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Annual Update 2003: Cardiovascular Drugs

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Abstract

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Introduction

This month's Annual Update 2003 is dedicated to Cardiovascular Drugs and is comprised of a Compendium of 128 drugs that are in active clinical development for cardiovascular conditions or which have been launched for the first time since 2002. The Compendium also includes products that had previously been marketed for another indication and that are now being studied or have been introduced for a new cardiovascular indication. Due to space limitations, drugs for thrombotic disorders will be covered in the July issue of Drugs of the Future. Drugs for stroke will also be discussed in a future Annual Update dedicated to Neurologic Drugs. Products featured in the monograph updates section include AGI-1067, aliskiren fumarate, avasimibe, azelnidipine, azimilide hydrochloride, bosentan, candesartan cilexetil, conivaptan hydrochloride, eplerenone, ezetimibe, fasudil hydrochloride, iloprost, mozavaptan, NCX-4016, nolomirole hydrochloride, olmesartan medoxomil, omapatrilat, pexelizumab, pitavastatin calcium, raloxifene, ranolazine, rosuvastatin calcium, sirolimus, sitaxsentan sodium, SLV-306, tecadenosan, toborinone, tolvaptan and treprostinil sodium.

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Drug	Source	Condition	Phase
1069	Aventis Pharma	Angina pectoris	I
1766	Aventis Pharma	Angina pectoris	I
ABT-578	Medtronic	Restenosis, arterial	I
AC-3056	Amylin	Hyperlipidemia and atherosclerosis	I
AGI-1067	AtheroGenics	Hyperlipidemia and atherosclerosis	III
Aliskiren Fumarate[2]	Novartis/Speedel	Hypertension	II
ALT-711	Alteon	Heart failure	II
	Alteon	Hypertension, systolic	II
Ambrisentan	Myogen	Hypertension, pulmonary	II
(*S*)-Amlodipine	Sepracor	Hypertension	II
Angiogenix	Endovasc	Ischemia, myocardial	II
Avasimibe[2]	Pfizer	Hyperlipidemia and atherosclerosis	III
AVE-7688	Aventis Pharma	Hypertension	I
AZD-7009	AstraZeneca	Fibrillation, atrial	I
Azelnidipine[2]	Sankyo/Ube	Hypertension	L-2003
Azimilide Hydrochloride[2]	Procter & Gamble	Fibrillation, atrial	III
BioBypass-CAD	GenVec	Coronary artery disease	II
BioBypass-PVD	GenVec	Vascular disease, peripheral	II
BO-653	Chugai	Coronary artery disease	II
	Chugai	Restenosis, arterial	II
Bosentan[2]	Actelion	Hypertension, pulmonary	L-2001
BTG-511	BTG	Hypercholesterolemia	II
Caldaret Hydrate	Mitsubishi Pharma/Takeda	Myocardial infarction	II
	Mitsubishi Pharma/Takeda	Heart failure, chronic	II
Candesartan Cilexetil[1,2]	Takeda/AstraZeneca	Heart failure, congestive	Prereg
CETi-1	Avant	Hyperlipidemia and atherosclerosis	II
Clevidipine	The Medicines Co.	Hypertension	II
Conivaptan Hydrochloride[2]	Yamanouchi	Heart failure	II
CS-505	Sankyo	Hyperlipidemia and atherosclerosis	II
CS-780	Sankyo	Angina pectoris	I
D-003	Labs. Dalmer	Hyperlipidemia and atherosclerosis	I
DITPA	University of Arizona	Heart failure	I
DRF-4832	Dr. Reddy's Laboratories	Hyperlipidemia and atherosclerosis	Clinical
Dronedarone Hydrochloride	Sanofi-Synthélabo	Arrhythmia and atrial fibrillation	III
DS-992	AnGes/Daiichi Pharmaceutical	Coronary artery disease	II
	AnGes/Daiichi Pharmaceutical	Vascular disease, peripheral	II
DTI-0009	Aderis/Fujisawa	Fibrillation, atrial	II
DX-88	Dyax	Surgery, arterial coronary	I/II
E2F Decoy	Corgentech	Surgery, arterial coronary	III
	Corgentech	Vascular disease, peripheral	III
Eflucimibe	Pierre Fabre/Lilly	Hyperlipidemia and atherosclerosis	II
EMR-62204	Merck KGaA	Heart failure	II
Enalapril Maleate/Nitrendipine	Vita-Invest	Hypertension	L-2002
Eplerenone[1,2]	Pfizer	Heart failure (post-MI)	Prereg
	Pfizer	Hypertension	L-2002
Eprosartan Mesilate/Hydrochlorothiazide	Biovail	Hypertension	L-2002
ETC-216	Esperion	Angina pectoris	II
ETC-588	Esperion	Hyperlipidemia and atherosclerosis	II
	Esperion	Angina pectoris	II
ETC-642	Esperion	Hyperlipidemia and atherosclerosis	I
Everolimus[2]	Guidant	Restenosis, arterial	Clinical
Ezetimibe[2]	Schering-Plough/Merck & Co.	Hypercholesterolemia	L-2002
Ezetimibe/Simvastatin	Schering-Plough/Merck & Co.	Hypercholesterolemia	III
Fasidotril[2]	Bioprojet/Lilly	Heart failure	II
	Bioprojet/Lilly	Hypertension	II
Fasudil Hydrochloride[1,2]	Schering AG	Angina pectoris	II
FM-VP4	Forbes Medi-Tech	Dyslipidemia	II
Generx	Collateral Therapeutics	Coronary artery disease	III
Genvascor	Collateral Therapeutic	Vascular disease, peripheral	I/II
GLP-1(7-36)amide	Amylin	Heart failure, congestive	II
GW-501516	GlaxoSmithKline/Ligand	Dyslipidemia	I

Continuation

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Drug	Source	Condition	Phase
GW-590735	GlaxoSmithKline	Dyslipidemia	I
HE-2200	Hollis-Eden	Hyperlipidemia and atherosclerosis	II
Iloprost[1,2]	Schering AG	Hypertension, pulmonary	III
Implitapide[2]	Bayer/PPD	Hyperlipidemia and atherosclerosis	II
Irbesartan[1,2]	Sanofi-Synthélabo/Bristol-Myers Squibb	Heart failure	III
Iroxanadine	Biorex R&D	Hyperlipidemia and atherosclerosis	II
	Biorex R&D	Myocardial infarction	II
	Biorex R&D	Restenosis, arterial	II
Isosorbide Dinitrate/Hydralazine Hydrochloride	NitroMed	Heart failure	Prereg
ITF-1697	Italfarmaco	Myocardial infarction	II
Ivabradine Hydrochloride	Servier	Angina pectoris	III
JTT-705	Japan Tobacco	Hyperlipidemia and atherosclerosis	II
Landiolol	Ono	Arrhythmia	L-2002
Levocarnitine Propionate Hydrochloride	Sigma-Tau	Intermittent claudication	III
Lovastatin/Niacin	Kos Pharmaceuticals/Quintiles	Hyperlipidemia and atherosclerosis	L-2003
LY-510929	Lilly/Ligand	Dyslipidemia	I
LY-518674	Lilly/Ligand	Dyslipidemia	I
MC-1	Medicure	Myocardial infarction	I
	Medicure	Angioplasty, coronary	II
	Medicure	Surgery, arterial coronary	I
MC-4232	Medicure	Hypertension	I/II
MK-767	Merck & Co.	Dyslipidemia	III
Motexafin Lutetium	Pharmacyclics	Hyperlipidemia and atherosclerosis	I/II
	Pharmacyclics	Coronary artery disease	I
	Pharmacyclics	Restenosis, arterial	II
Mozavaptan[2]	Otsuka	Heart failure	II
Naxifylline	CV Therapeutics/Biogen	Heart failure, congestive	II
NCX-1000	NicOx	Hypertension, portal	I
NCX-4016[2]	NicOx	Restenosis, arterial	II
	NicOx	Vascular disease, peripheral	II
Nesiritide	Scios (Johnson & Johnson)/ GlaxoSmithKline	Heart failure	L-2001
Nicorandil[1,2]	Chugai	Heart failure	III
Nolomirole Hydrochloride[2]	Chiesi	Heart failure	III
NV-04	Novogen	Hyperlipidemia and atherosclerosis	I
	Novogen	Hypertension	I
NV1FGF	Aventis Pharma	Vascular disease, peripheral	II
Olmesartan Medoxomil[2]	Sankyo/Forest	Hypertension	L-2002
Olmesartan Medoxomil/ Hydrochlorothiazide	Sankyo/Forest	Hypertension	R-2003
Omapatrilat[2]	Bristol-Myers Squibb	Hypertension	Prereg
Ono-1714	Ono	Hypotension	II
Oxypurinol	Cardiome	Heart failure, congestive	II/III
Pexelizumab	Alexion/Procter & Gamble	Myocardial infarction	II
	Alexion/Procter & Gamble	Surgery, cardiopulmonary bypass	III
Piboserod Hydrochloride[2]	GlaxoSmithKline	Fibrillation, atrial	II
Pitavastatin Calcium[2]	Kowa/Nissan Chemical	Hyperlipidemia and atherosclerosis	Prereg
PMD-2850	Protherics	Hypertension	II
Pranidipine[2]	Otsuka	Angina pectoria	III
	Otsuka	Hypertension	III
Pravastatin Sodium/Aspirin	Bristol-Myers Squibb	Coronary artery disease	R-2003
Raloxifene Hydrochloride[2]	Lilly	Coronary artery disease	III
Ranolazine[2]	CV Therapeutics	Angina pectoris	Prereg
Resten-NG	AVI BioPharma	Restenosis, arterial	II
Rosuvastatin Calcium	AstraZeneca/Shionogi	Hyperlipidemia and atherosclerosis	L-2003
RSD-1235	Cardiome	Fibrillation, atrial	III
S-8921	Shionogi	Hyperlipidemia and atherosclerosis	II
Sabiporide Mesilate[2]	Boehringer Ingelheim	Angina pectoris	I
SB-480848	GlaxoSmithKline	Hyperlipidemia and atherosclerosis	II
SB-659032	GlaxoSmithKline	Hyperlipidemia and atherosclerosis	I
Sirolimus[2]	Cordis	Restenosis, arterial	L-2002
Sitaxsentan Sodium[2]	Encysive Pharmaceuticals	Hypertension, pulmonary	III

Continuation

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Drug	Source	Condition	Phase
SLV-306[2]	Solvay	Heart failure, congestive	II
	Solvay	Hypertension	II
SLV-320	Solvay	Heart failure	I
SPP-301	Speedel	Hypertension	II
SR-121463A	Sanofi-Synthélabo	Heart failure	II
SSR-149744	Sanofi-Synthélabo	Fibrillation, atrial	I
ST-261	Sigma-Tau	Intermittent claudication	III
TAK-475	Takeda	Hyperlipidemia and atherosclerosis	II
TBC-3711	Encysive Pharmaceuticals	Heart failure	I
	Encysive Pharmaceuticals	Hypertension	I
	Encysive Pharmaceuticals	Hypertension, pulmonary	I
Tecadenoson[2]	CV Therapeutics	Arrhythmia, supraventricular	III
Tedisamil Hydrochloride	Solvay	Arrhythmia	III
Tezosentan Sodium	Actelion/Genentech	Heart failure	III
Toborinone[2]	Otsuka	Heart failure	III
Tolvaptan[2]	Otsuka	Heart failure	II
Torcetrapib	Pfizer	Hyperlipidemia and atherosclerosis	II
TP-10	Avant	Myocardial infarction	II
Treprostinil Sodium[2]	United Therapeutics	Hypertension, pulmonary	L-2002
Trinam	Ark Therapeutics	Stenosis	I
Valsartan[1]	Novartis	Myocardial infarction	III
	Novartis	Heart failure	L-2002
VAS-991	Vasogen	Heart failure	III
VEGF-2 Gene Therapy	Corautus Genetics	Angina pectoris	I/II
	Corautus Genetics	Vascular disease, peripheral	I/II
VLTS-589	Valentis	Vascular disease, peripheral	I/II
VMDA-3601	Dong-A/ViroMed	Vascular disease, peripheral obstructive	I
VT-111	Viron Therapeutics	Angina pectoris	I
VX-702	Vertex	Angina pectoris	II
ZP-120	Zealand Pharma	Heart failure	I

[1]Launched for another indication. [2]Monograph previously published in Drugs of the Future.

Compendium of Cardiovascular Drugs

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Hyperlipidemia and atherosclerosis

Atherosclerosis, which literally means "hardening of the arteries," is a disease of the blood vessels in which both degenerative and regenerative processes come into play. Atherosclerosis is a type of arteriosclerosis, the latter being a general term denoting thickening and hardening of the arteries that occurs, to a certain extent, as a normal part of aging. Although the consequences of atherosclerosis generally manifest in middle-aged or elderly persons, the process of atherogenesis generally begins during childhood, with a preclinical phase that can last for decades. Abnormally high levels of cholesterol represent the major risk factor for atherosclerosis leading to coronary heart disease and myocardial infarction.

According to the American Heart Association, more than 100 million Americans have total blood cholesterol levels above 200 mg/dl, and approximately 40.6 million adults have levels in excess of 240 mg/dl. Atherosclerotic cardiovascular disease is, consequently, a major public health problem, constituting the leading cause of death in the U.S. and developing countries. According to the American Heart Association, atherosclerosis currently accounts for 133,000 hospital discharges and 15,279 deaths per 100,000 population each year in the U.S. Furthermore, atherosclerosis is a leading cause of death from heart attack and stroke, thereby contributing to nearly three-fourths of all deaths from cardiovascular disease. According to figures quoted by Hollis-Eden, the U.S. market for cholesterol-lowering drugs is anticipated to exceed USD 37 billion in 2008.

Atherosclerosis should first be treated through dietary and lifestyle modifications. Only when these techniques fail should drug therapy be initiated. Drugs for atherosclerosis typically work by lowering blood levels of low-density lipoprotein (LDL) cholesterol (all marketed drugs have this mechanism of action) or by boosting levels of high-density lipoprotein (HDL) cholesterol. Data obtained in primary prevention studies has confirmed that LDL cholesterol-lowering drugs reduce the risk of major coronary events, coronary death and total mortality in patients with established coronary heart disease, even in the short term.

HMG-CoA reductase inhibitors

HMG-CoA reductase inhibitors (statins) are the most widely prescribed lipid-lowering drugs in the U.S. and many other countries. Clinical trials have repeatedly demonstrated a reduction of approximately 30% in the relative risk of major coronary events, accompanied by significant increases in survival, among patients receiving statin therapy.

AstraZeneca obtained the first approval of **rosuvastatin calcium** (Crestor™) last year in The Netherlands, where it is indicated for the treatment of patients with primary hypercholesterolemia (type IIa including heterozygous familial hypercholesterolemia) or mixed dyslipidemia (type IIb) as an adjunct to diet when response to diet and exercise is inadequate; it is also indicated in patients with homozygous familial hypercholesterolemia either alone or as an adjunct to diet and other lipid-lowering treatments. Rosuvastatin, a so-called "superstatin," demonstrated superior efficacy in lowering LDL cholesterol as compared to currently available statins in a number of clinical trials, with reductions of 52-63% and significantly greater reductions compared with the same doses of atorvastatin. Rosuvastatin also significantly increased HDL cholesterol and reduced total cholesterol and triglycerides. The product has been launched to date in Canada (February 2003), The Netherlands (March 2003) and the U.K. (April 2003). Marketing approval has been recommended in the U.S., where the product will be indicated for the management of hypercholesterolemia, mixed dyslipidemia and isolated hypertriglyceridemia. Worldwide rights to rosuvastatin were licensed by AstraZeneca in 1998 from Shionogi; the latter retains rights to comarket the product in Japan.

Another statin in late-stage clinical development is **pitavastatin calcium**, which is being codeveloped by Kowa and Nissan Chemical. The product was recently approved in Japan for the treatment of hypercholesterolemia and will be marketed there by Kowa and Sankyo. Sankyo is developing the drug for the U.S. market and phase II development is being undertaken by Novartis in Europe.

Table I: ACAT inhibitors in development for the treatment of hypercholesterolemia and atherosclerosis.

Drug Name	Source	Status
Avasimibe	Pfizer	Phase III
CS-505	Sankyo	Phase II
Eflucimibe	Pierre Fabre/Lilly	Phase II

ACAT inhibitors

Acyl-coenzyme A:cholesterol *O*-acyltransferase (ACAT) is the major enzyme involved in the esterification of cholesterol, a process that plays an important role in different tissues. ACAT, located in the endoplasmic reticulum, is involved in cholesterol absorption in the intestine and in the accumulation of cholesterol in macrophages in the arterial wall. In the liver, ACAT is implicated in the storage of cholesteryl esters and the assembly and secretion of very-low-density lipoproteins (VLDL).

Although long considered attractive candidates for the treatment of hypercholesterolemia, no ACAT inhibitors have yet attained marketing status in any country. ACAT inhibitors in development for the treatment of hypercholesterolemia and atherosclerosis are presented in Table I.

Cholesterol absorption inhibitors

The novel hypolipidemic agent **ezetimibe** was approved for the first time in the U.S. (as Zetia™) and Germany (as Ezetrol™) during October 2002, and was launched a few weeks later in the U.S., its first market. As the first hypolipidemic agent to act by blocking the absorption of dietary cholesterol, ezetimibe represents a novel treatment option for patients with hypercholesterolemia, alone or in combination with statins. Ezetimibe is also indicated for the therapy of two less common forms of hyperlipidemia: homozygous familial hypercholesterolemia (in combination with a statin) and homozygous sitosterolemia (as monotherapy). Ezetimibe was developed by the Merck/Schering-Plough joint venture, which was established in 2000 for the development and marketing of new prescription drugs in cholesterol management.

Schering-Plough has signed an agreement with Merck & Co. for the codevelopment of a fixed-dose combination product incorporating ezetimibe and Merck's simvastatin (Zocor®) in a single tablet. An **ezetimibe/simvastatin** fixed-combination tablet would offer a novel approach to cholesterol management, with the potential to achieve high levels of cholesterol reduction through two complementary mechanisms of action, while maintaining a good safety profile. The combination product is in phase III testing.

