastatin, 10 mg po od x 6 wks → R 80 mg po od Atorvastatin, 80 mg po od x 6 wks → R 80 mg po od	206	Rosuvastatin was well tolerated and more effective than atorvastatin in improving lipid ratios in hypercholesterolemia	13
Familial hypercholesterolemia	Randomized, double-blind, multicenter	Rosuvastatin, 20 mg x 18 wks → Rosuvastatin, 80 mg x 6 wks Rosuvastatin, 40 mg x 18 wks → Rosuvastatin, 80 mg x 6 wks Rosuvastatin, 80 mg x 18 wks → Rosuvastatin, 80 mg x 6 wks Atorvastatin, 20 mg x 18 wks → Rosuvastatin, 80 mg x 6 wks Atorvastatin, 40 mg x 18 wks → Rosuvastatin, 80 mg x 6 wks Atorvastatin, 80 mg x 18 wks → Rosuvastatin, 80 mg x 6 wks	47	Rosuvastatin was effective in severe heterozygous familial hypercholesterolemia	14
Famial hypercholesterolemia	Randomized, double-blind multicenter	Rosuvastatin, 20-80 mg od x 18 wks (n = 435) Atorvastatin, 20-80 mg od x 18 wks (n = 187)	622	Rosuvastatin was more effective than atorvastatin in increasing HDL-cholesterol and apolipoprotein A levels in heterozygous familial hypercholesterolemia	16, 17
Hypercholesterolemia	Randomized, double-blind, multicenter	Rosuvastatin, 5 mg/d x 12 wks (n = 120) Rosuvastatin, 10 mg/d x 12 wks (n = 115) Pravastatin, 20 mg/d x 12 wks (n = 137) Simvastatin, 20 mg/d x 12 wks (n = 130)	502	Rosuvastatin (5 and 10 mg) was more effective than pravastatin and simvastatin in primary hypercholesterolemia, and more patients reduced target LDL-cholesterol levels	18, 19
Hypercholesterolemia	Randomized, double-blind, multicenter	Rosuvastatin, 5 mg od po x 12 wks (n = 128) Rosuvastatin, 10 mg od po x 12 wks (n = 129) Atorvastatin, 10 mg od po x 12 wks (n = 127) Placebo (n = 132)	516	Rosuvastatin 5 and 10 mg daily was more effective than atorvastatin for the treatment of primary hypercholesterolemia	20, 21
Hypercholesterolemia	Randomized, open, multicenter	Rosuvastatin, 5 mg po od x 6 wks → R + Fenofibrate, 67 mg po x 18 wks (n = 60) Rosuvastatin, 10 mg po od x 6 wks → R + Fenofibrate, 67 mg po x 18 wks (n = 53) Placebo x 6 wks → Rosuvastatin, 10-40 mg po od x 18 wks (n = 51) Placebo x 6 wks → Fenofibrate, 67 mg po x 18 wks (n = 49)	216	Rosuvastatin alone or in combination with fenofibrate favorably modified lipid subfractions in patients with type 2 diabetes and hyperlipidemia. All treatment regimens were well tolerated	22
Hypertriglyceridemia	Randomized, double-blind, multicenter	Rosuvastatin, 5 mg po od x 6 wks (n = 25) Rosuvastatin, 20 mg po od x 6 wks (n = 27) Rosuvastatin, 10 mg po od x 6 wks (n = 23) Rosuvastatin, 40 mg po od x 6 wks (n = 25) Rosuvastatin, 80 mg po od x 6 wks (n = 27) Placebo (n = 26)	156	Rosuvastatin was effective in decreasing triglycerides, LDL- and VLDL-cholesterol levels and atheroprotective lipid fractions in hypertriglyceridemia	24, 33

(Continued)

Table XIII: Clinical studies of rosuvastatin (continuation).