MTTP inhibitors

Microsomal triglyceride transfer protein (MTTP) is a heterodimeric transfer protein that limits the production of atherogenic apolipoprotein B (apoB)-containing lipoproteins. MTTP is a key factor in the assembly of VLDL, the direct precursor to LDL. MTTP inhibition has been shown to reduce plasma LDL and VLDL levels in rabbits, and MTTP is considered an attractive target for the treatment of dyslipidemias and prevention of atherosclerosis. **Implitapide**, an MTTP inhibitor from Bayer, has been outlicensed to MRL International, a division of PPD Development. The latter will undertake further phase I and phase II testing to evaluate the compound's potential for the treatment of hyperlipidemia and atherosclerosis.

Other LDL cholesterol-lowering drugs

Following the receipt of FDA approval in December 2002, Kos Pharmaceuticals launched the combination cholesterol management product Advicor™ in January 2003. Advicor™ contains extended-release **niacin**, a vitamin B complex, and **lovastatin**, an inhibitor of HMG-CoA reductase. Advicor™ is approved for the treatment of primary hypercholesterolemia and mixed dyslipidemia in patients previously treated with either component and who require additional lipid modification for LDL or HDL cholesterol and triglycerides beyond that achieved by the individual components. The product is marketed in the U.S. by Quintiles.

Table II presents further information on this and other LDL cholesterol-lowering agents recently marketed or in active clinical development for the treatment of hyperlipidemia and atherosclerosis.

Table II: Other LDL cholesterol-lowering drugs recently launched and in development for the treatment of hyperlipidemia and atherosclerosis.

Drug Name	Source	Mechanism of Action	Status
Lovastatin/Niacin	Kos Pharmaceutical/Quintiles	Combination product	L-2003
BTG-511	BTG	Bile acid sequestrant	Phase II
FM-VP4	Forbes Medi-Tech	Lipid-lowering agent	Phase II
S-8921	Shionogi	Bile acid transporter inhibitor	Phase II
TAK-475	Takeda	Squalene synthase inhibitor	Phase II

Table III: HDL-increasing agents in development for the treatment of atherosclerosis.

Drug Name	Source	Mechanism of Action/Description	Status
CETP Vaccine (CETi-1)	Avant	Cholesterol ester transfer protein inhibitor, chimeric peptide vaccine	Phase II
ETC-588	Esperion	HDL cholesterol-increasing agent	Phase II
JTT-705	Japan Tobacco	Cholesterol ester transfer protein inhibitor	Phase II
Torcetrapib	Pfizer	Cholesterol ester transfer protein inhibitor	Phase II
ETC-642	Esperion	Reverse lipid transport peptide	Phase I

Table IV: PPAR agonists in development for the treatment of dyslipidemia and atherosclerosis.

Drug Name	Source	Mechanism of Action	Status
MK-767	Merck & Co.	PPARα and PPARγ agonist	Phase II
GW-501516	GlaxoSmithKline/Ligand	PPARδ agonist	Phase I
GW-590735	GlaxoSmithKline	PPAR agonist	Phase I
LY-510929	Lilly/Ligand	PPAR agonist	Phase I
LY-518674	Lilly/Ligand	PPARα agonist	Phase I
DRF-4832	Dr. Reddy's Laboratories	PPARα and PPARγ agonist	Clinical

HDL cholesterol-targeted therapies

HDL is one of the major lipid-transporting elements in the blood. It is known as the "good" cholesterol because it transports excess lipids from peripheral cells in the arterial walls to the liver, where they are subsequently eliminated in bile. This process is known as reverse cholesterol transport or reverse lipid transport.

The impact of elevated HDL levels on cardiovascular morbidity and mortality is significant: a 1% increase in HDL levels translates into a 3-4% decrease in cardiovascular risk. The first recommendations for raising HDL levels generally include diet and lifestyle modifications: increasing dietary consumption of monounsaturated fats, exercise and the avoidance of alcohol and tobacco. If drug therapy is required, the most effective HDL-elevating therapies at this time include nicotinic acid and estrogen (the latter in postmenopausal women). New therapeutic strategies for increasing HDL levels are under investigation, as indicated in Table III.

PPAR receptor agonists

The peroxisome proliferator-activated receptor (PPAR) family of transcription factors plays a key role in regulating dietary fat storage and catabolism. Since they were first cloned just a decade ago, PPARs have become established as an important target for the treatment of type 2 diabetes, with several PPAR agonists marketed for this indication. Other compounds in this class are being studied for the treatment of obesity, dyslipidemia, cancer and other human health disorders associated with high intake of dietary fat. As indicated in Table IV, several PPAR agonists are in development for the treatment of dyslipidemia and atherosclerosis.

Antiinflammatory strategies

Atherosclerosis, long held to be a straightforward disorder of lipoprotein metabolism, has more recently been shown to be a much more complex, chronic inflammatory disease of the arterial intima. According to the inflammatory disease theory, the atherosclerotic process is initiated when lipoproteins accumulate in the arterial intima and undergo chemical modification. This event stimulates local inflammation in the blood vessel wall, attracting monocytes from the circulation. The modified lipoproteins are taken up by monocyte-derived macrophages. The resulting fat-laden macrophages, or foam cells, localize in the vessel wall at the site of the early fatty streak lesion and intensify the inflammatory response, forming an intermediate lesion. If the inflammatory response is not interrupted, the arterial wall thickens and undergoes a process of remodeling. As inflammation continues, increased numbers of macrophages and T-lymphocytes emigrate from the blood to the lesion, where they multiply and become activated. This stimulates the release of hydrolytic enzymes, cytokines, chemokines and growth factors. Each of these inflammatory elements contributes to further damage and focal necrosis, resulting in the accumulation of fibrous tissue that forms an advanced lesion. The process is repeated in a cyclical fashion until the artery can no longer dilate far enough to compensate for blockage.

Regardless of the underlying cause of inflammation, reversal or inhibition of the harmful inflammatory processes leading to atherosclerosis, while leaving protective inflammatory responses intact, is the subject of increasing attention from researchers. Several antiinflammatory molecules are in development at this time, as shown in Table V.

Table V: Antiinflammatory agents in development for the prevention and treatment of atherosclerosis and hyperlipidemia.

Drug Name	Source	Mechanism of Action	Status
AGI-1067	AtheroGenics	Antioxidant, composite vascular protectant	Phase III
SB-480848	GlaxoSmithKline	Lipoprotein-associated phospholipase A_2 inhibitor	Phase II
AC-3056	Amylin	Antioxidant	Phase I
NV-04	Novogen	Antioxidant	Phase I
SB-659032	GlaxoSmithKline	Lipoprotein-associated phospholipase A_2 inhibitor	Phase I

Table VI: Miscellaneous drugs in development for the treatment of atherosclerosis and hyperlipidemia.

Drug Name	Source	Mechanism of Action/Description	Status
HE-2200	Hollis-Eden	Immunopotentiating and antiinflammatory agent	Phase II
Iroxanadine	Biorex R&D	Drug targeting endothelial cell dysfunction	Phase II
Motexium Lutetium	Pharmacyclics	Agent for photoangioplasty	Phase I/II
D-003	Laboratorios Dalmer	Mixture of high aliphatic primary acids isolated and purified from sugar cane wax	Phase I

Miscellaneous drugs

In addition to the many groups described above, other drugs are under investigation for the treatment and/or prevention of atherosclerosis that work via less clearly defined mechanisms of action or whose mechanisms have not yet been elucidated. Table VI presents information on these miscellaneous antiatherosclerotic and antihyperlipidemic agents.

Coronary artery disease

Coronary artery disease is a life-threatening condition resulting from uncontrolled atherosclerosis. It typically presents as angina and progresses via myocardial infarction to congestive heart failure. Coronary artery disease may be asymptomatic (*i.e.*, silent ischemia) or may cause symptoms of chest pain and shortness of breath. In some patients the disease develops slowly and silently for decades, going virtually unnoticed until it causes a heart attack.

Coronary artery disease affects approximately seven million Americans. Each year, some 500,000 Americans die of heart attacks caused by coronary artery disease, making it the number one cause of mortality among both men and women in that country. According to the American Heart Association's Heart Disease and Stroke Statistics - 2003 Update, the estimated total cost of coronary artery disease in the U.S. for 2003 is predicted to reach USD 129.9 billion.

In the initial stages, the disease is typically treated by lifestyle modifications, often in combination with drug therapy. Drug classes used to treat coronary artery disease include lipid-lowering drugs, aspirin and other platelet antiaggregatory or anticoagulant drugs, antianginal agents and antihypertensive drugs. As disease progresses, these drug classes may be used in combination. In more serious cases, surgical intervention is necessary via coronary angioplasty or coronary bypass surgery.

Antioxidants

BO-653, a phenolic antioxidant and lipid peroxidation inhibitor discovered by Chugai, is in phase II testing in Japan and phase I in the U.S. for the treatment of coronary artery disease. This same product is also being developed for the treatment of restenosis, as indicated elsewhere in this article.

Angiogenic gene therapy

Generx™ (Ad5-FGF4) is a nonsurgical angiogenic gene therapy that is being developed by Collateral Therapeutics as a potential treatment for patients with stable exertional angina due to coronary artery disease. Generx™ uses an adenovirus serotype 5 to deliver FGF4. It is designed to be administered by an interventional cardiologist via a one-time intracoronary infusion through a standard cardiac catheter. Generx™ is now being evaluated in a worldwide phase III clinical development program by parent company Schering AG.

GenVec's lead cardiovascular product candidate, **BioBypass®-CAD** (AdGVVEGF121.10), is in late-stage phase II clinical trials to evaluate its potential use in the treatment of coronary artery disease. It is being studied alone and as an adjunct to surgical procedures. BioBypass®-CAD is intended to induce new blood vessel formation in tissues with inadequate blood flow. Vascular endothelial growth factor (VEGF) is a natural protein needed for the body's normal process of growing new blood vessels. BioBypass®-CAD delivers the VEGF 121 gene to the heart so that new blood vessels are formed in

the diseased ischemic tissue. The gene is carried to the site of disease by GenVec's proprietary adenoviral vector.

AnGes, a Japanese biotechnology start-up developing gene-based drugs, oligodeoxynucleotides and novel gene vectors, has discovered and developed a hepatocyte growth factor gene medicine (HGF-DNA, **DS-992**), a potentially revolutionary new treatment for coronary artery disease and peripheral occlusive artery disease. This product, which has been licensed to Daiichi Pharmaceutical, is under phase II evaluation in the U.S. for both indications. It is also being tested in clinical studies in Japan and Europe, and is expected to reach its first market – Japan – in 2004. Intramuscular injection of DS-992 in the disease area stimulates the formation of HGF, which induces the regeneration of blood vessels (angiogenesis) and improves blood circulation. No serious side effects have been observed in clinical trials to date, and preliminary efficacy results are promising.

Selective estrogen receptor modulators

The incidence of heart disease in women rises sharply after menopause, leading to the suggestion that estrogen may have protective effects on the heart. Lilly is conducting the RUTH (Raloxifene Use for The Heart) phase III trial to assess the potential cardioprotective effects of **raloxifene hydrochloride**, a selective estrogen receptor modulator that is widely marketed (as Evista™) for osteoporosis, in women. RUTH is designed to determine if raloxifene can reduce the risk of heart attack and heart-related death, as well as the incidence of invasive breast cancer, in postmenopausal women who have or are at increased risk of cardiovascular disease. The trial is fully enrolled with 10,101 participants. Women are currently in their third to fifth year of this trial.

Combination products

In June 2003, the FDA approved Bristol-Myers Squibb's Pravigard PAC (**pravastatin sodium/buffered aspirin**) for use along with diet to reduce the occurrence of cardiovascular events, including death, heart attack or stroke, in patients with heart disease. The combination therapy is supplied as separate pills packaged together in several different dose combinations.

Photodynamic therapy

Final phase I results of photodynamic therapy with Pharmacyclics' **motexafin lutetium** injection (Antrin®), reported by the company in October 2002, indicate that the treatment is feasible and well tolerated in patients with coronary artery disease. The phase I study assessed the safety and tolerability of escalating doses of motexafin lutetium and light in patients with blocked coronary arteries. Patients received the study drug intravenously 18-24 h before standard balloon angioplasty and stent placement. Photodynamic therapy was performed on the balloon-treated vessel segment before placement of a stent. Of 80 patients enrolled at 7 U.S. sites, 79 received motexafin lutetium with activation of the drug with light delivered endovascularly. Seventy-five patients had follow-up coronary angiography at up to 6 months. The treatment was well tolerated and there was no stenosis observed at the edges of the stented portions of the artery. Furthermore, no major treatment-related angiographic or biochemical adverse events, abnormalities or dose-limiting toxicities were noted. Moreover, there were no incidences of emergency coronary artery bypass, death, stroke or myocardial infarction in the treated patients.

Angina pectoris

Angina pectoris, more commonly known simply as angina, is a condition characterized by recurring pain or discomfort in the chest occurring when some part of the heart does not receive enough blood. When the heart's oxygen requirement exceeds the supply available in the blood nourishing the organ, angina results. Angina is frequently a symptom of coronary artery disease.

Angina is experienced as a sensation of squeezing or pressing pain, generally localized to the chest area under the breastbone. However, pain may also be experienced in the shoulders, arm, neck, jaw or back. Angina is usually provoked by physical exertion, and tends to wane within a few minutes if the individual rests or takes medication. Other frequent triggers of angina pain include emotional stress, extreme heat or cold, heavy meals, alcohol and cigarette smoking.

The two most commonly encountered forms of angina pectoris are stable and unstable. Stable angina, the most common form, emerges gradually and occurs in a regular or characteristic pattern, and tends to result from somewhat predictable causes. Unstable angina, also known as acute coronary syndrome, may emerge suddenly as a severe episode or as frequently recurring bouts of angina.

According to the American Heart Association, around 6,300,000 Americans are currently living with angina pectoris. This figure includes 2,300,000 men and 4,000,000 women. Approximately 400,000 new cases of stable angina and 150,000 cases of unstable angina are reported each year. On average, angina costs per patient exceed USD 14,000 per year in medical costs and lost wages.

The objectives of antianginal drug therapy include the elimination of cardiac ischemia, reduction or complete elimination of angina attacks, prevention of myocardial infarction and improvement of long-term survival. Stable angina is typically treated with drugs that either increase the supply of oxygen to the heart (*e.g.*, coronary vasodilators, nitroglycerin) or decrease myocardial demand for oxygen (*e.g.*, antihypertensive agents). Lifestyle modifications, with the objective of eliminating or modifying

cardiovascular risk factors, is important in the treatment as well as the prevention of angina.

Nitrates

Nitrates, exemplified by nitroglycerin, are among the most widely used drugs to treat angina. Nitrates act as potent venodilators and, at higher doses, as arterial dilators. In this fashion they redistribute blood flow and relieve coronary spasm and dynamic stenosis. Nitrates also induce the formation of nitric oxide (NO), and thus are able to produce coronary vasodilation even under conditions of impaired endogenous NO production, such as in coronary artery disease. Sankyo is developing **CS-780**, a novel nitrate and potential antianginal agent, in phase I trials.

Calcium channel blockers

Calcium channel blockers are a chemically heterogeneous class of drugs that selectively inhibit the opening of L-type calcium channels in vascular smooth muscle and myocardium, thereby producing vasodilation and decreasing peripheral vascular resistance. Calcium antagonists are widely used in the treatment of angina. In spite of the relatively large number of calcium channel blockers on the market for this indication, this remains an active area of research.

Otsuka is conducting phase III clinical trials in Japan evaluating **pranidipine** (Acalas®) in the treatment of both angina and hypertension. The data obtained will be used to reapply for marketing approval in Japan, as a previous application was rejected.

Asahi Kasei has signed licensing agreements with Schering AG, granting the latter development rights to both oral and injectable formulations of the calcium antagonist **fasudil hydrochloride** as a potential new treatment for angina. Fasudil (Eril®) has been marketed by Asahi in Japan since 1995 for the treatment of vasospasm following surgery for subarachnoid hemorrhage.

pFOX inhibitors

CV Therapeutics is developing **ranolazine** (Ranexa™) for the potential treatment of chronic angina. Ranolazine is the first in a potential new class of compounds that are believed to work by partial inhibition of fatty acid oxidation (pFOX inhibition). Preclinical research indicates that compounds that work via pFOX inhibition may increase the efficiency of oxygen use by the heart, by shifting the heart's metabolism to a fuel source which requires less oxygen to generate the same amount of energy. The company filed an NDA for this product in December 2002. If approved by the FDA, ranolazine would represent the first new class of antianginal therapy in the U.S. in more than 20 years.

Miscellaneous drugs

In addition to the major drug classes described above, pharmaceutical companies continue to investigate potential new drugs for angina pectoris that work via a variety of other mechanisms of action. Table VII presents information on these miscellaneous agents for angina.

Myocardial infarction

Myocardial infarction, commonly known as heart attack, occurs when the blood supply to part of the heart muscle itself (the myocardium) is severely reduced or stopped. The reduction or interruption of blood flow happens when one or more of the coronary arteries supplying blood to the myocardium is blocked, typically as a result of atherosclerosis. The atherosclerotic plaque can eventually burst, tear or rupture, creating a "snag" where a blood clot forms and blocks the artery.

According to the American Heart Association (Heart Disease and Stroke Statistics - 2003 Update), this year an estimated 650,000 Americans will have a new coronary attack. Approximately 450,000 will have a recurrent

Table VII: Miscellaneous drugs in development for the treatment of angina pectoris.

Drug Name	Source	Mechanism of Action	Status
Angiogenix™	Endovasc	Nicotinic agonist, angiogenesis inducer	Phase II
Ivabradine Hydrochloride	Servier	HCN (I_f) current] blocker	Phase III
ETC-216	Esperion	Recombinant human ApoA-I Milano	Phase II
ETC-588	Esperion	HDL cholesterol-increasing agent	Phase II
VX-702	Vertex	p38 mitogen-activated protein kinase inhibitor	Phase II
VEGF-2 Gene Therapy	Corautus	Angiogenic gene therapy	Phase I/II
1069	Aventis Pharma	Guanylate cyclase inhibitor	Phase I
1766	Aventis Pharma	Guanylate cyclase inhibitor	Phase I
Sabiporide Mesilate	Boehringer Ingelheim	Na^+/H^+ exchange inhibitor	Phase I
VT-111	Viron Therapeutics	Serine protease inhibitor	Phase

attack. Depending upon gender and clinical outcome, people who survive the acute stage of a heart attack have a rate of illness and death that is anywhere from 1.5-15 times greater than that of the general population. Heart attack survivors are at significant risk for another heart attack, sudden death, angina, heart failure and stroke. The cost associated with myocardial infarction and other coronary heart disease is also substantial: in 1998 (the most recent year for which statistics are available), USD 10.6 billion was paid to Medicare beneficiaries for conditions associated with coronary heart disease, including USD 10,428 per discharge related to acute myocardial infarction.