Indication	Design	Treatments	N	Conclusions	Ref.
Hypercholesterolemia	Randomized double-blind multicenter	Rosuvastatin, 5-10 mg/d po x 52 wks (n = 138) Rosuvastatin, 10-20 mg/d po x 52 wks (n = 134) Atorvastatin, 10-20 mg/d po x 52 wks (n = 140)	412	Rosuvastatin was safe and more effective than atorvastatin in improving serum lipid levels and enabled more patients to meet their LDL-C goals, making it a promising alternative for the treatment of hypercholesterolemia	27, 29
Hypercholesterolemia	Randomized, double-blind multicenter	Rosuvastatin, 5-10 mg po od x 52 wks (n = 123) Rosuvastatin, 10-20 mg po od x 52 wks (n = 116) Pravastatin, 20-40 mg po od x 52 wks (n = 118) Simvastatin, 20-40 mg po od x 52 wks (n = 120)	477	Rosuvastatin was safe and yielded greater overall improvements in patients' lipid profiles than pravastatin and simvastatin, enabling more patients to meet their LDL-cholesterol goals	28, 30
Hypercholesterolemia	Randomized, double-blind pooled data	Study I: (n = 142) Rosuvastatin, 1 mg po od x 6 wks (n = 13) Rosuvastatin, 2.5 mg po od x 6 wks (n = 13) Rosuvastatin, 5 mg po od x 6 wks (n = 17) Rosuvastatin, 10 mg po od x 6 wks (n = 16) Rosuvastatin, 20 mg po od x 6 wks (n = 13) Rosuvastatin, 40 mg po od x 6 wks (n = 18) Rosuvastatin, 80 mg po od x 6 wks (n = 16) Atorvastatin, 10 mg po od x 6 wks (n = 13) Atorvastatin, 80 mg po od x 6 wks (n = 10) Placebo (n = 13) Study II: (n = 64) Rosuvastatin, 40 mg po od x 6 wks (n = 16) Rosuvastatin, 80 mg po od x 6 wks (n = 32) Placebo (n = 16)	206	The dose-ranging treatment schedule with rosuvastatin showed clinically and statistically significant dose-dependent reductions in LDL-cholesterol as well as a good tolerability in hypercholesterolemic patients	31
Hypercholesterolemia	Open, multicenter	Rosuvastatin, 10-40 mg/d x 24 wks (n = 45) Niacin-XR, 0.5-2 g/d x 24 wks (n = 66) Rosuvastatin, 10 mg/d + Niacin-XR, 0.5-2 g/d x 24 wks (n = 70) Rosuvastatin, 10-40 mg/d + Niacin-XR, 0.5-1 g/d x 24 wks (n = 72)	270	The rosuvastatin plus extended-release niacin combination was well tolerated; it did not increase the risk of myopathy or liver dysfunction and had an additive effect in increasing HDL-cholesterol but not in decreasing LDL-cholesterol	34
Hypercholesterolemia	Double-blind, multicenter	Rosuvastatin, 40 mg po od x 6 wks → Rosuvastatin, 80 mg/d po x 6 wks Rosuvastatin, 40 mg po x 6 wks → Cholestyramine, 8 g po bid + Rosuvastatin, 80 mg/d po x 6 wks	147	Rosuvastatin plus cholestyramine was well tolerated and produced similar improvements in serum lipids as rosuvastatin alone	35
Hypercholesterolemia	Multicenter pooled data	Rosuvastatin Placebo Other statins		Rosuvastatin had a safety profile that appeared to be comparable to that of other statins in patients with hypercholesterolemia	36

those receiving atorvastatin at all time points, and more patients in the rosuvastatin group achieved NCEP goals (15-17).

A 12-week, multicenter, double-blind, randomized study compared rosuvastatin with pravastatin and simvastatin in 502 patients with primary hypercholesterolemia. 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). Significantly larger reductions in total cholesterol and apo B levels and improvements in lipid ratios were observed with both doses of rosuvastatin as compared to the other agents. 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. All treatments were well tolerated (18, 19). Similar findings emerged from a multicenter, randomized, double-blind, placebo-controlled, parallel-group study conducted in 516 patients with primary hypercholesterolemia treated with rosuvastatin (5 or 10 mg once daily for 12 weeks) or atorvastatin (10 mg once daily for 12 weeks) (20, 21).