The goals of myocardial infarction therapy are to break up or prevent blood clots, prevent platelets from gathering and sticking to the plaque, stabilize plaque and prevent further ischemia. Treatment must be initiated as soon as myocardial infarction is diagnosed, but within 1-2 h of onset of symptoms, in order to prevent significant damage from occurring. Drugs typically administered to heart attack victims include anticoagulants (*e.g.*, heparin, warfarin), antiplatelets (*e.g.*, aspirin, dipyridamole) and thrombolytics (*e.g.*, alteplase, streptokinase), as well as ACE inhibitors and β-blockers.

Angiotensin AT_1 antagonists

Blockade of angiotensin II receptors is an alternative method of interfering with the renin-angiotensin system. This strategy, which has been successfully exploited in the treatment of arterial hypertension and congestive heart failure, is also the subject of investigation in the area of myocardial infarction.

Patient enrollment was completed in July 2001 in the VALsartan In Acute Myocardial INfarction Trial (VALIANT) trial, the first-ever international trial aimed at determining the effects of Novartis's angiotensin receptor blocker **valsartan** (Diovan®) in high-risk patients who have experienced myocardial infarction. The trial is one of a series of several major clinical trials examining the protective benefits of valsartan in addition to its known blood pressure-lowering properties, for which the drug is currently marketed. The trial, which will compare valsartan alone and in combination with the ACE inhibitor captopril compared with captopril alone, is expected to be completed in 2004. VALIANT is a prospective, double-blind, randomized, active-controlled mortality and morbidity trial involving patients who have recently experienced an acute myocardial infarction (within 12 h to 10 days of onset of symptoms) complicated by either clinical or radiological signs of heart failure and/or evidence of left ventricular systolic dysfunction. The primary endpoint is all-cause mortality and secondary endpoints include cardiovascular death, hospitalization for heart failure, cardiovascular morbidity, coronary revascularization procedures, cardiovascular procedures and all-cause mortality or hospitalization.

Complement inhibitors

In early 2002, Avant Immunotherapeutics' announced the results of a phase II study of the complement inhibitor **TP-10** showing that the compound failed to meet the primary endpoint in adult patients undergoing high-risk cardiac surgery. A total of 564 patients were randomized to receive 1 of 4 doses of TP-10 (1, 3, 5 or 10 mg/kg) or placebo as a 30-min i.v. infusion, and were followed for 28 days following surgery. The primary efficacy endpoint of the study was the comparison of TP-10-treated patients *versus* placebo who experienced either death or myocardial infarction, or required prolonged intubation or prolonged intraarterial balloon pump therapy. TP-10 was found to be well tolerated. Additional analysis of data from the trial suggested a treatment benefit in male but not female patients. Further analysis revealed that the male population experienced a statistically significant 36% reduction in the primary endpoint as well as a significant 43% reduction in the combined endpoint of death or myocardial infarction. A similar treatment effect was not seen in the female population. Avant Immunotherapeutics is seeking a partner to further the development of this class of compounds.

Alexion and partner Procter & Gamble have completed two large phase II studies evaluating the complement inhibitor **pexelizumab** in patients with myocardial infarction.

Miscellaneous drugs

In addition to the major classes described above, several other drugs are in development for the treatment of myocardial infarction. These products are listed in Table VIII, together with their mechanisms of action and status of development for this indication.

Table VIII: Miscellaneous drugs in development for the treatment of myocardial infarction.

Drug Name	Source	Mechanism of Action	Status
Caldaret Hydrate	Mitsubishi Pharma/Takeda	Na^+/Ca^{2+} exchange inhibitor	Phase II
Iroxanadine	Biorex R&D	Drug targeting endothelial cell dysfunction	Phase II
ITF-1697	Italfarmaco	Undisclosed	Phase II
MC-1	Medicure	Cardioprotectant, naturally occurring small molecule	Phase I

Coronary angioplasty and restenosis

The primary cause of death in the Western world is cardiovascular disease, and the most common cause is the narrowing and blockage of arteries due to atherosclerosis. In more than 50% of these cases, percutaneous transluminal coronary angioplasty is performed to eliminate the blockage. Over one million coronary angioplasty procedures are performed annually in the U.S. to open narrowed or occluded arteries. This typically involves the insertion of a balloon that is inflated to compress the plaque against the arterial wall, followed in as many as 70% of the cases by the insertion of a wire-mesh scaffold or stent to prevent or minimize the likelihood of restenosis, or reblockage. A similar procedure is also commonly used to treat blocked peripheral arteries. Without stents, the incidence of vascular restenosis within the first few months runs as high as 40%, depending on the configuration and location of the vascular lesion and other clinical factors. With the use of stents to help keep dilated coronary arteries open, the incidence of restenosis is reduced substantially, but remains unacceptably high.

Numerous drugs, including many antiplatelet agents, anticoagulants, ACE inhibitors, and cytotoxic agents, have been administered to patients following coronary angioplasty and stenting but have failed to significantly reduce the overall incidence of vascular reblockage. Novel therapeutic interventions are needed.

Antioxidants

Chugai is conducting phase II trials evaluating the ability of the antioxidant molecule **BO-653** to prevent post-percutaneous transluminal coronary angioplasty restenosis. BO-653 is developed as an oral capsule formulation.

Gene therapy

AVI BioPharma is conducting phase II trials evaluating **Resten-NG™**, a NeuGene® antisense compound targeting c-myc, for treating cardiovascular restenosis. Results from two independent studies reported at the American College of Cardiology meeting in April 2003 demonstrated the feasibility of treating cardiovascular restenosis by delivering Resten-NG™ systemically, using the company's proprietary microbubble delivery technology, to treat arteries, potentially avoiding or reducing the need to use special drug delivery catheters or drug-coated stents.

Novel therapeutics

Medicure's lead compound **MC-1** has produced positive results in the phase II MEND-1 trial conducted in Canada and the U.S. by the Duke Clinical Research Institute. The randomized, placebo-controlled, blinded study enrolled 60 patients at high risk for cardiac damage and assessed the cardioprotective effect of MC-1 in mitigating damage caused by ischemia and ischemia-reperfusion in heart disease patients undergoing angioplasty. Both the primary and secondary endpoints were met. The primary endpoint was infarct size during the procedure, as determined by the amount of CK-MB released over 24 h following percutaneous coronary intervention. Improvement was also shown in certain secondary endpoints, and clinical tolerability and safety were reported to be good. Medicure is seeking partners to further the development of this naturally occurring small molecule.

Endothelial dysfunction is the target of Biorex's R&D program. Key discoveries in the past decade have revealed that the vascular endothelium is an important regulatory organ that is involved in maintaining cardiovascular homeostasis in health and contributes significantly to the pathogenesis of several cardiovascular diseases. Injury or activation of endothelial cells disrupts these normal regulatory mechanisms and results in abnormal endothelial cell function, called endothelial dysfunction. Clinically, endothelial dysfunction can be described as generalized or localized vasospasm, thrombosis, atherosclerosis, and restenosis. **Iroxanadine** (BRX-235), a compound designed to repair damaged endothelial cells and restore normal endothelial cell function, is in phase II testing for the treatment of arterial restenosis.

NicOx's **NCX-4016**, a nitric oxide-donating derivative of acetylsalicylic acid, is currently in phase II clinical trials for the treatment of restenosis.

Photodynamic therapy

Pharmacyclics is enrolling patients in a phase II, double-blind, multicenter, randomized clinical trial evaluating **motexafin lutetium** injection plus infrared light activation for the prevention of restenosis and for the primary treatment of *de novo* atherosclerotic lesions in femoral and popliteal arteries.

Coronary artery bypass graft surgery

Coronary artery bypass graft surgery is an operation designed to detour blood around an occluded segment of a coronary artery in an effort restore blood flow to the heart muscle. Usually a vein grafted from the leg is used for the bypass, although arm veins or other vessels may be used instead. If successful, the surgery can eliminate chest pain, improve exercise capability and lengthen life. Approximately 500,000 bypass procedures are performed each year in the U.S. alone. Approximately 8-12% of such grafts are less than optimal, however, and the mortality rate for patients who must undergo repeat coronary artery bypass graft is nearly 10%.

Complement inhibitors

Alexion and Procter & Gamble announced in February 2003 that enrollment of patients in PRIMO-CABG (Pexelizumab for Reduction in Infarction and Mortality in Coronary Artery Bypass Graft Surgery), a pivotal phase III clinical trial of **pexelizumab** in the management of patients undergoing coronary artery bypass graft surgery with cardiopulmonary bypass, had been completed. PRIMO-CABG is a 3,000-patient, randomized trial of placebo *versus* pexelizumab bolus followed by a continuous infusion over 24 h. Its primary composite endpoint is reduction in the incidence of all-cause mortality and myocardial infarction. Results should be reported during the second half of 2003. Pexelizumab is a monoclonal antibody that targets the C5 component of complement, an important component of the innate immune system. During a heart bypass procedure, complement is released by the body. This complement causes inflammation, which can lead to side effects such as chest pain, heart attacks, heart failure, or impairment of memory, language and motor skills. The purpose of this study is to find out whether pexelizumab, which blocks complement release, can reduce such side effects and be taken safely.

Plasma kallikrein inhibitors

Over 600,000 patients undergo cardiopulmonary bypass in conjunction with coronary artery bypass graft in the U.S. each year, and serious blood loss is a major problem. Dyax is conducting phase II trials to determine whether **DX-88**, a highly specific and potent recombinant inhibitor of kallikrein, may offer an alternative therapy to help reduce blood loss associated with this surgery and, possibly, the adverse effects of the inflammatory response. Kallikrein is a key regulator of inflammatory and blood clotting processes. Activated kallikrein is thought to play a role in a number of inflammatory and autoimmune diseases or conditions, including blood loss following major surgical procedures. Due to its high specificity to kallikrein, DX-88 may have fewer side effects and/or greater effectiveness in the treatment of inflammation than naturally occurring inhibitors.

Antisense therapy

Corgentech is developing **E2F Decoy**, a novel antisense oligonucleotide that binds to and inactivates the cell-cycle transcription factor E2F, as a potential agent for prolonging the durability of bypass vein grafts, in phase III clinical trials. After being harvested from the leg or arm, the vein grafts are bathed for about 10 min in an E2F Decoy solution. E2F is responsible for activating at least a dozen genes that are required for vascular cell growth and multiplication. Its blockade prevents the proliferation of these abnormal cells (neointimal hyperplasia) that eventually results in atherosclerotic lesions.

Cardioprotectants

Medicure is developing **MC-1**, a naturally occurring small molecule with cardioprotective activity, in the treatment of various cardiovascular indications. In preclinical studies, MC-1 has demonstrated effectiveness in significantly reducing damage to the heart muscle, as well as improving cardiac function and contractile force. The company has initiated phase I trials in the setting of coronary artery bypass graft surgery.

Peripheral vascular disease

Peripheral arterial occlusive disease is the result of atherosclerotic and thrombotic processes, and is associated with a substantial morbidity and mortality (such as gangrene and amputation). Blood flow can be restored through operative bypass surgery, vascular repair surgery or pharmacological dissolution of the blood clot. Primarily due to dietary changes, peripheral arterial disease is increasing in prevalence in industrialized countries worldwide. Currently around 8 million patients are diagnosed with peripheral arterial occlusive disease each year in the U.S. alone, and as many as 150,000 amputations are required each year due to severe disease.

Intermittent claudication is a symptom of vascular disease. It is characterized by muscle pain, ache, cramp, numbness or fatigue in association with exercise and which is relieved by rest. It is most often caused by atherosclerotic narrowing of the iliac and femoral arteries, often combined with lesions in distal arteries of the leg. Intermittent claudication occurs when the leg muscles do not receive the oxygen-rich blood required during exercise, causing leg pain that is experienced as cramping, tightness or fatigue in the hips, thighs or calves. It may affect as many as 5% of men and 2.5% of women over 60 years of age. For some the symptoms improve with therapy, especially exercise therapy, medication or surgery. For 10-20% they progress, and in perhaps one in 20 amputation is necessary because of a gangrenous limb.

Nitric oxide donors

In October 2002, NicOx received IND approval allowing the evaluation in U.S. phase II trials of **NCX-4016**, a nitric oxide-donating derivative of acetylsalicylic acid, in the treatment of several peripheral arterial occlusive diseases. The IND has allowed expansion of NicOx's broad development program for NCX-4016 in the field of cardiovascular and metabolic diseases, which includes diabetes-related renal and vascular complications, and the treatment of endothelial dysfunction in patients with peripheral vascular disease. In total, the phase II

Table IX: Angiogenic gene therapies in development for the treatment of peripheral vascular diseases.

Product Name	Source	Description	Status
BioBypass®-PVD	GenVec	Adenovirus vector delivering the gene for VEGF 121	Phase II
NV1FGF	Aventis Pharma	Non-viral vector (naked plasmid) encoding human FGF-1	Phase II
Genvascor	Collateral Therapeutics	Adenovirus vector to deliver the gene for FGF-4	Phase I/II
VEGF-2 Gene Therapy	Corautus	Gene encoding VEGF-2 formulated as naked plasmid DNA	Phase I/II
VLTS-589	Valentis	Gene therapy that encodes the Del-1 (developmental endothelial locus-1) protein	Phase I/II
VMDA-3601	ViroMed/Dong-A	Naked DNA containing cDNA for the VEGF gene	Phase I
DS-992	AnGes/Daiichi Pharmaceutical	Hepatocyte growth factor gene medicine	Clinical

development program will involve the recruitment of approximately 120 patients by mid-2003.

Angiogenic gene therapy

Therapeutic angiogenesis, the induction of new blood vessel growth to correct poor blood circulation in cardiovascular states such as coronary artery disease and stroke, is being pursued as a novel method of restoring blood flow and preventing tissue death. Gene therapy is considered one of the most promising methods of obtaining this novel therapeutic objective. The development of angiogenic gene therapies for the treatment of peripheral vascular diseases is an active field of reseach at this time, as indicated in Table IX.

Antisense therapy

Corgentech is developing **E2F Decoy**, a novel antisense oligonucleotide that binds to and inactivates the cell-cycle transcription factor E2F, as a potential agent for preventing peripheral artery bypass graft failure. Phase III studies are under way in the U.S. and Canada for this indication. E2F is responsible for activating at least a dozen genes that are required for vascular cell growth and multiplication. Its blockade prevents the proliferation of these abnormal cells (neointimal hyperplasia) that eventually results in atherosclerotic lesions.

Miscellaneous

Sigma-Tau has completed phase III studies evaluating **ST-261** (propionyl-L-carnitine) in the treatment of intermittent claudication, and is currently preparing an NDA for filing.

Heart failure

Heart failure, often called congestive heart failure, is a progressive disorder of left ventricular myocardial remodeling that culminates in a complex clinical syndrome characterized by impaired cardiac function and circulatory congestion. The condition occurs when the heart is damaged or overworked and unable to pump out all the blood that returns to it from the systemic circulation. As less blood is pumped out, blood returning to the heart backs up and fluid builds up in other parts of the body. Heart failure also impairs the kidneys' ability to dispose of sodium and water, further complicating fluid retention. Two major forms of heart failure exist: systolic and diastolic. Systolic heart failure occurs when the contractile ability of the heart decreases, while diastolic heart failure occurs when the heart loses its ability to relax.

The American Heart Association estimates that approximately 4.7 million Americans have congestive heart failure. As many as 550,000 new cases of heart failure are diagnosed each year. Heart failure causes 39,000 deaths each year and contributes to another 225,000 in the U.S. alone. Chronic heart failure is the most costly cardiovascular illness in the U.S., resulting in annual expenditures of more than USD 40 billion. Hospital-related costs alone accounted for USD 19.4 billion in 2001. In the U.S. as well as most European countries, heart failure consumes 1-2% of the national annual healthcare budget.

There is no definitive cure for heart failure. However, several classes of drugs are available that improve cardiac function and relieve symptoms, significantly prolonging life and improving quality of life for patients. These include diuretics, beta-blockers, ACE inhibitors, phosphodiesterase inhibitors and many more. Identification and treatment of underlying conditions such as hypertension is an important component of the therapeutic regimen for heart failure.

Diuretics

Diuretics play an important role in the management of patients with both acute and chronic heart failure, and are the most effective agents available for relieving pulmonary and peripheral edema in the setting of overt fluid overload. They are inexpensive, effective and well tolerated by most patients. Early use of high-dose diuretics was associated with unwanted side effects, but at the currently recommended lower dose levels and with the introduction of potassium-sparing diuretics, most of these adverse events cease to be problematic. Diuretics are

Table X: Diuretics in development for the treatment of heart failure.

Drug Name	Source	Mechanism of Action	Status
Conivaptan Hydrochloride	Yamanouchi	Vasopressin V_{1a}/V_2 antagonist	Phase II
Mozavaptan	Otsuka	Vasopressin V_2 antagonist	Phase II
Naxifylline	CV Therapeutics/Biogen	Adenosine A_1 antagonist	Phase II
SR-121463A	Sanofi-Synthélabo	Vasopressin V_2 antagonist	Phase II
Tolvaptan	Otsuka	Vasopressin V_2 antagonist	Phase II
SLV-320	Solvay	Adenosine A_1 antagonist	Phase I

frequently prescribed in combination with ACE inhibitors and β-blockers for patients with symptomatic heart failure.

New diuretics in development for the treatment of heart failure are presented in Table X.

Angiotensin AT_1 antagonists

During the early 1970s, the antagonism of angiotensin II at its receptor site was proposed as an alternative to ACE inhibition for suppressing Ang II activity. The approach could offer potentially improved treatments for hypertension and heart failure, as angiotensin II may be generated by enzymes other than ACE. Several angiotensin II blockers have been launched for the indication of hypertension, and the first compounds in this class are nearing the market for the indication of heart failure, although some setbacks have been reported. Current evidence suggests that while not the treatment of choice, angiotensin II blockers may represent a good therapeutic alternative for patients in whom ACE inhibitors are contraindicated or clearly not tolerated, or in addition to ACE inhibitors for patients who are intolerant of β-blockers.

During the summer of 2002, the U.S. FDA approved Novartis's **valsartan** (Diovan®) as the first angiotensin II blocker for the treatment of heart failure (NYHA class II-IV) in patients who are intolerant of ACE inhibitors. The primary basis for the new U.S. indication was Val-HeFT, a study of 5,010 heart failure patients from 16 countries. The overall results of Val-HeFT show that valsartan improves heart failure morbidity and slows the progression of disease compared to placebo in patients taking other heart failure therapy prescribed by their physicians. Overall mortality was similar in the active drug and placebo groups. In Val-HeFT, valsartan provided the greatest benefit in patients who did not take an ACE inhibitor. In these patients, the angiotensin II blocker improved survival by 41%, reduced morbidity by 49% and reduced the risk for hospitalization for heart failure by 57%.

At least two other angiotensin II blockers are under clinical evaluation for the treatment of heart failure: **irbesartan** (Sanofi-Synthélabo/Bristol-Myers Squibb), in phase III, and **candesartan cilexetil** (Takeda/Astra-Zeneca), in phase III in the E.U. for this new indication and undergoing regulatory review in Japan; both are already marketed for the treatment of arterial hypertension.

Aldosterone antagonists

Pharmacia (now Pfizer) reported in January 2003 that both primary endpoints had been met in the EPHESUS (Eplerenone Post-AMI HEart failure efficacy and SUrvival Study) trial of **eplerenone** (Inspra™). The randomized, double-blind, placebo-controlled trial enrolled 6,644 patients at 674 centers in 37 countries. It evaluated the impact of eplerenone plus standard therapy on survival and morbidity in patients who had recently suffered a heart attack and also had early complications of heart failure, as identified by left ventricular dysfunction. The primary endpoints were death from any cause and death or hospitalization from cardiovascular causes. Based on the results of this trial, the company has filed a supplemental NDA for eplerenone in the treatment of postmyocardial infarction heart failure. Eplerenone was previously approved by the FDA in September 2002 for the treatment of high blood pressure.

Endothelin antagonists

In 2002, a dose-optimization study evaluated Actelion's **tezosentan sodium** (Veletri™), an intravenous dual endothelin ETA/ETB receptor antagonist, for the treatment of acute heart failure. The study was the result of the full evaluation of an earlier clinical trial program (RITZ), which was concluded unsuccessfully in 2001. The dose-optimization study showed that lower doses are efficacious in terms of improvements in important hemodynamic parameters. These improvements were not associated with clinically relevant side effects. Based on these results showing the potential of tezosentan, and taking into consideration the need for an acute heart failure drug providing more than symptomatic relief, Actelion has decided to proceed with two phase III registration studies with tezosentan evaluating mortality/morbidity benefits (VERITAS-1 and VERITAS-2). These studies will run through 2004. Genentech is Actelion's development partner for tezosentan.

Encysive Pharmaceuticals (formerly Texas Biotechnology) is conducting phase I trials with **TBC-3711**, an

endothelin antagonist with potential in heart failure and other cardiovascular indications.

Vasopeptidase inhibitors

Although the renin-angiotensin system has been established as a prime target for cardiovascular disease therapy, the search for a new generation of drugs is being actively pursued with the aim of further decreasing cardiovascular morbidity and mortality. A new therapeutic strategy has been planned based on the design of compounds that are able to inhibit two or more endothelial cell peptidases. The development of vasopeptidase inhibitors, which inhibit the activity of both ACE and neutral endopeptidase (NEP), has been an active field of study in recent years and is considered especially promising for the treatment of heart failure. Bioprojet and Lilly are codeveloping the vasopeptidase inhibitor **fasidotril**, a potential new treatment for heart failure, in phase II trials. Phase II studies will continue into 2003, with potential U.S. submission in 2008 for congestive heart failure.

Brain natriuretic peptide

Scios' **nesiritide** (Natrecor®) is a recombinant form of B-type natriuretic peptide, a naturally occurring hormone in the body that aids healthy functioning of the heart and that was developed by the company as a revolutionary new treatment for heart failure. The agent causes arteries and veins to dilate, alleviating symptoms by improving blood movement around the heart without a change in heart rate. In August 2001, the FDA approved nesiritide for the treatment of acutely decompensated congestive heart failure in patients who have dyspnea at rest or with minimal activity. The approval was based on scientific data from a number of controlled clinical trials in patients with acute congestive heart failure, the most recent of which (the VMAC study) involved 489 patients who were randomized to treatment with nesiritide, intravenous nitroglycerin or placebo for 3 h. The study showed that patients receiving nesiritide had greater improvement in shortness of breath than those receiving placebo. The major adverse reaction associated with nesiritide is hypotension. Nesiritide is administered intravenously, primarily in a standard fixed-dose regimen that does not require titration. Scios began shipping the product in mid-August 2001, just one week after approval.

Combination products

The efficacy of BiDil®, a combination product from NitroMed incorporating **isosorbide dinitrate** and **hydralazine hydrochloride**, in treating heart failure in African American patients is being evaluating in a pivotal confirmatory clinical trial (A-HeFT). If approved, BiDil® will be the first medication specifically indicated for use in African Americans. This is considered an important research development, as studies have shown that African Americans are about twice as likely as white patients to suffer from heart failure. This disparity is attributed to various factors, including a pathophysiology found primarily in African American patients that may involve nitric oxide insufficiency. BiDil® may work by restoring depleted NO levels and by protecting the NO that is formed in these patients' vascular endothelial cells.

Miscellaneous drugs

In addition to the major mechanisms of action described above, several drugs are in development for heart failure that work via a wide range of other mechanisms. These products are presented in Table XI.

Arrhythmia

The term arrhythmia refers to any change from the normal sequence of electrical impulses, causing abnormal heart rhythms. This can cause the heart to pump less effectively. Some arrhythmias are so brief (for example, a temporary pause or premature beat) that the overall heart rate or rhythm isn't greatly affected. But if arrhythmias last for some time, they may cause the heart rate to be too slow or too fast or the heart rhythm to be erratic.

Common types of arrhythmia include tachycardia (abnormally fast heartbeat: greater than 100 beats per minute [bpm]) and bradycardia (abnormally slow heartbeat: less than 60 bpm). Atrial fibrillation is a condition in which the electrical signal to the upper chambers of the heart becomes irregular and results in rapid, uncoordinated cardiac contraction. Other types of arrhythmia include premature beats and ventricular arrhythmia.

Digitalis was introduced in England in 1785; digoxin, its modern-day derivative, remains an important treatment for fast heart rates caused by atrial fibrillation. Antiarrhythmic agents are sometimes referred to as Class I (sodium channel blockers), Class II (β-adrenergic blockers), Class III (potassium channel blockers) and Class IV (calcium channel blockers); only drugs from Classes II and IV are commonly used today. Newer antiarrhythmic drugs adhere less closely to this somewhat antiquated classification system. Pacemakers, defibrillators and other implantable devices, as well as surgical intervention, represent important therapeutic options for patients with arrhythmia.

Potassium channel blockers

Solvay is dedicating considerable resources to the development of **tedisamil hydrochloride**, a novel potassium channel blocker currently being evaluated in an extensive phase III program. The product is administered i.v. in the acute phase to convert atrial fibrillation to sinus

Table XI: Miscellaneous drugs in development for heart failure.

Drug Name	Source	Mechanism of Action	Status
Nicorandil*	Chugai	Potassium channel activator	Phase III
Nolomirole Hydrochloride	Chiesi	Dopamine D_2 agonist/alpha$_2$-adrenoceptor agonist	Phase III
Toborinone	Otsuka	Positive inotropic, PDE III inhibitor	Phase III
VAS-991	Vasogen	Immunomodulating therapy that involves i.m. administration of syngeneic blood following *ex vivo* treatment with elevated temperature, oxidation and ultraviolet light	Phase III
Oxypurinol	Cardiome	Xanthine oxidase inhibitor	Phase II/III
ALT-711	Alteon	A.G.E. crosslink breaker	Phase II
Caldaret Hydrate	Mitsubishi Pharma/Takeda	Na^+/Ca^{2+} exchange inhibitor	Phase II
EMR-62204	Merck KGaA	Na^+/H^+ exchange inhibitor	Phase II
GLP-1(7-36)amide	Amylin	Recombinant glucagon-like peptide	Phase II
SLV-306	Solvay	NEP inhibitor/ECE inhibitor	Phase II
DITPA	University of Arizona	Thyroid hormone analogue	Phase I
ZP-120	Zealand Pharma	ORL1 agonist	Phase I

*Marketed for another indication

rhythm, then continued as oral maintenance therapy. The anticipated launch date for the i.v. form is 2004, followed by a slated 2006 launch of the oral form.

Following a recent meeting with the FDA, Cardiome plans to move forward with a phase III trial of **RSD-1235**, a dual-acting potassium and sodium channel blocker formulated for i.v. use, for the acute termination of atrial fibrillation in the hospital setting. Patient enrollment is scheduled to begin in the second half of 2003. The first of the upcoming phase III trials will evaluate the ability of RSD-1235 to convert atrial fibrillation in 420 patients enrolled across 40 sites in North America and Europe. In previous studies in patients with atrial fibrillation, RSD-1235 demonstrated conversion in 61% of patients and was well tolerated, with no significant adverse events even at dose levels higher than the expected effective dose.

Phase III trials are currently under way in the U.S., Canada and Europe evaluating the efficacy of **azimilide hydrochloride**, a potassium channel blocker from Procter & Gamble, in the treatment of atrial fibrillation.

β-Adrenergic blockers

Lanodiolol (Onoact®) was launched last fall in Japan by Ono for the treatment of intraoperative tachyarrhythmia (atrial fibrillation, atrial flutter and sinus tachycardia). Lanodiolol improves tachyarrhythmia by selectively blocking β_1-adrenoceptors located mainly in the heart and by inhibiting the action of catecholamine.

Sanofi-Synthélabo has recently encountered obstacles in the development of **dronedarone hydrochloride**, a dual β- and α-adrenoceptor antagonist targeted to the treatment of atrial fibrillation, but continues to pursue development of the compound. The ANDROMEDA study, a morbidity/mortality study in high-risk patients with congestive heart failure and ventricular dysfunction, was discontinued in January 2003 upon a recommendation made by the DSMB. The decision was made after an interim safety analysis indicated a potential excess risk of death in patients on active treatment. The double-blind, placebo-controlled study was conducted in Denmark, Hungary, Norway, Poland, Sweden and The Netherlands. Of the target 1,000 patients, 627 had been enrolled. In addition to ANDROMEDA, the phase III program includes two pivotal trials – EURIDIS in Europe, and ADONIS in North America, South America, Australia and South Africa – in the maintenance of sinus rhythm in patients with atrial fibrillation. Both of these trials have completed enrollment and continue as planned.

Adenosine A_1 agonists

CV Therapeutics is developing **tecadenoson** (CVT-510), a selective adenosine A_1 receptor agonist, for the potential control of heart rate during acute atrial arrhythmias. In July 2002, CVT completed patient enrollment in a phase III clinical trial of tecadenoson in patients with paroxysmal supraventricular tachycardias. In addition, a broad phase IIb development program aimed at defining an optimized dosage in patients with atrial fibrillation is currently under way.

Earlier this year, Aderis received a milestone payment from partner Fujisawa related to the final report from a phase II study of intravenous **DTI-0009**, an adenosine A_1 agonist under development to control heart rate during atrial fibrillation. Results from a phase II dose-escalation study in the electrophysiology laboratory demonstrated a dose-related slowing of conduction in the heart in patients being studied that could translate to slowing of an uncontrolled heart rate in atrial fibrillation. Final results are pending from three other phase II trials in patients with atrial fibrillation. DTI-0009 is designed to act selectively at the adenosine A_1 receptor to slow conduction and thereby slow an abnormally high heart rate response.

Miscellaneous drugs

Piboserod hydrochloride, a 5-HT_4 antagonist from GlaxoSmithKline that was previously studied for the treatment of irritable bowel syndrome, is in phase II trials as a potential treatment for atrial fibrillation.

The potential clinical utility of AstraZeneca's **AZD-7009**, an atrial selective repolarization-delaying agent developed for the treatment of atrial fibrillation, is being assessed in phase I clinical trials.

Sanofi-Synthélabo has reported that **SSR-149744**, an antiarrhythmic agent with an undisclosed mechanism of action, is undergoing phase I clinical testing. This agent is targeted to the treatment of atrial fibrillation.

Arterial hypertension

Arterial hypertension, commonly referred to as high blood pressure, is an extremely common and highly preventable chronic condition in which blood pressure in the arteries is higher than normal. Hypertension is defined by both the World Health Organization and the American Heart Association as a consistent systolic pressure of 140 or higher and diastolic pressure of 90 or higher. If not properly controlled, it represents a significant risk factor for several serious cardiovascular and renal conditions. Hypertension may be a primary disease, called essential hypertension or idiopathic hypertension, or it may be caused by other diseases, in which case it is classified as secondary hypertension. Essential hypertension accounts for 90-95% of all cases. Isolated systolic hypertension, a form of hypertension in which systolic pressure is abnormally high but diastolic pressure is not, is a frequent and significant problem in the elderly. Isolated systolic hypertension places patients at risk of heart attack, heart failure, stroke and death, and is not effectively treatable with existing antihypertensive drugs. The condition is the most common form of hypertension, affecting more than 50% of all people over the age of 60.

Hypertension is the most common cardiovascular condition in the world, affecting nearly 691 million people worldwide. This includes some 50 million individuals in the U.S. alone. The prevalence of hypertension among adult populations worldwide is approximately 20%, but in the U.S. this figure is closer to 25%. More than 30% of all people with high blood pressure are unaware of their condition. According to the American Heart Association's Heart Disease and Stroke Statistics - 2003 Update, the estimated total cost of hypertensive disease in the U.S. for 2003 is predicted to reach USD 50.3 billion.

Hypertension is typically treated with diuretics, beta-blockers, calcium antagonists, ACE inhibitors or angiotension II blockers. Antihypertensive therapy is recommended for all persons with a heavy burden of coronary heart disease risk factors, even those with blood pressure readings in the normal range. More aggressive therapy is recommended for hypertensive patients with diabetes, renal insufficiency or other comorbid conditions.

Table XII: Calcium antagonists recently launched and in development for the treatment of hypertension.

Drug Name	Source	Status
Azelnidipine	Sankyo/Ube	L-2003
Pranidipine	Otsuka	Phase III
(*S*)-Amlodipine	Sepracor	Phase II
Clevidipine	The Medicines Co.	Phase II

Calcium antagonists

Verapamil, the first calcium channel blocker, reached the market in 1963. Nearly 20 such compounds are now available for the treatment of arterial hypertension, the newest of which was launched just this year. Calcium channel blockers are well established in the treatment of essential hypertension, and new compounds continue to be developed.

The long-acting calcium antagonist **azelnidipine** (Calblock®), developed by Sankyo and Ube, was launched in Japan earlier in 2003 for the treatment of hypertension. Azelnidipine produces a 24-h stable antihypertensive effect when administered once a day. It is a slow-effect dihydropyridine calcium antagonist, but unlike other similar drugs, it does not cause an associated increase in heart rate with chronic administration. Other calcium antagonists are in late-stage clinical trials, as shown in Table XII.

Angiotensin AT_1 antagonists

Sankyo's angiotensin II receptor blocker **olmesartan medoxomil** (Benicar™), was approved and launched last year in the U.S. for use in the treatment, alone or in combination with other antihypertensive agents, of high blood pressure. Taken once daily, olmesartan demonstrates superior antihypertensive activity compared with the leading ARB losartan potassium (Merck & Co.'s Cozaar®). Olmesartan is comarketed in the U.S. by Forest. In addition, a combination product containing **olmesartan medoxomil/hydrochlorothiazide** was approved in 2003.

Teveten HCT Plus®, another combination antihypertensive agent incorporating the angiotensin II receptor blocker **eprosartan mesilate/hydrochlorothiazide**, was launched for the first time last year in Germany. The product, which originated at SmithKline Beecham, is marketed by Biovail and is manufactured for the latter by Solvay.

Protherics is developing **PMD-2850**, a novel angiotensin vaccine designed to provoke an antibody response and block the hypertensive effects of angiotensin. Results from a phase I trial showed that the product was able to lower blood pressure in normal volunteers. An analysis of the trial data confirmed a statistically significant reduction in 24-h blood pressure in immunized normal volunteers receiving a low-salt diet as compared to volunteers who

did not receive the vaccine. This effect was more marked during the night, when immunized subjects had, on average, a diastolic blood pressure more than 6 mmHg lower than control subjects. These results provide strong evidence of pharmacological proof of concept for the angiotensin vaccine. Protherics is now conducting phase II trials in patients with mild to moderate hypertension.

Renin inhibitors

Renin is a proteolytic enzyme synthesized in the kidney. The blockade of angiotensin II production through the inhibition of renin has received considerable attention due to the specificity of the enzyme; angiotensinogen is the only known substrate for renin. A possible advantage of renin inhibitors is that they may have few side effects due to their specific nature. The first renin inhibitors studied were peptide compounds and had poor bioavailability. Subsequent efforts to develop orally active renin inhibitors were met with many difficulties. Speedel Pharma's **aliskiren fumarate** (SPP-100), potentially the first renin inhibitor to reach the market, is being rapidly developed through an ambitious fast-track program. In September 2002, Speedel announced that Novartis had exercised its call-back option for aliskiren fumarate for further development for the treatment of hypertension. Aliskiren is the first orally active renin inhibitor to be developed through phase II clinical studies. Speedel licensed aliskiren form Novartis in 1999 and conducted fast-track development, including the design and development of a new synthesis yielding multikilogram quantities, the design of an oral solid dosage form, and the successful and rapid development program in essential hypertension through phase II and pilot studies in congestive heart failure and chronic renal failure.

Vasopeptidase inhibitors

As mentioned above, Bioprojet and Lilly are codeveloping the vasopeptidase inhibitor **fasidotril** for the treatment of heart failure. In addition to heart failure, the drug is in phase II trials for hypertension, with potential U.S. submission as early as 2006 for this indication.