The results of an open-label, 18-week, forced-titration phase of a 24-week, double-blind study comparing rosuvastatin, fenofibrate and rosuvastatin plus fenofibrate combinations in type 2 diabetic patients with Frederickson type IIb and IV hyperlipidemia showed improvements in lipid subfractions on rosuvastatin alone and in combination with fenofibrate. All treatments were well tolerated (22).

A multicenter, double-blind study was conducted in 216 patients with type 2 diabetes who were randomized to rosuvastatin (5 or 10 mg) or placebo for 6 weeks, after which those with LDL cholesterol levels of 1.3 mmol/l or greater received force-titrated rosuvastatin (10, 20 and then 40 mg), fenofibrate (67 mg o.d., b.i.d. and then t.i.d.) or rosuvastatin (5 or 10 mg) plus fenofibrate (67 mg). Triglycerides were reduced the most by rosuvastatin 10 mg plus fenofibrate, while each of the two drugs alone reduced triglycerides to the same extent. Both doses of rosuvastatin improved these patients' atherogenic lipid profiles (23).

A 12-week study in patients with hypertriglyceridemia demonstrated beneficial effects for rosuvastatin (5-80 mg) on atherogenic and atheroprotective lipid fractions (24).

Male and postmenopausal female Japanese patients with primary hypercholesterolemia were randomized to receive rosuvastatin 1, 2 or 4 mg once daily in a multicenter, 8-week, double-blind trial. The treatment was well tolerated and improved lipid parameters, including significant, dose-dependent reductions in total and LDL cholesterol (25). Another randomized, placebo-controlled, dose-ranging trial evaluated rosuvastatin 1-40 mg in 142 men and postmenopausal women with hyperlipidemia. Results of the 6-week trial revealed that the drug induced dose-related reductions in LDL cholesterol and improved other lipid parameters, with safety comparable to placebo (26).

Phase III data on rosuvastatin reinforced its superior impact on lipid profiles compared to currently available statins. In these 52-week studies in hypercholesterolemic patients, after 12 weeks of initial therapy, the doses of rosuvastatin (5 and 10 mg) and the comparator statins (atorvastatin 10 mg, pravastatin 20 mg and simvastatin 20 mg) were titrated up as necessary to reach the LDL cholesterol goals recommended by the NCEP. In these studies, rosuvastatin produced significantly superior reductions in LDL cholesterol compared with the other statins (27-30).

Two dose-ranging studies of rosuvastatin have been conducted. In the first study, 142 mildly hypercholesterolemic patients were randomized in a double-blind fashion to placebo or rosuvastatin (1, 2.5, 5, 10, 20 or 40 mg) or atorvastatin (10 or 80 mg) once daily for 6 weeks. The second study was a randomized, double-blind trial in which 64 patients received placebo or rosuvastatin (40 or 80 mg) for 6 weeks. Data from both studies showed that rosuvastatin produced significant, dose-dependent LDL cholesterol reductions and was well tolerated (31).

Rosuvastatin (5, 10, 20, 40 and 80 mg) was evaluated in a 12-week, randomized, double-blind, placebo-controlled trial in 156 hypertriglyceridemic patients. Treatment lasted 6 weeks following a 6-week dietary run-in period. Rosuvastatin treatment resulted in significant reductions in all atherogenic lipid fractions and subfractions and increased HDL cholesterol levels (32, 33).

As part of a multicenter, open-label trial, 270 patients with mixed dyslipidemia were randomized to one of the following treatments (titrated over 24 weeks): rosuvastatin 10-40 mg, extended-release niacin (ERN) 0.5-2 g, ERN 0.5-1 g plus rosuvastatin 10-40 mg or ERN 0.5-2 g plus rosuvastatin 10 mg. Rosuvastatin up to 40 mg/day was well tolerated with ERN up to 2 g; ERN enhanced the HDL cholesterol-elevating effect of rosuvastatin (34).

In a multicenter trial, 147 patients with primary hypercholesterolemia were given rosuvastatin 40 mg once daily for 6 weeks after a 6-week dietary run-in, followed by randomization to rosuvastatin 80 mg/day alone or in combination with cholestyramine 8 g b.i.d. for 6 weeks. Rosuvastatin alone was better tolerated and produced similar improvements in LDL cholesterol, total cholesterol, triglycerides and HDL cholesterol as the rosuvastatin-cholestyramine combination (35).