Bristol-Myers Squibb is reportedly considering its options regarding the future of **omapatrilat**, a vasopeptidase inhibitor that was previously regarded as a highly promising potential agent for hypertension. In July 2002, the FDA's Cardiovascular and Renal Drugs Advisory Committee issued a negative decision regarding an NDA for omapatrilat (Vanlev®), filed in December 2001, due to the unacceptably high rate of life-threatening angioedema in clinical trials. The FDA subsequently issued an approvable letter, requesting one more clinical trial before considering approval.

Aldosterone antagonists

Aldosterone plays an important role in regulating electrolyte composition by promoting sodium retention and potassium excretion. The main renal effect of aldosterone is to stimulate sodium/potassium transport in the distal tubules, thus enhancing sodium reuptake and potassium excretion. Aldosterone has several adverse effects on the cardiovascular system, including myocardial fibrosis, left ventricular hypertrophy, fluid retention, potassium and magnesium excretion, which in chronic states of hyperaldosteronism can lead to significant morbidity and mortality. Elevated aldosterone levels have been observed in conditions such as edema, congestive heart failure, essential hypertension and complications of kidney disease and hepatic cirrhosis.

The first selective aldosterone blocker, Pfizer's **eplerenone** (Inspra™), was launched in the U.S. in 2002 for the treatment of arterial hypertension, alone or in combination with other antihypertensive agents. Clinical trials in approximately 3,000 patients demonstrated that eplerenone was effective in lowering high blood pressure both alone and in combination with other antihypertensive agents, and that it was well tolerated.

Endothelin antagonists

Endothelin is the most potent and long-acting vasoconstrictor isolated from mammalian cells. The 21-amino acid endothelin peptide, which has mitogenic, vasoconstrictor and bronchoconstrictor effects, was originally discovered in porcine aorta cells and subsequently identified in many other cell types (neurons, glia, vascular smooth muscle, endothelium and gastric mucosa). Endothelin antagonists were first proposed to have therapeutic potential in the treatment of conditions such as congestive heart failure, hypertension and other cardiovascular disorders some ten years ago.

Two endothelin antagonists are known to be in active development as antihypertensive agents at this time: Speedel's **SPP-301** and Encysive Pharmaceuticals' **TBC-3711**, in phase II and phase I, respectively.

Combination products

Vita-Invest reported in July 2002 that it had launched Eneas®, its fixed-dose combination product for the treatment of essential hypertension, in Spain. Eneas contains the ACE inhibitor **enalapril maleate** and the calcium antagonist **nitrendipine** and is indicated for the treatment of patients who do not respond to monotherapy with either component alone. Eneas is the first evidence-based fixed-dose combination of an ACE inhibitor and a calcium channel blocker that has been shown to have positive effects on cardiovascular morbidity and mortality.

Table XIII: Miscellaneous drugs in development for the treatment of arterial hypertension.

Drug Name	Source	Mechanism of Action	Status
ALT-711	Alteon	A.G.E. crosslink breaker	Phase II
SLV-306	Solvay	NEP inhibitor/ECE inhibitor	Phase II
MC-4232	Medicure	Undisclosed	Phase I/II
AVE-7688	Aventis	ACE inhibitor/NEP inhibitor	Phase I
NV-04	Novogen	Antioxidant	Phase I

Miscellaneous drugs

In addition to the major drug classes described above, other antihypertensive agents with a variety of mechanisms of action are also known to be in active development. Information on these products is presented in Table XIII.

Pulmonary hypertension

Pulmonary hypertension is a rare and serious progressive lung disorder characterized by blood pressure above the normal range within the pulmonary arterial system. Symptoms are often nonspecific and may include fatigue after minimal exertion, edema, dizzy spells, anginal chest pain and fainting. Some patients may experience a racing pulse or palpitations. Two subtypes of the disorder exist: primary pulmonary hypertension occurs in the absence of a known cause, while secondary pulmonary hypertension occurs as a result of another medical condition, generally scleroderma, COPD or systemic lupus erythematosus.

Although the true prevalence of primary pulmonary hypertension is unknown, it is relatively rare, occurring in approximately 1-2 patients per million population. In the U.S., some 300 new cases are diagnosed each year. The long-term prognosis for patients with primary pulmonary hypertension is grim. The 5-year survival rate for patients diagnosed with pulmonary hypertension is approximately 50%, although with effective medical treatment and/or organ transplantation, patients can expect to live somewhat longer.

Various approaches can be taken in the treatment of pulmonary hypertension. Some treatment regimens are designed to reduce or facilitate the work of the right ventricle. Anticoagulants can decrease the blood's tendency to clot and allow it to flow more freely, while diuretics can decrease the amount of fluid in the body, thereby reducing the workload of the heart. Calcium channel blockers relax smooth muscles in blood vessels and the cardiac wall, improving the heart's ability to pump blood. Prostacyclin, a vasodilator, helps the blood vessels to dilate and prevents blood clots from forming. Only a handful of drugs have been specifically approved for the indication of pulmonary hypertension, although off-label use of marketed drugs in the classes listed above is widespread.

Prostacyclin analogues

Prostacyclin is a potent endogenous vasodilator, platelet antiaggregatory agent and cytoprotectant. The use of prostaglandin or of its analogues in the treatment of pulmonary hypertension is supported by the existence of an imbalance between thromboxane and prostacyclin metabolites, as well as a reduction of prostacyclin synthase in the pulmonary arteries, in patients with the condition.

The prostacyclin analogue **treprostinil sodium** (Remodulin™) was launched in the U.S. in June 2002 for the treatment of pulmonary hypertension. Developed and marketed by United Therapeutics, treprostinil is specifically approved for the treatment of pulmonary arterial hypertension in patients with NYHA class II-IV symptoms, to reduce symptoms associated with exercise.

Another promising prostacyclin analogue in development is Schering AG's **iloprost**, currently marketed in an injectable form for the treatment of thromboangitis obliterans and severe arterial occlusive disease. Iloprost (Ventavis®), which has orphan drug status for primary pulmonary hypertension, received a positive opinion from Europe's Committee for Proprietary Medicinal Products in May 2003. A decision by the European Commission is expected in the second half of the year. The benefits of iloprost were demonstrated in a multicenter, randomized, double-blind, placebo-controlled phase III trial in 203 adult patients with stable pulmonary hypertension. Inhaled iloprost or placebo was added to the current therapy of the patients, excluding prostacyclin or its analogues. The primary endpoint of the study was a combined response criterion of improvement of at least 10% compared to baseline in exercise capacity (6-min walk test) at 12 weeks, improvement by at least 1 NYHA class at 12 weeks, and no deterioration of pulmonary hypertension or death at any time before 12 weeks. The rate of responders to iloprost was 16.8%, while in the placebo group it was 4.9%. The drug's effects include direct vasodilatation of the pulmonary arterial bed, with subsequent significant improvement in pulmonary artery pressure, pulmonary vascular resistance and cardiac output, as well as mixed venous oxygen saturation.

Endothelin antagonists

Endothelin was originally discovered in porcine aorta cells and subsequently identified in many other cell types.

Three endothelin isopeptides (endothelin-1, -2 and -3) and two receptor subtypes (ET_A and ET_B) are known to exist. Endothelin antagonists were first proposed to have therapeutic potential in the treatment of conditions such as congestive heart failure, hypertension and other cardiovascular disorders some 10 years ago. Endothelin has more recently been found to play a pivotal role in the development of pulmonary hypertension, and high endothelin concentrations correlate strongly with disease severity.

Endothelin antagonists are now considered to represent an especially promising new approach to the treatment of pulmonary hypertension. In December 2001, the selective endothelin ET_A antagonist **bosentan** (Tracleer®; Actelion) became the first endothelin antagonist to reach the market for pulmonary hypertension. This product was originally discovered at Roche but was abandoned due to side effects encountered during clinical trials for other indications. Actelion later licensed bosentan from Roche and pursued development of the product for the pulmonary hypertension indication. The FDA-approved indication for bosentan is to improve exercise ability and decrease the rate of clinical worsening in pulmonary hypertension patients with significant limitation of physical activity (WHO class III and IV).

Other endothelin antagonists are advancing steadily through the development pipeline as potential new agents for the treatment of pulmonary hypertension. The most advanced of these is **sitaxsentan sodium**, an ET_A antagonist in phase III trials at Encysive Pharmaceuticals (formerly Texas Biotechnology). Encysive also has a follow-up ET_A antagonist designated **TBC-3711** in phase I clinical testing for this and various other cardiovascular indications. Finally, **ambrisentan**, an ET_A antagonist originally discovered by Abbott, has advanced to phase II testing under the direction of licensee Myogen.

Portal hypertension

Portal hypertension is a condition in which blood flow through the portal vein of the liver is impeded as a result of cirrhosis. As blood flow through the portal vein is slowed down, blood pressure increases and blood that is unable to flow through the portal vein is circumvented through other blood vessels, which are unable to handle the increased pressure. These swollen vessels, called varices, have thin walls and can burst easily. Bleeding from a broken blood vessel is a serious, sometimes fatal condition.

NCX-1000, an NO-donating derivative of ursodeoxycholic acid, is under development at NicOx for the treatment of chronic liver diseases and their complications such as portal hypertension and cirrhosis. In animal models of liver inflammation, NCX-1000 was shown to be significantly effective in reducing inflammation and organ damage and in decreasing portal hypertension. NicOx received an IND in February 2003 allowing the company to start phase I clinical studies in the U.S. and Europe evaluating NCX-1000 for the treatment of portal hypertension.

Hypotension

Hypotension is a condition in which blood pressure is abnormally low, causing symptoms of dizziness and lightheadedness. When the blood pressure is too low, there is inadequate blood flow to the heart, brain and other vital organs. Hypotension may be caused by some medications, including anxiolytics, antihypertensives, diuretics, antidepressants and narcotic analgesics, by alcohol or as a result of dehydration, shock, heart failure, myocardial infarction and other serious medical conditions. A separate, common cause of low blood pressure is orthostatic hypotension, which is caused by a sudden change in body position (*e.g.*, from lying down to standing up).

Nitric oxide synthase inhibitors

ONO-1714, an inhibitor of inducible nitric oxide synthase, is being developed by Ono in phase II clinical trials as a potential treatment for hypotension during dialysis.

Miscellaneous cardiovascular conditions

Ark Therapeutics is developing **Trinam™** (EG-004), a product incorporating a vascular endothelial growth factor (VEGF) gene coupled to an adenoviral vector and incorporated into a proprietary biodegradable local delivery device, for a novel indication. The product is designed to prevent *de novo* stenosis and prolong the time to failure of hemodialysis access grafts. The product has been granted orphan drug status in the U.S. for this indication, and has been evaluated in a phase I trial, in which successful gene transfer and good tolerability were demonstrated. The company has received FDA approval to conduct phase II/III trials, and is in discussions with the agency regarding the design of such trials.

Information sources on the internet

American College of Cardiology
www.acc.org

American Heart Association
www.americanheart.org

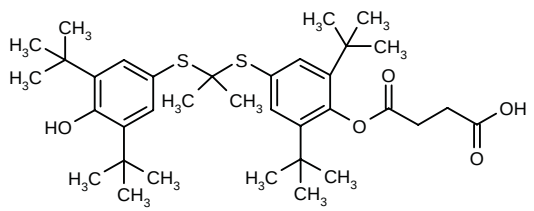
Angioplasty.org
www.ptca.org

National Heart, Lung and Blood Institute
www.nhlbi.nih.gov

Monograph Updates of Cardiovascular Drugs

N.E. Mealy
Prous Science, P.O. Box 540, 08080 Barcelona, Spain

AGI-1067



AGI-1067, a new oral agent from AtheroGenics targeting atherosclerosis by reducing inflammation in the blood vessel walls, is the first in the vascular protectant (v-protectant) class of compounds that function by blocking the expression of a selective set of inflammatory genes, including vascular cell adhesion molecule (VCAM-1), which have been implicated in the initiation and progression of atherosclerosis.

AtheroGenics has begun enrollment of patients in its pivotal phase III ARISE (Aggressive Reduction of Inflammation Stops Events) trial, a double-blind, placebo-controlled study that will be conducted at over 180 cardiac centers in the U.S., Canada, the U.K. and South Africa and will evaluate clinical outcome measures such as death due to cardiovascular disease, myocardial infarction, stroke, coronary revascularization and unstable angina in patients with coronary artery disease (CAD). The study will assess the incremental benefits of AGI-1067 over current standard-of-care therapies. The trial will enroll 4,000 patients who will continue to receive other appropriate heart disease medications and who will be followed for an average of 18 months or until a minimum of 1,160 primary events have occurred. The FDA has confirmed that the ARISE trial protocol is adequate to support an NDA for AGI-1067 for secondary prevention in patients with coronary artery disease. Results from the phase II CART-1 (Canadian Antioxidant Restenosis Trial) study indicated that AGI-1067 has a direct antiatherosclerotic effect on the coronary blood vessels, including improvements in lumen volume, plaque volume and total vessel volume. The CART-1 study was a double-blind, randomized, placebo-controlled clinical trial that compared the effects of AGI-1067 and its parent drug probucol in 305 patients subjected to percutaneous coronary intervention (PCI). The study treatments consisted of oral AGI-1067 (70, 140 or 280 mg once daily), probucol (500 mg b.i.d.) or placebo during the last 14 days before PCI and for 4 additional weeks after the procedure, together with an extra dose of 280 mg of AGI-1067, 1000 mg of probucol or matching placebo during the evening before PCI. AGI-1067 dose-dependently increased the luminal area and volume of the blood vessel at the PCI site, thereby reducing the incidence of restenosis by 26%. Probucol induced similar beneficial effects on the blood vessel but was associated with a higher incidence of Q-Tc prolongation (17.4%) compared to placebo (4.8%) and all three AGI-1067 doses (4.8%, 2.4% and 2.5% for 70, 140 and 280 mg, respectively). AGI-1067 also improved the luminal dimensions of reference blood vessel segments not subjected to PCI, suggesting a direct effect on atherosclerosis (1-6).

AtheroGenics and the Montreal Heart Institute were awarded a grant from the Canadian Institutes of Health Research to support the Canadian Antioxidant Restenosis Trial 2 (CART-2). The phase IIb clinical trial, which began in December 2001, will enroll 500 patients and will evaluate the impact of a 12-month oral dosing regimen of AGI-1067 (280 mg) on the reversal of atherosclerosis, as identified in a poststudy analysis of the CART-1 data, and the prevention of postangioplasticity restenosis (7).

Oral administration of AGI-1067 (50 and 150 mg/kg/day for 1 year) to hypercholesterolemic cynomolgus

monkeys was well tolerated and resulted in reduced levels of LDL cholesterol, with an increase in HDL cholesterol at the higher dose. AGI-1067 (150 mg/kg/day for 12 weeks) reduced the extent of atherosclerosis in mice deficient in either the LDL receptor or apolipoprotein E, as quantitatively assessed by cholesterol ester content measurement in the aorta. Comparatively, probucol (150 and 250 mg/kg/day) had only modest antiatherosclerotic and LDL cholesterol-lowering effects in these animal models. AGI-1067, but not probucol (both 133 mg/kg/day s.c. for 1 week), reduced the expression of proinflammatory molecules in the lungs of lipopolysaccharide-challenged C57BL/6 mice. These data suggest that AGI-1067 may be a promising therapeutic agent for coronary artery disease (8).

1. *Phase III ARISE trial of AGI-1067 opens enrollment*. DailyDrugNews.com (Daily Essentials) July 2, 2003.

2. Tardif, J.-C., Grégoire, J., Schwartz, L. et al. *Effects of AGI-1067 and probucol after percutaneous coronary interventions*. Circulation 2003, 107(4): 552.

3. *AtheroGenics presents review of 2001, looks at year ahead*. DailyDrugNews.com (Daily Essentials) Feb 20, 2002.

4. *AtheroGenics to advance AGI-1067 in atherosclerosis*. DailyDrugNews.com (Daily Essentials) July 1, 2002.

5. *ARISE phase III protocol adequate to support AGI-1067 NDA*. DailyDrugNews.com (Daily Essentials) March 17, 2003.

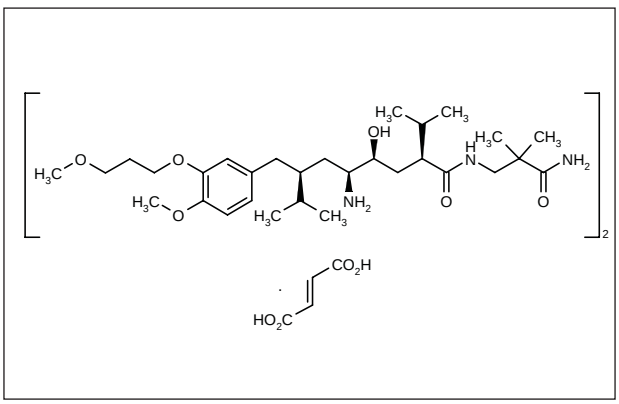
6. *Effect of AGI-1067 on atherosclerosis assessed in pivotal trial*. DailyDrugNews.com (Daily Essentials) Jan 16, 2003.

7. *AtheroGenics awarded CIHR grant for CART-2 atherosclerosis trial*. DailyDrugNews.com (Daily Essentials) Nov 19, 2002.

8. Sundell, C.L. et al. *AGI-1067: A multifunctional phenolic antioxidant, lipid modulator, anti-inflammatory and antiatherosclerotic agent*. J Pharmacol Exp Ther 2003, 305(3): 1116.

Original monograph - Drugs Fut 2003, 28(5): 421.

Aliskiren Fumarate



The first orally active renin inhibitor, aliskiren fumarate (SPP-100) was licensed by Speedel from Novartis in 1999 and developed for the treatment of hypertension through a fast track program. Late last year, Novartis exercised its call-back option for the compound for further development for the treatment of hypertension. With clinical development for this indication completed through phase IIb, aliskiren is now moving into phase III development. Pilot studies have also been conducted in congestive heart failure and chronic renal failure (1, 2).

In a randomized, double-blind, crossover study, 18 healthy volunteers received placebo or enalapril 20 mg and aliskiren 40 and then 80 mg/day, or 160 and then 640 mg/day in 3 periods of 8 days each. Study subjects were maintained on a constant 100 mmol/day sodium diet. Aliskiren was well tolerated and dose-dependently reduced angiotensin II, with the 160-mg dose producing an effect equal to that of enalapril 20 mg (3).

A multicenter, randomized, double-blind, active comparator (100 mg losartan once daily) trial in 266 patients with mild to moderate hypertension assessed the efficacy of oral aliskiren fumarate (37.5, 75, 150 or 300 mg once daily for 4 weeks). Treatment with aliskiren resulted in dose-dependent reductions in daytime ambulatory systolic blood pressure (SBP), with mean changes at the end of 4 weeks of –1.3 ± 9.5, –5.5 ± 10.6, –8.5 ± 10.4 and –10.5 ± 10.7 mmHg for the respective doses of aliskiren *versus* –11.1 ± 13.4 mmHg for losartan; the reductions at doses of 75, 150 and 300 mg aliskiren were significant and the effects at the two higher doses were not significantly different from losartan. Similar effects were observed on daytime ambulatory diastolic blood pressure (DBP) and nighttime ambulatory SBP and DBP. Treatments were well tolerated, with similar safety profiles obtained for both agents; the incidence of adverse events did not increase with the dose of aliskiren (4).

1. *Speedel enters agreement with Roche for new class of renin inhibitors*. DailyDrugNews.com (Daily Essentials) March 25, 2002.

2. *Novartis exercises option to license back oral renin inhibitor*. DailyDrugNews.com (Daily Essentials) Sept 20, 2002.

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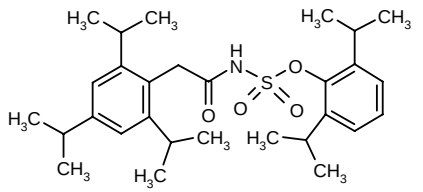
Original monograph - Drugs Fut 2001, 26(12): 1139.

Avasimibe



Avasimibe (CI-1011) is a new ACAT inhibitor which is in phase III clinical development at Pfizer for the treatment of hypercholesterolemia and atherosclerosis.

An *in vitro* study showed that avasimibe enhanced cholesterol efflux from human monocyte-derived macrophages, thus limiting foam cell development. A reduced B_{max} in binding studies with increasing concentrations of avasimibe suggests an alteration of scavenger receptor function in response to ACAT inhibitors (1).

In the presence of HDL lipoproteins, avasimibe (0.01-0.5 μM) concentration-dependently reduced cholesteryl ester content in phorbol ester-treated human monocytic leukemia cells incubated with serum acetyl-LDL (150 μg/ml). The reduction occurred only in non-lipid-loaded cells and without an increase in free intracellular cholesterol. At 0.2 and 0.5 μM, the effect of avasimibe was enhanced by the addition of atorvastatin (5 μM). This enhancement was reversed by the inclusion of mevalonate (200 μM) or geranyl-geraniol (10 μM). The authors suggest that the synergistic effect of avasimibe and atorvastatin *in vitro* may underlie published *in vivo* results (2).

1. Rodriguez, A., Usher, D.C. *Anti-atherogenic effects of the acyl-CoA:cholesterol acyltransferase inhibitor, avasimibe (CI-1011), in cultured primary human macrophages*. Atherosclerosis 2002, 161(1): 45.

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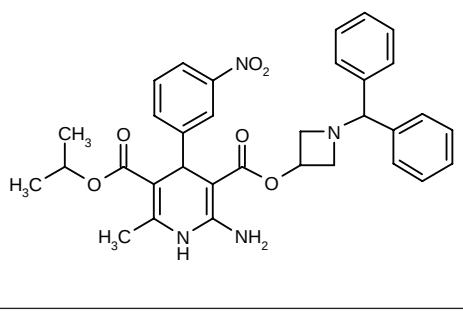
Azelnidipine



The long-acting calcium antagonist azelnidipine (Calblock®, CS-905, RS-9054), developed by Sankyo and Ube, has been launched in Japan for the treatment of hypertension. Azelnidipine produces a 24-h stable antihypertensive effect when administered once a day. It is a slow-effect dihydropyridine calcium antagonist, which unlike other similar drugs, does not cause an associated increase in heart rate with chronic administration (1).

A study involving 46 patients with essential hypertension compared the efficacy of azelnidipine (16 mg/day) and amlodipine (5 mg/day) on blood pressure for 24 h following 6 weeks of treatment. Both agents decreased systolic blood pressure by 13 mmHg; azelnidipine decreased pulse rate by 2 beats/min whereas amlodipine increased pulse rate by 4 beats/min. Analysis of the pharmacokinetic data revealed a $t_{1/2}$ of 28.5 ± 19.8 h for amlodipine and 8.68 ± 1.33 h for azelnidipine. It was concluded that the hypotensive effects of both agents were similar despite the difference in $t_{1/2}$ values (2).

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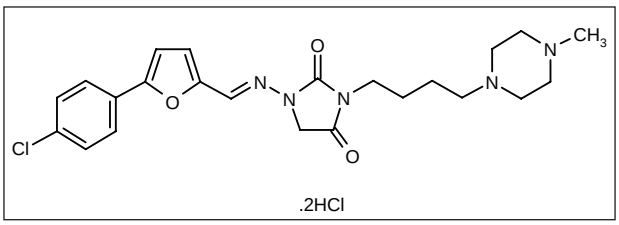
Azimilide Hydrochloride



The potassium channel blocker azimilide hydrochloride (NE-10064, Stedicor®) is undergoing phase III clinical trials in the U.S., Canada and Europe by Procter & Gamble for the treatment of atrial fibrillation.

Azimilide was found to inhibit cellular membrane outward delayed rectifier potassium currents, ultrarapid delayed rectifier currents and transient outward potassium currents in human atrial myocytes (1).

Azimilide (0.1-30 μM) prolonged the action potential duration (APD) at a cycle length of 1000 ms in Purkinje fibers and papillary muscle from canine hearts in a reverse-frequency-dependent manner. In papillary muscle, azimilide was ineffective in preventing the pinacidil-mediated shortening of APD and caused a rate-dependent depression in the maximal upstroke velocity of the action potential. The drug inhibited both the rapid and slow component of the delayed rectifier potassium current, as well as the L-type calcium current (IC_{50} = 0.39, 0.59 and 7.5 μM, respectively), without affecting the transient outward or inward rectifier potassium currents. In conclusion, azimilide has multiple sites of action and blocks calcium- and use-dependent sodium channels at the highest concentrations tested (2).

The pharmacokinetics of azimilide dihydrochloride (125 mg) in patients with normal and severe renal impairment were evaluated. Renal clearance of azimilide was attenuated in patients with renal impairment as compared to volunteers with normal renal function (4.8 ml/h/kg *vs.* 14.1 ml/h/kg). No other significant differences were observed in the pharmacokinetic parameters between the two groups (3).

A study evaluated the total symptom burden at the time of arrhythmia recurrence in patients with atrial fibrillation who took part in 2 trials where they were randomized to either azimilide 125 mg/day or placebo. Compared to placebo, azimilide significantly reduced the number of symptoms reported by patients at recurrence of arrhythmia in both trials, without significantly affecting heart rate (4).

In the ALIVE trial, patients with a recent myocardial infarction and low left ventricular ejection fraction were treated with placebo or azimilide 100 mg. Evaluation of patients who entered the trial with atrial fibrillation (n=93) showed that more patients given azimilide had restored sinus rhythm at 1 year compared to placebo (34% *vs.* 6%). In addition, more placebo-treated patients than azimilide-treated patients developed atrial fibrillation during the trial (19 *vs.* 8) (5).

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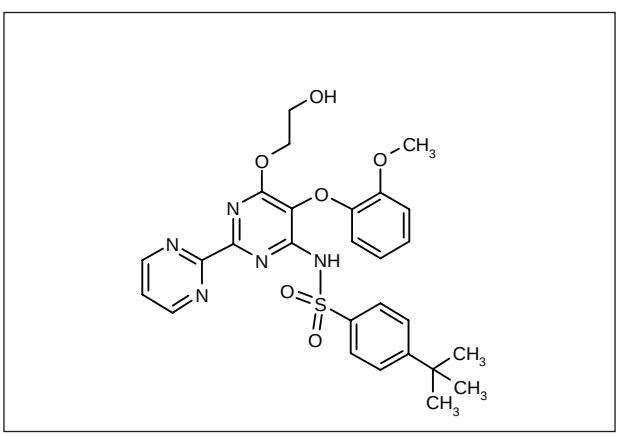
Bosentan



Bosentan (Tracleer®) is an orally available dual endothelin ET_A/ET_B receptor antagonist developed by Actelion. The drug was launched in The Netherlands, Spain, Portugal and Finland during the first quarter of 2003 and is now available in the U.S., where it was first introduced in 2001, Canada, Switzerland and all E.U. markets with the exception of Denmark, Belgium and Luxembourg, for the treatment of pulmonary arterial hypertension. Actelion also filed for marketing approval for this indication in Japan and Brazil in April 2003. Clinical programs for bosentan were initiated in late 2002 and early 2003 in idiopathic pulmonary fibrosis and pulmonary fibrosis related to scleroderma (phase II/III BUILD program) and in metastatic melanoma (1-4).

Researchers investigated the potential utility of endothelin receptor blockade as a novel treatment strategy for malignant melanoma based on evidence linking ET_A receptors to angiogenic processes and ET_B receptors to melanocyte development and function. They used the dual ET_A/ET_B receptor antagonist bosentan and primary and metastatic melanoma tissue samples. All samples tested were found to express ET_B receptors, and several metastatic tumor samples expressed low levels of ET_A receptors. Bosentan inhibited the proliferation of all cell lines with IC_{50} values of 2-30 μg/ml (5).

Bosentan, Ro-47-8634, Ro-48-5033, Ro-64-1056 and glibenclamide (all at final concentrations of 1, 5 or 25 μM) were tested to evaluate their effects on the activity of the pregnane X receptor in CV-1 monkey kidney cells transiently transfected with a luciferase reporter plasmid containing 3 copies of the ER6 response element of CYP3A4 and the human or mouse pregnane X receptor. Bosentan (EC_{50} = 19.9 μM), Ro-47-8634 and glibenclamide all activated the pregnane X receptor. A molecular mechanism for the CYP-inducing activity of bosentan in humans was therefore demonstrated (6).

Bosentan (100 mg/kg/day) was found to exert a protective effect on the kidney of diabetic rats. Blood pressure was unaffected by the agent, indicating a direct action on endothelin receptors. Urinary protein excretion was significantly higher and the renal content of collagen I and fibronectin significantly lower in diabetic rats who received the vehicle as compared to diabetic rats who received bosentan or nondiabetic controls (7).

Of 32 patients with pulmonary arterial hypertension enrolled in a double-blind, placebo-controlled trial, 29 continued in a 1-year extension study of open-label bosentan (125 mg b.i.d.) treatment. Benefits in exercise capacity were maintained for 6 months with bosentan in the long-term study, and an improvement in NYHA functional class was maintained for 1 year in all but 1 patient (8).

Treatment with bosentan in pediatric patients with pulmonary arterial hypertension was well tolerated and improved hemodynamic parameters according to the results from an open-label study in 19 patients. Patients were divided into groups according to weight (10-20 kg, 20-40 kg and > 40 kg) and were administered once-daily doses of 31.25, 62.5 and 125 mg bosentan, respectively. Following 4 weeks of treatment, doses were titrated up to the respective target doses of 31.25, 62.5 and 125 mg b.i.d. Following single and multiple dosing, variability in exposure to the drug was < 2-fold and exposure decreased over time in all groups. The mean change from baseline in pulmonary arterial pressure and pulmonary vascular resistance was –8.0 mmHg and –300 $dyn \cdot s \cdot m^2/cm^5$, respectively (9).

Results from the phase III ENABLE program evaluating bosentan in 1,613 patients with severe chronic heart failure (NYHA class IIIb/IV) showed no statistical significance in the endpoints of risk reduction in time to death or hospitalization due to chronic heart failure, or improvement in clinical status at 9 months (10).

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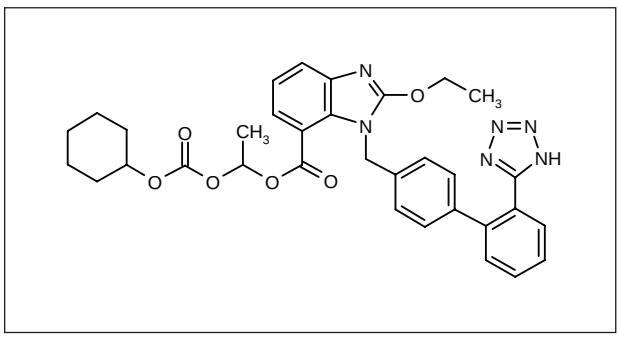
Candesartan Cilexetil



Candesartan cilexetil (Atacand®, AstraZeneca; Blopress®, Takeda) is currently available for the treatment of hypertension. It is also in late-stage clinical development for the treatment of heart failure, and clinical study results are summarized below.

Candesartan (target dose of 16 mg once daily) or placebo was added to angiotensin-converting enzyme (ACE) inhibitor therapy in 28 heart failure patients in a

randomized study. At 1 month, the addition of candesartan did not reduce oxidative stress or improve endothelial function in these patients. Exercise capacity was also not enhanced, and left ventricular ejection duration was not improved (1).

Candesartan 2, 4, 8 or 16 mg or placebo was given once daily for 12 weeks to 218 patients with congestive heart failure in a multicenter, double-blind, randomized trial. Throughout the trial, pulmonary capillary wedge pressure and mean pulmonary arterial pressure were significantly and dose-dependently reduced by candesartan. Significant and dose-dependent increases in plasma renin activity and angiotensin II levels, and decreases in aldosterone and atrial natriuretic peptide (ANP) were also observed. Candesartan was safe and improved clinical symptoms and, compared with placebo, stabilized patient functional class (2).

In a study in which 20 patients with mild heart failure were given candesartan or placebo for 4 weeks, candesartan significantly increased arterial baroreflex sensitivity and significantly decreased muscle sympathetic nerve activity. Arterial pressure was reduced by candesartan although heart rate was unaffected (3).

In 31 patients with chronic heart failure, the addition of losartan or candesartan to therapy for 6 months significantly reduced levels of ANP and plasma ET-1, which were positive correlated after treatment (4).

Patients with chronic heart failure (n=15) underwent 24-h ambulatory electrocardiographic monitoring and simultaneous posture recording before and after 8 weeks of candesartan treatment. Cardiac autonomic nervous activity, assessed using heart rate variability, was found to be changed in the left (but not right) lateral decubitus and supine positions from sympathetic to parasympathetic prevalence with candesartan (5).

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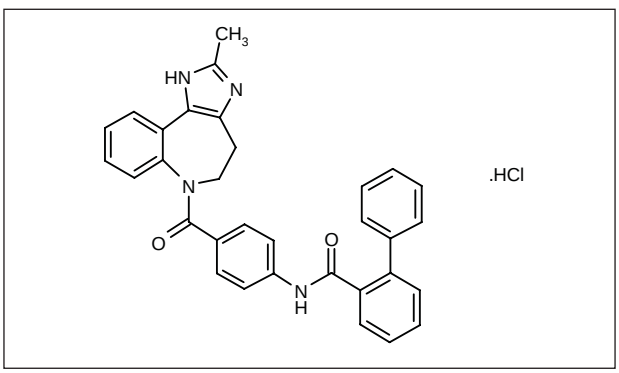
Original monograph - Drugs Fut 1993, 18(7): 609.

Conivaptan Hydrochloride



A dual vasopressin V_{1a}/V_2 receptor antagonist, Yamanouchi's conivaptan hydrochloride (YM-087, CI-1025) continues in phase II trials in the U.S. and the E.U. as an injectable formulation for the treatment of heart failure. It is also in phase III clinical evaluation in the U.S. for hyponatremia.

The long-term effect of conivaptan (1 mg/kg/day), alone and in combination with captopril (50 mg/kg/day), on vasopressin V_{1a} and V_2 receptor blockade was assessed in a rat model of congestive heart failure (CHF) over 4 weeks. Combination treatment reduced blood pressure, plasma natriuretic peptide levels, lung mass and left and right ventricular mass, and caused aquaresis. Results suggested that conivaptan may be a useful adjunctive therapy to ACE inhibitors for the management of the vasoconstriction and fluid retention that characterize CHF (1).

The acute hemodynamic and aquaretic effects of conivaptan (0.3-3.0 mg/kg as single oral doses at intervals of 3-4 days) were evaluated in rats with heart failure resulting from myocardial infarction. Conivaptan dose-dependently elevated urine volume, reduced urine osmolality and, at the highest dose, blocked alteration of left ventricular end-diastolic pressure, lung and right ventricular weight, while lowering blood pressure. A beneficial effect on cardiac function could therefore be expected with conivaptan via vasopressin V_{1a} and V_2 receptor inhibition (2).

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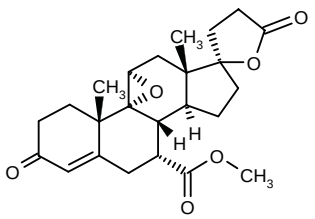
Eplerenone



The first selective aldosterone blocker (SAB), Pfizer's Inspra™ (eplerenone), was approved by the FDA in the fall last year and subsequently launched for the once-daily oral treatment of hypertension. Clinical trials in approximately 3,000 patients demonstrated that eplerenone is effective in lowering high blood pressure, both alone and in combination with other antihypertensive therapies, and is well tolerated. An NDA for the hypertension indication has also been submitted in Japan (1-3).

Eplerenone has also been evaluated in the phase III EPHESUS (Eplerenone Post-AMI HEart failure efficacy and SUrvival Study) trial as a treatment for heart failure. More than 6,600 patients took part at over 650 centers in 37 countries, in an attempt to evaluate whether an SAB would have a beneficial effect on survival and morbidity in patients who have suffered a heart attack and also have early complications of heart failure, as identified by left ventricular dysfunction. Both primary endpoints – death from any cause and death or hospitalization from cardiovascular causes – have been met in this trial, and a supplemental NDA submission for the treatment of postmyocardial infarction heart failure was filed in April (4).

In rats undergoing chronic aldosterone/salt treatment for 4 weeks, eplerenone 100 mg/kg/day attenuated hypertension, albuminuria, renal vascular injury and upregulation of cytokines (5).

The effects of eplerenone on left ventricular (LV) dysfunction and remodeling were evaluated in a dog model of chronic heart failure. The animals received eplerenone (10 mg/kg p.o. b.i.d.) or no therapy for 3 months following multiple sequential intracoronary microembolizations. Eplerenone prevented progressive LV systolic and diastolic dysfunction compared to untreated animals, as evidenced by attenuation of the decrease in LV ejection fraction, the increase in LV end-diastolic and end-systolic volumes, and the decrease in LV end-diastolic wall stress. Moreover, it attenuated LV remodeling, as indicated by significant reductions in volume fraction of replacement fibrosis, volume fraction of interstitial fibrosis and myocyte cross-sectional area (6, 7).