Analysis of pooled safety data from phase II and III trials of rosuvastatin demonstrated that the drug's safety profile compares favorably with those reported for other statins (36).

Combinations of an HMG-CoA reductase inhibitor such as rosuvastatin and an ACAT inhibitor demonstrated a synergistic effect in lowering plasma cholesterol and triglyceride levels, as claimed in a recent patent (37).

Data from many of the clinical studies described herein are summarized in Table XIII.

1. *AstraZeneca seeks U.S. and European approval of new superstatin Crestor.* DailyDrugNews.com (Daily Essentials) June 28, 2001.

2. Holdgate, G.A., Ward, W.H.J., Davidson, R.G., Thornton, M., March, R., McTaggart, F. *Kinetics of inhibition of HMG-CoA reductase by a new statin, rosuvastatin.* Atherosclerosis Suppl 2001, 2(2): Abst P166.

3. Holdgate, G.A. et al. *Rosuvastatin: Kinetics of inhibition of HMG-CoA reductase.* 14th Int Symp Drugs Affect Lipid Metab (Sept 9-12, New York) 2001, 104.

4. Oopin, C., Davidson, R., Taggart, M.C., Chapman, M.J., Fruchart, J.C., Rouis, M. *Rosuvastatin reduces MMP-9 and MMP-7 secretion by human monocyte-derived macrophages.* 14th Int Symp Drugs Affect Lipid Metab (Sept 9-12, New York) 2001, 87.

5. Stalker, T.J., Lefer, A.M., Scalia, R. *A new HMG-CoA reductase inhibitor, rosuvastatin, exerts anti-inflammatory effects on the microvascular endothelium: The role of mevalonic acid.* Br J Pharmacol 2001, 133(3): 406.

6. Stalker, T.J., Lefer, A.M., Scalia, R. *ZD4522, a new HMG-CoA reductase inhibitor, inhibits leukocyte-endothelium interactions in the rat mesenteric microcirculation.* FASEB J 2001, 15(4, Part 1): Abst 150.5.

7. Scalia, R., Stalker, T.J., Lefer, A.M. *Mechanisms of the anti-inflammatory action of rosuvastatin, a new HMG-CoA reductase inhibitor.* Atherosclerosis Suppl 2001, 2(2): Abst W5.3.

8. McTaggart, F., Buckett, L., Davidson, R., Holdgate, G., McCormick, A., Schneck, D., Smith, G., Warwick, M. *Preclinical and clinical pharmacology of rosuvastatin, a new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor.* Am J Cardiol 2001, 87(5A): 28B.

9. Warwick, M.J., Dane, A.L., Raza, A., Schneck, D.W. *Pharmacokinetics and safety profile of the new HMG-CoA reductase inhibitor ZD4522 (single and multiple doses).* Can J Cardiol 2000, 16(Suppl. F): 196F.

10. Martin, P.D., Dane, A.L., Nwose, D., Schneck, D.W., Warwick, M.J. *Effect of age and gender on the pharmacokinetics of rosuvastatin: A new HMG-CoA reductase inhibitor.* Clin Pharmacol Ther 2001, 69(2): Abst PII-96.

11. Simonson, S.G., Martin, P.D., Mitchell, P.D., Schneck, D.W. *Pharmacokinetics and pharmacodynamics of rosuvastatin in hepatically impaired subjects.* Clin Pharmacol Ther 2001, 69(2): Abst PIII-88.

12. Caslake, M.J., Stewart, G., Day, S., Daly, E., Nwose, O.M., Chapman, M.J., Durrington, P., Laggner, P., Pears, J., Packard, C.J. *Rosuvastatin normalises atherogenic levels of apo B-containing lipoprotein subfractions.* 14th Int Symp Drugs Affect Lipid Metab (Sept 9-12, New York) 2001, 15.

13. Olsson, A.G., Caplan, R.J., McKellar, J., Raza, A., Pears, J.S. *A new statin, rosuvastatin, produces significant improvements in serum lipids and lipid ratios in patients with hypercholesterolaemia.* Atherosclerosis Suppl 2001, 2(2): Abst P165A.

14. Stein, E.A., Lamkin, G., Laskarzewski, P.M., Cressman, M.D. *ZD4522 (rosuvastatin) compared with diet and maximal lipid therapy in patients with heterozygous familial hypercholesterolemia.* J Am Coll Cardiol 2001, 37(2, Suppl. A): 291A.

15. Stein, E., Strutt, K.L., Miller, E., Southworth, H. *ZD4522 is superior to atorvastatin in the treatment of patients with heterozygous familial hypercholesterolemia.* J Am Coll Cardiol 2001, 37(2, Suppl. A): 292A.

16. Stein, E., Strutt, K.L., Miller, E., Southworth, H. *Rosuvastatin (20, 40 and 80 mg) reduces LDL-C, raises HDL-C and achieves treatment goals more effectively than atorvastatin (20, 40 and 80 mg) in patients with heterozygous familial hyperchlesterolemia.* Atherosclerosis Suppl 2001, 2(2): Abst P176.

17. Stein, E.A., Strut, K.L., Miller, E., Southworth, H. *Effect of rosuvastatin on high-density lipoprotein cholesterol and apolipoprotein A1 in patients with heterozygous familial hypercholesterolemia.* 14th Int Symp Drugs Affect Drug Metab (Sept 9-12, New York) 2001, 105.

18. Paoletti, R., Famhy, M., Mahla, G., Mizan, J., Southworth, H. *ZD4522 is superior to pravastatin and simvastatin in reducing low density lipoprotein cholesterol, enabling more hypercholesterolemic patients to achieve target low density lipoprotein cholesterol guidelines.* J Am Coll Cardiol 2001, 37(2, Suppl. A): 291A.

19. Paoletti, R., Fahmi, M., Mahla, G., Caplan, R., Raza, A. *Rosuvastatin is more effective than pravastatin or simvastatin at improving the lipid profiles of hypercholesterolaemic patients.* Atherosclerosis Suppl 2001, 2(2): Abst P164.

20. Davidson, M., Ma, P., Stein, E., Hutchinson, H.G., Caplan, R., Raza, A., Gotto, A. *Rosuvastatin is more effective than atorvastatin at improving the lipid profiles of patients with primary hypercholesterolaemia.* Atherosclerosis Suppl 2001, 2(2): Abst W6.4.

21. Davidson, M.H., Ma, P.T.S., Stein, E., Hutchinson, H.G., Chitra, R., Raza, A., Gotto, A. Jr. *ZD4522 is superior to atorvastatin in decreasing low density lipoprotein cholesterol and increasing high density lipoprotein cholesterol in patients with type IIa or IIb hypercholesterolemia.* J Am Coll Cardiol 2001, 37(2, Suppl. A): 292A.

22. Durrington, P.N., Tuomilehto, J., Hamann, A., Pears, J., Kallend, D. *Effects of rosuvastatin alone and in combination with fenofibrate on lipid subfractions in patients with type 2 diabetes: Results at 24 weeks.* Circulation 2001, 104(17, Suppl. 2): Abst 856.

23. Durrington, P., Hamann, A., Tuomiletto, J., Smith, K., Kallend, D. *Rosuvastatin alone and in combination with fenofibrate in hyperlipidaemic patients with type 2 diabetes.* 37th Annu Meet Eur Assoc Study Diabetes (Sept 9-13, Glasgow) 2001, Abst 631.

24. Hunninghake, D.B., Chifra, R.R., Simonson, S.G., Schneck, D.W. *Rosuvastatin markedly improved the atherogenic lipid profile in hypertriglyceridaemic patients.* Eur Heart J 2001, 22(Suppl.): Abst P1527.

25. Yamamoto, A., Kawaguchi, A. *Rosuvastatin provides potent, dose-dependent lipid-lowering effects in Japanese patients with primary hypercholesterolaemia.* Atherosclerosis Suppl 2001, 2(2): Abst P189.

26. Pears, J.S., Olsson, A.G., Caplan, R.J., McKellar, J., Raza, A. *Dose-ranging study of the HMG-CoA reductase inhibitor ZD4522 in patients with primary hypercholesterolemia.* Can J Cardiol 2000, 16(Suppl. F): 196F.