To investigate the role of aldosterone in the development of stroke, stroke-prone spontaneously hypertensive rats on a 1% NaCl/stroke-prone diet were treated with eplerenone 100 mg/kg/day or vehicle for 10 weeks. Vehicle-treated animals demonstrated signs of stroke and died, whereas all but 1 eplerenone-treated animal survived without signs of stroke. Also, less cerebral injury was seen in the brains of eplerenone-treated rats (8).

Using a rodent model of CHF, the effect of eplerenone (100 mg/kg/day), trandolapril (0.3 mg/kg/day) or the combination of both was evaluated 10 days following extensive myocardial infarction. Endothelium-independent relaxation of aortic rings induced by acetylcholine was improved following monotherapy with eplerenone or trandolapril and normalized following combination therapy, with a maximum relaxation (R_{max}) of 66 ± 6%, 77 ± 5% and 83 ± 4%, respectively. Additionally, vascular superoxide anion formation was elevated in placebo-treated animals, partially reduced following monotherapy and normalized following combination therapy. It was concluded that eplerenone may be a useful therapeutic option in heart failure (9).

The efficacy of eplerenone (100 mg/kg/day p.o.) in improving LV remodeling and function following myocardial infarction was investigated in rats subjected to left anterior descending coronary artery ligation. Animals treated with eplerenone demonstrated significantly improved LV function and remodeling as compared with the control animals (10, 11).

Rats double transgenic for the human renin and angiotensinogen genes subjected to angiotensin II-induced cardiac injury were administered eplerenone or vehicle. Compared with vehicle-treated animals, rats treated with eplerenone demonstrated decreased cardiac hypertrophy (4.5 ± 0.4 mg/g *vs.* 5.7 ± 0.2 mg/g), significantly attenuated albuminuria and perivascular fibrosis, as well as AP-1 and NF-κB DNA binding inhibition. Additionally, monocyte and lymphocyte infiltration and dendritic cell activation and infiltration to the heart and kidneys were attenuated in treated animals. It was concluded that eplerenone may be useful in the prevention of cardiovascular disease (12).

The major *in vitro* metabolites of eplerenone in humans and dogs appear to be 6β-hydroxyeplerenone and 21-hydroxyeplerenone. Cytochrome CYP3A4 and CYP3A12 primarily catalyze hydroxylation of eplerenone in humans and dogs, respectively, and metabolism of the agent best correlated with CYP3A-selective dextromethorphan *N*-methylation and testosterone 6β-hydroxylation activities. The *in vitro* V_{max} and K_m for 6β-hydroxylation and 21-hydroxylation in human lipo-

somes were 0.973 nmol/min/mg and 217 μM, and 0.143 nmol/min/mg and 211 μM, respectively. Hepatic clearance was calculated to be 2.30 ml/min/kg. The results suggest that eplerenone would not substantially inhibit drug metabolism catalyzed by CY3A4 or other P-450 isoforms (13).

Clinical studies in patients with essential hypertension examined the effects of eplerenone on blood pressure and electrolytes. An initial daily dose of 50 mg of eplerenone was given to the patients, which was later increased to 100 mg/day and then 200 mg/day if the target blood pressure had not been achieved. Patients who responded to the treatment showed significant reductions in systolic and diastolic blood pressure values compared to patients who had not responded to eplerenone. However, the differences in the mean serum potassium levels were smaller and unrelated to the blood pressure response to eplerenone. These results are indicative of a dissociation between the blood pressure and plasma electrolyte effects of eplerenone (14).

In a multicenter, randomized, double-blind study, 202 hypertensive patients with LV hypertrophy were treated with either eplerenone 50-200 mg once daily, enalapril 10-40 mg once daily or eplerenone 50-200 mg plus enalapril 10 mg for 9 months. Left ventricular mass was reduced to a similar degree by each agent alone, but significantly more by the combination than with eplerenone alone. The combination treatment also resulted in a somewhat larger reduction in blood pressure (15).

A multicenter, randomized, double-blind study compared treatment of 269 patients with elevated systolic blood pressure with eplerenone 50-200 mg once daily and amlodipine 2.5-10 mg once daily. Although the treatments reduced systolic blood pressure to a similar degree, the incidence of peripheral edema was lower with eplerenone and eplerenone reduced microalbuminuria more than amlodipine (16).

A 12-week, double-blind, placebo-controlled, parallel, fixed-dose study was conducted in 400 patients with stage I-III hypertension who received eplerenone doses ranging from 25-200 mg once daily. Clinic and ambulatory blood pressure measurements taken after the end of the study showed that eplerenone effectively reduced blood pressure values, with the greatest efficacy at the dose of 100 mg. Adverse events and withdrawals with this drug were similar to those in the group treated with placebo (17).

The efficacy and safety of doses of 50-200 mg eplerenone once daily were compared with doses of 2.5-10 mg amlodipine once daily in a 24-week, double-blind clinical trial that included patients with systolic hypertension and/or widened pulse pressure. Both drugs showed similar efficacy in reducing systolic blood pressure, pulse pressure and vascular compliance, although eplerenone was more effective in reducing microalbuminuria and was also associated with less peripheral edema than amlodipine (18).

A multicenter, double-blind clinical trial was conducted to determine the potential benefits of administering eplerenone to patients with mild to moderate hypertension who had not responded to monotherapy with calcium channel blockers or β-blockers. A total of 268 patients with uncontrolled blood pressure (defined as diastolic blood pressure of 95- < 110 mmHg) despite receiving a fixed dose of calcium channel blockers or β-blockers were randomized to supplement their baseline therapy with either placebo or eplerenone (50 mg/day, later increased to 100 mg/day if unresponsive) for 8 weeks. In this study, response to the treatment was defined as a diastolic blood pressure of < 90 mmHg or a reduction of at least 10 mmHg compared to baseline. The addition of eplerenone further reduced the blood pressure values of the patients and increased the response rates from 62% on calcium channel blockers plus placebo to 72% and from 50% on β-blockers plus placebo to 75%. No significant differences were found in the safety profiles of the study groups, and the percentage of patients who withdrew from the study due to lack of response was lower with eplerenone than with placebo (19).

An open-label clinical trial determined the effects of adding a second antihypertensive agent in 582 patients with mild to moderate hypertension who had not responded to first-line eplerenone monotherapy (at a maximum dose of 200 mg/day). The second antihypertensive drug (including ACE inhibitors, calcium channel blockers, β-blockers or diuretics) was well tolerated, improved the mean systolic and diastolic blood pressure of the patients and had no effects on their serum potassium levels. Only 2 patients were withdrawn from the study due to hyperkalemia (20).

A randomized, double-blind trial compared once-daily treatment of 348 black and 203 white patients with mild to moderate hypertension with eplerenone 50 mg, losartan 50 mg or placebo. After 16 weeks, eplerenone was found to significantly reduce diastolic and systolic blood pressure in both black and white patients compared with placebo, and was more effective than losartan in all patients combined and in black patients. In white patients, eplerenone and losartan demonstrated similar efficacy (21).

Patients who had morning plasma renin activity of 1.0 ng/ml/h or less or an active renin value of 25 pg/ml or less were included in a randomized, double-blind clinical trial to assess the efficacy and safety of eplerenone and losartan. The patients were initially randomized to receive either 100 mg eplerenone once daily or 50 mg losartan once daily, and changes (in the form of dose increases or addition of hydrochlorothiazide 12.5 mg) were introduced at specific times throughout the trial if the patient's blood pressure remained uncontrolled. Eplerenone was found to be more effective and as safe as losartan in low-renin hypertension (22).

In a multicenter, randomized, double-blind trial, 168 patients with low-renin hypertension were given eplerenone 100 mg once daily or losartan 50 mg once daily. Significantly greater changes in blood pressure were seen in the eplerenone group at week 8; at week 16, blood pressure reductions were similar on both treatments. More patients in the losartan group took hydrochlorothiazide 12.5 mg after 8 weeks due to uncontrolled blood pressure (23).

Patients (n=341) with mild to moderate hypertension taking either an ACE inhibitor or an angiotensin II antagonist were enrolled in a multicenter, double-blind trial in which they were randomized to eplerenone 50 mg once daily or placebo for 8 weeks. The addition of eplerenone was safe in these patients and led to significantly greater reductions in systolic blood pressure than treatment with an ACE inhibitor alone and to significantly greater reductions in systolic blood pressure/diastolic blood pressure compared to angiotensin II antagonist monotherapy (24).

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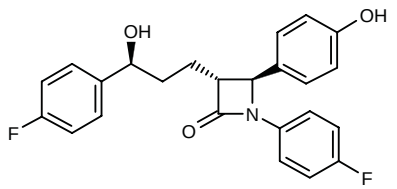
Ezetimibe



The first in a new class of cholesterol-lowering agents that inhibits the intestinal absorption of cholesterol was approved in the U.S. and Germany last year. Ezetimibe (Zetia™ in the U.S., Ezetrol™ elsewhere), discovered by Schering-Plough and developed in a global (except Japan) partnership with Merck & Co., is indicated for use as monotherapy or together with statins in patients with high cholesterol to reduce LDL and total cholesterol. The drug was also approved for use in two rare genetic disorders: homozygous familial hypercholesterolemia and homozygous sitosterolemia. Earlier this year, the product successfully completed the European mutual recognition procedure with Germany acting as the reference member state, and it was also recently approved in Canada (1-6).

In a double-blind, randomized study, 50 patients with homozygous familial hypercholesterolemia on diet and statin therapy (atorvastatin or simvastatin) were assigned to continued treatment with the statins alone (80 mg/day) or the addition of ezetimibe to low- (40 mg) or high-dose (80 mg) statin therapy. The mean change from baseline in LDL cholesterol was significantly greater in the ezetimibe groups, with respective reductions on statin monotherapy, ezetimibe + low- or high-dose statin and ezetimibe + high-dose statin of 6.7%, 20.7% and 27.5%. Treatments were well tolerated (7).

A study determined the efficacy and safety of 10 mg/day ezetimibe administered to patients with homozygous familial hypercholesterolemia being treated simultaneously with statins. Addition of ezetimibe to therapy with atorvastatin or simvastatin led to a clinically important decrease in LDL cholesterol levels compared to high-dose atorvastatin or simvastatin alone (8).

Patients with primary hypercholesterolemia (n=668) stabilized on diet were randomized in a double-blind, placebo-controlled phase III trial to 12 weeks of treatment with ezetimibe 10 mg/day, simvastatin 10, 20, 40 or 80 mg/day, ezetimibe + simvastatin or placebo. Coadministration of ezetimibe with simvastatin was associated with significant incremental reductions in LDL cholesterol and triglycerides, and increase in HDL cholesterol. Pooled data analysis indicated that, compared to simvastatin alone, ezetimibe + simvastatin produced an additional 13.8% reduction in LDL cholesterol, an additional 7.5% reduction in triglycerides and an additional 2.4% increase in HDL cholesterol levels. The safety profile of the combination was similar to placebo (9).

In a multicenter, double-blind, randomized, placebo-controlled phase III study, 628 patients with primary hypercholesterolemia were assigned to receive ezetimibe 10 mg/day, atorvastatin, 10, 20, 40 or 80 mg/day, ezetimibe + atorvastatin or placebo for 12 weeks. In this study, coadministration of ezetimibe was associated with an added 12.1% decrease in LDL cholesterol, 3.0% increase in HDL cholesterol and 8.0% decrease in triglycerides (10).

The efficacy and safety of adding ezetimibe to statin therapy in patients with hypercholesterolemia, coronary heart disease (CHD) or multiple risk factors necessitating further LDL cholesterol reductions were examined in a double-blind, randomized, placebo-controlled study. In this study, 769 patients were randomized to receive placebo or ezetimibe 10 mg/day added to stabilized statins for 8 weeks. Mean changes in LDL cholesterol, HDL cholesterol and triglycerides compared to placebo of –21.5%, +1.7% and –11.4%, respectively, were obtained upon addition of ezetimibe. Moreover, among patients not at their NCEP LDL cholesterol goal at baseline, 71.5% of those treated with statin + ezetimibe reached that goal at the end of the study compared to only 18.9% of those on statin + placebo. The safety profile of ezetimibe + statin was similar to placebo (11, 12).

A subgroup analysis of patients with type 2 diabetes (n=191) from this trial was also performed. The addition of ezetimibe provided significant additional improvements in LDL cholesterol and triglycerides, with mean changes in LDL cholesterol from baseline of –1.7% and –27.5%, respectively, on placebo + statin and ezetimibe + statin, and in triglycerides of –4-9% and –15.8%, respectively. Furthermore, significantly more diabetic patients achieved NCEP LDL cholesterol goals on statin + ezetimibe (83.6%) compared to statin + placebo (17.5%). Safety profiles on statin alone and statin + ezetimibe were comparable in this subgroup and no significant changes in HbA1c levels were seen in either the ezetimibe or placebo group (13).

A multicenter, double-blind, placebo-controlled study found that administration of 10 mg/day ezetimibe for 3 weeks decreased the levels of the plant sterols sitosterol and campesterol, whereas placebo-treated patients showed increases in levels of both sterols. Treatment with ezetimibe was also safe and well tolerated. Further studies are needed to assess the effects of long-term treatment with ezetimibe in sitosterolemia (14).

The data from 4 multicenter, double-blind, randomized, placebo-controlled phase III trials evaluating the efficacy and safety of ezetimibe (10 mg) alone or in

combination with atorvastatin (10-80 mg), lovastatin (10-40 mg), pravastatin (10-40 mg) or simvastatin (10-80 mg) in patients with primary hypercholesterolemia were analyzed. The combination of ezetimibe and statins resulted in greater reductions in LDL cholesterol, total cholesterol and triglycerides, as well as greater increases in HDL cholesterol, compared to statins alone, effects which were generally consistent across all groups (15).

The results of 2 single-center, evaluator-blind, placebo-controlled, parallel-group studies aimed at establishing the possible interactions between simvastatin 10 and 20 mg daily and the new cholesterol absorption inhibitor ezetimibe at doses up to 10 mg daily have been reported. A total of 82 men with LDL cholesterol levels of 130 mg/dl or more were included in these studies. The coadministration of simvastatin and ezetimibe was well tolerated, did not increase the incidence of adverse events and showed no signs of liver or skeletal muscle toxicity. Compared to simvastatin alone, the combination therapy resulted in a greater decrease in the serum LDL cholesterol and total cholesterol levels of the subjects. Further clinical trials are needed to better characterize the efficacy and safety of this therapy (16).

A double-blind, placebo-controlled clinical trial evaluated the efficacy and safety of ezetimibe in 827 patients with primary hypercholesterolemia. Patients with plasma LDL cholesterol levels of 130-250 mg/dl and triglyceride levels below 350 mg/dl at baseline were randomized to receive either placebo or ezetimibe (10 mg orally once daily in the morning) for 12 weeks. At the end of the treatment, the plasma LDL cholesterol levels of the patients had decreased by a mean of 17.7% on ezetimibe but had increased by 0.8% on placebo. Ezetimibe was also more effective than placebo in reducing the levels of apolipoprotein B, total cholesterol and lipoprotein(a) and increasing those of HDL cholesterol. The drug had no significant effects on the levels of lipid-soluble vitamins, prothrombin time or cortisol release. The safety profiles of the treatment groups were similar, and the most frequent adverse events were headache and upper respiratory tract infections. Overall, 8% of patients treated with ezetimibe and 6% of those treated with placebo discontinued the study prematurely, mostly due to adverse events or patient's request. The results of this clinical trial confirmed that ezetimibe was an effective and well-tolerated therapeutic option in lipid management (17).

A randomized, double-blind clinical trial was conducted to compare the lipid-lowering effects of ezetimibe and statins. After a screening/washout period of 2-12 weeks and a placebo period of 4 weeks, 538 patients with primary hypercholesterolemia (defined as LDL cholesterol concentrations of 3.8-6.5 mmol/l and triglyceride levels of 4 mmol/l or less) received ezetimibe (10 mg orally once daily), pravastatin (10, 20 or 40 mg once daily), a combination of both drugs at the aforementioned doses or placebo for 12 weeks. The pooled results obtained at all dose levels revealed that the combination of pravastatin plus ezetimibe was more effective than placebo or either drug alone in reducing the plasma levels of LDL cholesterol, triglycerides, total cholesterol and apolipoprotein B. The combination therapy was also more effective than pravastatin in increasing the plasma levels of HDL cholesterol, but only at the dose levels of 10 and 40 mg. The percentage of patients who showed at least a 40% reduction in their plasma LDL cholesterol levels at the end of the study was higher with the combination therapy than with pravastatin (47% *vs.* 8%). All the study treatments were generally well tolerated. No significant differences were found among study groups in the incidence of adverse events, and few serious adverse events were reported. The authors concluded that ezetimibe was effective in enhancing the lipid-lowering effects of statins without increasing the risk of adverse events (18).

A randomized, double-blind, placebo-controlled, crossover study assessed the effects of 10 mg/day ezetimibe on cholesterol absorption and synthesis in 18 male patients suffering from mild or moderate hypercholesterolemia. Treatment with ezetimibe for 2 weeks decreased cholesterol absorption by 54% compared to placebo and increased cholesterol synthesis by 89%; these changes resulted in clinically relevant decreases in LDL and total cholesterol levels (19).

The percentage of patients with heterozygous familial hypercholesterolemia, coronary heart disease or multiple cardiovascular risk factors treated with 10 mg/day ezetimibe plus 10 mg/day atorvastatin for 4 weeks who reached target LDL cholesterol levels at or below 2.6 mmol/l was higher than in the group treated with atorvastatin alone (22% *vs.* 7%). The combination of ezetimibe and atorvastatin was well tolerated. These results suggested that this combination therapy is both highly effective and safe as a treatment for hypercholesterolemia (20).

Two double-blind, randomized, placebo-controlled phase III studies in 1,719 patients with primary hypercholesterolemia assessed the effects of fat or cholesterol intake on the efficacy of ezetimibe (10 mg/day for 12 weeks). Analysis of pooled data demonstrated that fat or cholesterol intake did not significantly alter the LDL cholesterol-lowering effects of ezetimibe (21).