27. Olsson, A., Southworth, H., Wilpshaar, J.W. *Long-term efficacy and safety of rosuvastatin: Results of a 52-week comparator-controlled trial versus atorvastatin.* Eur Heart J 2001, 22(Suppl.): Abst 1410.

28. Brown, W.V., Chitra, R.R., Zedler, B.K., Bays, H.E., Hassman, H.A. *Long-term efficacy and safety of rosuvastatin: Results of a 52-week comparator-controlled trial versus pravastatin and simvastatin.* Eur Heart J 2001, 22(Suppl): Abst P1526.

29. Olsson, A.G., Southworth, H., Wilpshaar, J.W. *A 52-week trial of rosuvastatin versus atorvastatin in patients with primary hypercholesterolemia.* 14th Int Symp Drugs Affect Lipid Metab (Sept 9-12, New York) 2001, 106.

30. Brown, W.V., McKenney, J.M., Zedler, B.K., Bays, H.E., Hassman, H.A., Caplan, R.J., Miller, E. *A 52-week trial of rosuvastatin versus pravastain and simvastatin in patients with primary hypercholesterolemia.* 14th Int Symp Drugs Affect Lipid Metab (Sept 9-12, New York) 2001, 105.

31. Olsson, A.G., Pears, J., Mckelclar, J., Mizan, J., Raza, A. *Effect of rosuvastatin on low-density lipoprotein cholesterol in patients with hypercholesterolemia.* Am J Cardiol 2001, 88(5): 504.

32. Hunninghake, D.B., Chitra, R.R., Simonson, S.G., Schneck, D.W. *Treatment of hypertriglyceridemic patients with rosuvastatin.* Diabetes 2001, 50(Suppl. 2): Abst 574-P.

33. Hunninghake, D.B., Chitra, R.R., Simonson, S.G., Schneck, D.W. *Effects of rosuvastatin on serum lipids and lipid subfractions in patients with hypertriglyceridemia.* 14th Int Symp Drugs Affect Lipid Metab (Sept 9-12, New York) 2001, 105.

34. Morgan, J.M., Cressman, M.D., Hutchinson, H.G., Capuzzi, D.M. *Beneficial effects of combination therapy with rosuvastatin and extended-release niacin in patients with a mixed dyslipidemia.* 14th Int Symp Drugs Affect Lipid Metab (Sept 9-12, New York) 2001, 90.

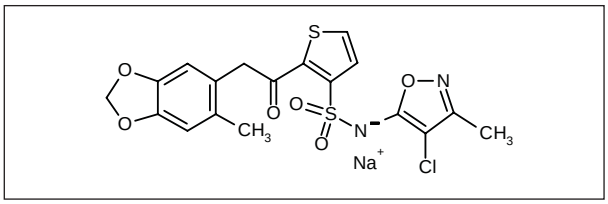
35. Ballantyne, C., Miller, E., Chitra, R. *Rosuvastatin alone produces similar lipid benefits compared with rosuvastatin plus cholestyramine in patients with primary hypercholesterolaemia.* 14th Int Symp Drugs Affect Lipid Metab (Sept 9-12, New York) 2001, 105.

36. Shepherd, J., Hunninghake, D., Harris, S., Hutchinson, H., Pears, J. *A review of the safety profile of rosuvastatin in an international phase II/III clinical trial programme.* 14th Int Symp Drugs Affect Lipid Metab (Sept 9-12, New York) 2001, 104.

37. Chao, Y.-S. (Merck & Co., Inc.) *Anti-hypercholesterolemic drug combination.* WO 0122962.

Original monograph - Drugs Fut 1999, 24(5): 511.

Sitaxsentan Sodium



Icos-Texas Biotechnology, an alliance formed by Icos and Texas Biotechnology, is proceeding with the phase II/III STRIDE (Sitaxsentan To Relieve ImpaireD Exercise in pulmonary hypertension) trial of sitaxsentan sodium (TBC-11251), an oral endothelin ET_A receptor antagonist, commenced in mid-2001 (1).

The objective of this double-blind, randomized, placebo-controlled trial is to demonstrate the safety and efficacy of sitaxsentan as a new once-daily treatment for patients with pulmonary arterial hypertension. The trial's primary endpoint is change in exercise capacity over the 12-week study period. The trial will also evaluate changes in 6-min walking distance, cardiopulmonary hemodynamics and quality of life as secondary endpoints. The North American trial is expected to enroll approximately 180 patients (2-3).

In another study, direct intrapulmonary infusion of sitaxsentan at increasing doses (0.3125-10 mg/min) produced pulmonary vasodilatation only in the 8 heart failure patients evaluated, but not the 4 control subjects. These findings suggest that ET-1 may be involved in the secondary pulmonary hypertension seen in heart failure and in regulating pulmonary vascular tone in heart failure (4).

In a laboratory study in adult pigs undergoing cardiopulmonary bypass, treatment with sitaxsentan reduced the rise in pulmonary vascular resistance seen in vehicle-treated animals without significantly altering systemic perfusion pressures (5).

The impact of pretreatment with sitaxsentan on hypoxic pulmonary hypertension was assessed in mature horses. While the drug had no effect on hemodynamic or ventilatory responses to acute hypoxia, the results suggested that endothelin may play a role in the slower phase of hypoxic pulmonary vasoconstriction (6).

1. *Icos and Texas Biotechnology initiate phase II/III trial of sitaxsentan in pulmonary hypertension.* DailyDrugNews.com (Daily Essentials) May 31, 2001.

2. *ET_A receptor antagonists in various stages of clinical testing at Icos-Texas Biotechnology.* DailyDrugNews.com (Daily Essentials) Jan 2, 2001.

3. *Icos reports product pipeline update.* DailyDrugNews.com (Daily Essentials) Jan 31, 2001.

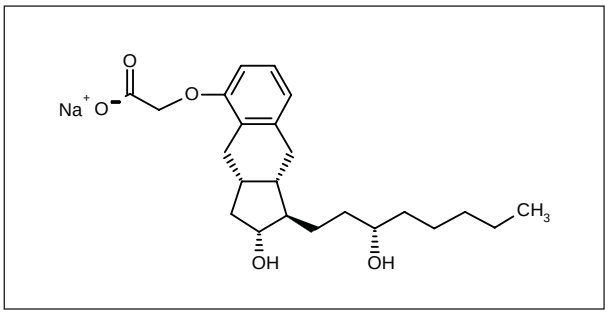
4. Ooi, H., Colucci, W.S., Gauthier, D.F., Keane, L.M., Zachariah, B.J., Givertz, M.M. *Endothelin mediates local pulmonary vascular tone in patients with heart failure: Demonstration by direct intrapulmonary infusion of sitaxsentan.* Circulation 2001, 104(17, Suppl. 2): Abst 2354.

5. Joffs, C., Walker, C.A., Hendrick, J.W., Almany, D.K., Fary, D.J., Davis, J.N., Goldberg, A.T., Crawford, F.A. Jr., Spoinale, F.G. *Endothelin receptor subtype A blockade selectively reduces pulmonary pressure after cardiopulmonary bypass.* J Thorac Cardiovasc Surg 2001, 122(2): 365.

6. Benamou, A.E., Marlin, D.J., Lekeux, P. *Endothelin in the equine hypoxic pulmonary vasoconstrictive response to acute hypoxia.* Equine Vet J 2001, 33(4): 345.

Original monograph - Drugs Fut 2000, 25(2): 159.

Treprostinil Sodium



The Cardiovascular and Renal Drugs Advisory Committee of the FDA recommended approval of United Therapeutics' treprostinil sodium (Remodulin™ Injection, UT-15, formerly Uniprost), a stable prostacyclin analogue, last year for the treatment of pulmonary arterial hypertension. A marketing application is also under review in France under the mutual recognition procedure and additional international filings will occur upon approval of the product in the U.S. and France (1, 2).

Treprostinil sodium (UT-15) delivered into the airways was compared to pegylated drug (UT-15 PEG) and iloprost in rats with chronic hypoxia-induced pulmonary hypertension. UT-15 caused a dose-dependent reduction in pulmonary artery pressure. UT-15 PEG was also effective and had a longer duration of action (3).

Long-term (1-year) treatment with UT-15 stabilized hemodynamics and improved exercise capacity in patients with advanced pulmonary arterial hypertension. The increase in 6-min walk distance was greater at 1 year than at 12 weeks and may have been due to the increased dose of the drug (4).

Long-term (6-24 months) treatment with UT-15 in 631 patients with pulmonary arterial hypertension improved exercise capacity in an apparently dose-related manner. The drug was tolerated in most patients (5) (Table XIV).

Table XIV: Clinical study of teprostinil.

Indication	Design	Treatments	N	Conclusions	Ref.
Pulmonary hypertension	Multicenter, open	Teprostinil, 16 ng/kg/min sc x 6 mo (n = 156) Teprostinil, 25 ng/kg/min sc x 12 mo (n = 102) Teprostinil, 24 ng/kg/min sc x 15 mo (n = 63) Teprostinil, 31 ng/kg/min sc x 18 mo (n = 46) Teprostinil, 38 ng/kg/min sc x 21 mo (n = 15)	631	Long-term treatment with teprostinil improved exercise in patients with pulmonary hypertension	6

Spanish investigators reported their findings from a long-term evaluation of continuous s.c. infusion of treprostinil in patients with severe pulmonary hypertension. In this international open-label trial, 20 patients received s.c. treprostinil in addition to conventional treatment and were examined for functional class, exercise capacity (6-min walk test) and hemodynamics at 6 and 12 months. Exercise capacity was improved at 6 months and significantly increased at 12 months, and NYHA class also showed a trend for improvement, with a reduction in the percentage of patients with NYHA class III-IV from 95% at baseline to 57% at 12 months. The beneficial effects of treprostinil were dose-dependent. No significant changes in hemodynamics were detected (6).

The exercise capacity of patients with pulmonary arterial hypertension (n = 52) was measured at baseline and after 1-18 months of treatment with treprostinil. As improvements were related only to baseline performance, and not drug dose or duration of treatment, treprostinil treatment appeared to equally benefit patients with different levels of exercise capacity (7).

1. *Approval of Remodulin recommended by the FDA for pulmonary arterial hypertension.* DailyDrugNews.com (Daily Essentials) Aug 14, 2001.

2. *MAA for UT-15 filed in France; new name accepted.* DailyDrugNews.com (Daily Essentials) Feb 6, 2001.

3. Emery, C.J., Lal, H., Marriott, H.M., Whittle, B.J.R., Shorr, R., Bentley, M., Zhao, X., Higenbottam, T.W. *Pulmonary vasodilation by airway delivered UT-15, a PGI_2 analogue: Prolongation by pegylation.* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A540.

4. McLaughlin, V.V., Sitbon, O., Barst, R.J., Schilz, R., Robbins, I., Rich, S. *Long term hemodynamic and exercise effects of UT-15, a subcutaneous prostacyclin analogue.* Circulation 2001, 104(17, Suppl. 2): Abst 1196.

5. McLaughlin, V., Silbon, O., Sigman, J., Blackburn, S. *Continuous subcutaneous infusion of Remodulin™, a prostacyclin analogue, in patients with pulmonary arterial hypertension: Long-term outcome.* Circulation 2001, 104(17, Suppl. 2): Abst 1203.

6. Lazaro, M., Escribano, P., Pombo, M., Garcia-tejada, J., Dalmau, R., Delgado, J.F., Tello, R., Velazquez, M.T., Gomez-Sanchez, M.A., Saenz de la Calzada, C. *Continuous subcutaneous infusion of UT-15 (stable prostacyclin analogue) in severe pulmonary hypertension: Long-term outcome.* Eur Heart J 2001, 22(Suppl.): Abst P1716.

7. Hamilton, G., Saba, T., Corris, P., Delcroix, M., Simonneau, G., Sitbon, O., Torbixki, A., Kuca, P., Peacock, A.J. *Improvement of exercise tolerance due to uniprost in patients with pulmonary arterial hypertension is related to baseline performance.* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A540.

Original monograph - Drugs Fut 2001, 26(4): 364.