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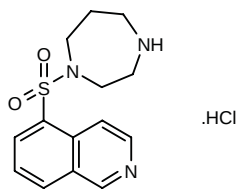
Fasudil Hydrochloride



Last year, Schering AG in-licensed the injectable formulation of the cardiovascular product fasudil hydrochloride (HA-1077, AT-877), a Rho kinase inhibitor, from Asahi Kasei. The intravenous formulation of fasudil (Eril®) is already marketed by Asahi Kasei in Japan for the treatment of vasospasm after cerebral hemorrhages. Schering plans to quickly move forward with clinical development for this indication in the U.S. and Europe. In 2001, Schering acquired the licensing rights for the oral formulation of fasudil, which the company is now codeveloping with Asahi Kasei for the treatment of angina pectoris. Phase II clinical trials are currently under way for this indication (1).

Neither Y-27632 (3 μM) nor fasudil (3 μM) affected basal or potassium-induced increased calcium mobilization in smooth muscle strips from rat caudal artery. These drugs therefore inhibit potassium-induced sustained contraction without affecting the calcium transient. The authors concluded that activation of Rho-associated kinase (ROCK) plays an important role in potassium-dependent contraction in such tissue and that ROCK activation may be dependent on the rise in intracellular calcium (2).

Long-term treatment of male Wistar-Kyoto rats with angiotensin II (AT_2) caused a significant increase in both blood pressure and left ventricular weight as compared to placebo. The combination of AT_2 plus fasudil resulted in a significant reduction of the AT_2-mediated increase in left ventricular weight, while failing to prevent the AT_2-mediated rise in blood pressure. Macrophage accumulation in the perivascular area, coronary vascular lesions and cardiomyocyte hypertrophy induced by AT_2 were all significantly suppressed by fasudil, as determined by immunohistology. Fasudil also reduced the AT_2-mediated superoxide anion production in aorta and improved the reduced endothelium-dependent relaxations observed in the AT_2 group (3).

Fasudil (100 mg/kg p.o. once daily) prevented the increase in right ventricular systolic pressure in monocrotaline-treated rats after 3 weeks and significantly increased survival at week 5, as compared to rats treated with monocrotaline alone. In rats with established pulmonary hypertension, administration of fasudil starting at week 3 post-monocrotaline injection also improved 5-week survival rate and prevented monocrotaline-induced medial thickening, as determined by histological examination. The authors concluded that Rho kinase is

involved in the pathogenesis of pulmonary hypertension (4).

Administration of fasudil 30 mg/kg p.o. once daily for 4 weeks starting 2 days prior to stent implantation in the left coronary artery of male pigs resulted in increased coronary diameter as compared to control animals. Fasudil also reduced neointimal area and inflammatory cell infiltrate score, and increased the number of apoptotic cells. Phosphorylation of target proteins of Rho kinase at the stent site and Bcl-2 expression were significantly reduced by fasudil. Long-term inhibition of Rho kinase, therefore, prevents in-stent restenosis by multiple mechanisms (5).

In a study in 20 patients with vasospastic angina, the vasoconstrictor responses to acetylcholine were measured before and after administration of intracoronary fasudil (300 mcg/min for 15 min). It was found that the coronary vasospasm and myocardial ischemia induced by acetylcholine were prevented by fasudil (6, 7).

Increasing fasudil doses of 5, 10 and 20 mg t.i.d. (n=45) or 20 and 40 mg t.i.d. (n=22) were administered every 2 weeks in a multicenter phase IIa study in patients with stable effort angina. In a double-blind phase IIb trial, 125 patients were assigned fasudil 5, 10, 20 or 40 mg t.i.d. for 4 weeks. In both studies, the maximum exercise time and the time to the onset of 1-mm S-T segment depression on treadmill exercise were prolonged. Fasudil was well tolerated (8).

The effect of intracoronary fasudil (4.5 mg) on myocardial ischemia induced by acetylcholine was determined in 18 patients with microvascular angina and normal coronary arteriograms. The drug effectively suppressed myocardial ischemia after acetylcholine challenge in 11 of 13 patients (9, 10).

Two studies evaluated treatment with fasudil in patients with stable effort angina. In the first study, increasing doses (15, 30 and 60 mg t.i.d.) given to 45 patients over 2 weeks significantly improved exercise time and time to onset of 1-mm S-T segment depression during exercise. In the other study in 104 patients, 4 weeks of oral fasudil (15, 30, 60 or 120 mg t.i.d.) led to significant and dose-related improvements in exercise measurements. The drug was well tolerated (11).

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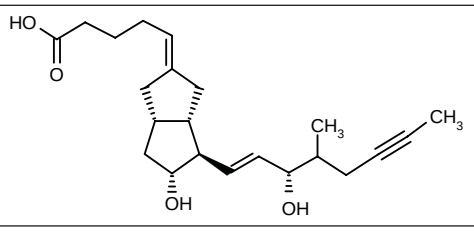
Original monograph - Drugs Fut 1989, 14(12): 1159.

Iloprost



The synthetic prostacyclin analogue iloprost (Ilomedin®) has been marketed by Schering AG since 1992 for the treatment of thromboangitis obliterans (Buerger's disease) and severe cases of arterial oclusion due to atherosclerosis. Iloprost (Ventavis®) has been designated an orphan medicinal product for primary pulmonary hypertension, and recently received a positive opinion from Europe's Committee for Proprietary Medicinal Products. A decision by the European Commission is expected in the second half of 2003.

The benefits of iloprost were demonstrated in a multicenter, randomized, double-blind, placebo-controlled phase III trial in 203 adult patients with stable pulmonary hypertension. Inhaled iloprost or placebo was added to the current therapy of the patients, excluding prostacyclin or its analogues. The primary endpoint of the study was a combined response criterion of improvement of at least 10% compared to baseline in exercise capacity (6-min walk test) at 12 weeks, improvement by at least 1 NYHA class at 12 weeks, and no deterioration of pulmonary hypertension or death at any time before 12 weeks. The response rate to iloprost was 16.8%, while in the placebo group it was 4.9%. A prespecified subgroup analysis of 49 patients with primary pulmonary hypertension receiving treatment with inhaled iloprost for 12 weeks showed a mean increase in the 6-min walk test of 44.7 m *versus* a change of –7.4 m in the placebo group. The drug's effects include direct vasodilatation of the pulmonary arterial

bed, with subsequent significant improvement in pulmonary arterial pressure, pulmonary vascular resistance and cardiac output, as well as mixed venous oxygen saturation (1).

An *in vitro* study using human pulmonary arterial smooth muscle cells examined the antiproliferative activity (*i.e.*, inhibition of [^{3}H]-thymidine incorporation at 30 h and decrease in cell number at 48 h) of iloprost, UT-15, cicaprost and beraprost. All agents significantly inhibited proliferation with a 10-fold difference in potency for each agent (UT-15 > iloprost > cicaprost > beraprost). The antiproliferative effects were reversed by 2,5'-dideoxyadenosine (ddA), but not SQ-22536. All agents increased intracellular cAMP, UT-15 having the most potent effect and iloprost the least; ddA inhibited the increase in cAMP, while inhibitory effects with SQ-22536 were variable. It was concluded that inhibition of human pulmonary artery smooth muscle cell proliferation observed with these agents may be via a cAMP-dependent pathway (2).

Iloprost and zardaverine were coadministered in a model of pulmonary hypertension in isolated rabbit lungs, leading to enhanced responses to iloprost, which consisted of a reduction in maximum degree and duration of pulmonary artererial pressure, amelioration of ventilation/perfusion distribution and prevention of the development of significant lung edema (3).

In a study in 10 healthy volunteers, inhalation of iloprost 15 μg mildly inhibited platelet aggregation for 6 h. Plasma cAMP was also increased 30 min after iloprost inhalation and normalized at 6 h (4).

A randomized, crossover study involving 18 patients with severe pulmonary hypertension (NYHA class III or IV) compared ultrasonic and jet nebulizers for the delivery of iloprost (2.8 μg). Iloprost inhaled via both ultrasonic and jet devices was well tolerated and decreased pulmonary arterial pressure (from 54.3 ± 2.1 to 47.1 ± 2.0 mmHg and from 53.5 ± 2.2 to 47 ± 2.2 mmHg, respectively) and mean pulmonary vascular resistance (1073 ± 109 to 804 ± 87 dyn.s.cm^{-5} and 1069 ± 125 to 810 ± 83 dyn.s.cm^{-5}, respectively). It was concluded that the ultrasonic nebulizer was preferable since it avoided drug wastage and the duration of inhalation could be reduced by one-third as compared to the jet nebulizer (12 min *vs.* 4 min) (5).

A study conducted in 15 children with congenital heart disease and pulmonary hypertension compared the efficacy of inhaled nitric oxide (iNO; 20 ppm) with aerosolized iloprost (25 ng/kg/min). Patients were first administered iNO for 10 min, followed by iloprost for 10 min when pulmonary vascular resistance returned to baseline levels, and then both agents simultaneously for 10 min. Treatment with iNO significantly decreased the pulmonary vascular resistance and systemic vascular resistance ratio (0.48 ± 0.38 to 0.27 ± 0.16) and significantly increased plasma cGMP (17.6 ± 11.9 to 34.7 ± 21.4 nmol/l). Administration of iloprost also resulted in a significant decrease in this ratio (0.49 ± 0.38 to 0.26 ± 0.11) and a significant increase in plasma cAMP (55.7 ± 22.9 to 65.1 ± 21.2 nmol/l). Combination afforded no additional benefits (6).

A study involving 20 pediatric patients with pulmonary vascular disease (primary pulmonary hypertension or congenital heart defects) or pulmonary hypertension due to increased pulmonary blood flow showed that assessment of acetylcholine-induced blood flow velocity and biochemical endothelial pathways (*e.g.*, endothelial-independent vasodilatation using nebulized iloprost [1.5-25 μg/kg]; NO synthesis via measurements of arginine, citrulline and ornithine) can provide information about the condition of pulmonary vasculature and therefore indicate the extent of pulmonary hypertension (7).

Ninety-nine patients with severe precapillary pulmonary arterial hypertension were subjected to 3 acute pulmonary vasoreactivity tests using aerosolized iloprost (5 μg), i.v. epoprostenol (9.7 ± 2.54 ng/kg/min) and iNO (35 ppm), in order to select candidates for chronic treatment with calcium channel blockers. Reductions in pulmonary vascular resistance (PVR) and right atrial pressure were observed with all 3 treatments. Epoprostenol-induced reductions in PVR were due to an increase in cardiac index, while reductions seen with iloprost and NO were mainly due to decreases in mean pulmonary arterial pressure. Epoprostenol increased heart rate and decreased mean blood pressure and systemic vascular resistance (SVR). Iloprost increased mean blood pressure and SVR. Nitric oxide decreased heart rate and increased mean blood pressure and SVR. The differential hemodynamic effects observed with the treatments were probably due to the differential selectivity of each agent on the pulmonary vascular bed and to nonvascular effects (8).

A case study involving a 17-year-old patient with severe pulmonary hypertension due to progressive systemic ventricular failure showed that treatment with i.v. prostacyclin (8 ng/kg/min) and dobutamine (6 μg/kg/min) combined with iloprost inhalation (6 x 15-min sessions/day for a total dose of 100 μg/day) hemodynamically stabilized the patient for 21 days until cardiac transplantation (9).

Patients with NYHA class III-IV severe pulmonary hypertension (n=30) taking part in a randomized, open-label trial were treated with NO plus iloprost (2.8 μg). After 2 h, they then received sildenafil 12.5 mg, sildenafil 50 mg, sildenafil 12.5 mg plus iloprost 1 h later, or sildenafil 50 mg plus iloprost 1 h later. Sildenafil and iloprost acted synergistically on hemodynamic parameters, and the greatest pulmonary vasodilatation was seen with the combination of sildenafil 50 mg and iloprost (10).

The hemodynamic effects of inhalation of iloprost 25 μg and oral administration of sildenafil 25 mg were compared in 6 patients with pulmonary hypertension. Both drugs reduced pulmonary vascular resistance by 26% from baseline (11).

Fifteen pediatric patients with connective tissue diseases were included in a study that assessed the safety and efficacy of iloprost (mean dose of 2 ng/kg/min i.v. once daily for a mean of 10.7 days) in the treatment of

ischemic digits. The drug restored normal blood flow in 74% of the patients and improved ischemic digits and fingertip necrosis in 26% and 53.5% of all patients, respectively. Iloprost also improved Raynaud's phenomenon in all but 1 of the affected patients. Iloprost was well tolerated, minor side effects of headache, transient hypotension, nausea and rash being reported, and resulted in significant pain relief (12, 13).

Iloprost was administered to 6 patients with connective tissue disease and severe Raynaud's phenomenon at an initial dose of 0.5 ng/kg/min, which was increased to a maximum of 2 ng/kg/min. Treatment was given for 5 days and then 1 day per month. Mild improvements in Raynaud's phenomenon characteristics were seen at 1 month and remained stable during the 12-month study period. Digital ulcers were improved (n=2) or healed (n=1) in the 3 affected patients. No withdrawals or severe side effects were seen (14).

In a study in 14 male heart transplant candidates with elevated pulmonary vascular resistance, patients inhaled NO in concentrations of 5, 10 and 30 ppm. After a 20-min washout period, patients inhaled aerosolized iloprost 50 mcg. No adverse reactions were seen with iloprost, which reduced pulmonary arterial pressure more than NO and was associated with increases in cardiac index and stroke index (15).

Aerosolized iloprost 50 mcg was evaluated as a treatment for elevated pulmonary vascular resistance in 29 male heart transplant candidates. Inhalation of iloprost lowered pulmonary arterial pressure and the pulmonary vascular resistance index, while increasing the cardiac index and stroke index. Systemic vascular resistance and blood pressure were not changed, and no adverse events were seen (16).

The hemodynamic effects of inhaled NO and iloprost were measured in 20 heart transplant candidates with elevated pulmonary vascular resistance. Patients inhaled NO in concentrations of 5, 10 and 30 ppm. A 20-min washout period was then followed by inhalation of aerosolized iloprost (50 μg in 3 ml solution). Iloprost appeared to be superior to NO for the evaluation of these patients and more effective than NO in reducing pulmonary arterial pressure (17).

The hemodynamic effects of inhaled iloprost (25 μg) were determined in 17 patients with precapillary pulmonary hypertension at rest and during exercise. The drug significantly reduced mean pulmonary arterial pressure and pulmonary vascular resistance during exercise without affecting systemic arterial pressure or heart rate (18).

Nebulized iloprost 105-140 μg/24 h was given 7 times a day to 51 patients with severe pulmonary hypertension. The treatment did not alter pulmonary function and preserved oxygen saturation at rest and during exercise (6-min walk test) over the course of 3 months (19).

Inhaled iloprost (25 μg) significantly improved pulmonary arterial pressure and pulmonary vascular resistance at rest and during exercise in 13 patients with chronic obstructive pulmonary disease. In the study, hemodynamic variables were measured in patients with right heart catheterization at rest and during increasing exercise workloads before and after inhalation of the drug (20).

A total of 203 patients with primary and nonprimary pulmonary hypertension enrolled in a randomized, placebo-controlled trial received either placebo or iloprost 2.5 or 5 μg 6 or 9 times daily. After 12 weeks with a median dose of 30 μg/day, iloprost significantly improved hemodynamic values, which deteriorated in the placebo group. The primary endpoint of a 1-class improvement in NYHA class plus a 10% improvement in the 6-min walk test was achieved by 16.8% and 4.9% of iloprost- and placebo-treated patients, respectively (21).

In an open study, 16 patients with primary or secondary pulmonary hypertension underwent right heart catheterization and exercise testing before and after inhalation of iloprost 14-28 μg. The drug reduced pulmonary arterial pressure and pulmonary vascular resistance while increasing cardiac output. The hemodynamic effects of iloprost were significantly greater during exercise than at rest (22).

Iloprost increased pulmonary clearance of big ET-1 in 15 patients with pulmonary arterial hypertension undergoing right heart catheterization and inhaling nebulized doses of 50 μg. The agent produced a significant decrease in the arteriovenous ratio of plasma big ET-1, an effect which may play a role in the activity of the drug in treating pulmonary arterial hypertension (23).

Patients with increased pulmonary vascular resistance after discontinuation of cardiopulmonary bypass (n=12) inhaled nebulized iloprost 0.2 μg/kg for 20 min in an evaluation of the drug's hemodynamic effects. The treatment decreased the transpulmonary gradient, mean pulmonary arterial pressure and the ratio of pulmonary vascular resistance to systemic vascular resistance. Echocardiography also revealed improvements in right ventricular function (24).

A study conducted in 24 patients with primary pulmonary hypertension examined the long-term effects of aerosolized iloprost (100-150 μg daily for at least 1 year) on exercise capacity and hemodynamic variables. Treatment was well tolerated with only mild coughing, minor headache and jaw pain reported in some patients. After 1 year of treatment, the mean walking distance in the 6-min walk test significantly increased from 96 to 363 ± 135 m, mean pulmonary arterial pressure significantly decreased from 59 ± 10 to 52 ± 15 mmHg, cardiac output significantly increased from 3.8 ± 1.4 to 4.4 ± 1.3 l/min and pulmonary vascular resistance decreased from 1205 ± 467 to 925 ± 469 dyn.s.cm^{-5} (25).

A 5-year-old boy with severe pulmonary hypertension was teated with repetitive inhalation of iloprost. During 3 years of treatment, the patient improved and experienced no side effects (26).

A study involving 11 patients with severe primary (PPH) and 7 patients with nonprimary pulmonary hypertension (NPPH) showed that treatment with nebulized iloprost (inhaled dose of about 30 μg) rapidly decreased

pulmonary and systemic artery levels of ANP and cGMP, while improving pulmonary vasodilatation and hemodynamics. In both PPH and NPPH patients, treatment significantly reduced mean pulmonary arterial pressure (–9.1 ± 2.5 and –7.9 ± 1.5 mmHg, respectively), pulmonary vascular resistance (–453 ± 103 and –381 ± 114 dyn.s.cm^{-5}, respectively), ANP (–99 ± 63 and –108 ± 47 pg/ml, respectively) and cGMP (–4.6 ± 0.9 and –4.2 ± 1.6 nM, respectively) (27).

The efficacy of single-dose aerosolized iloprost (30 μg over 15 min) in combination with i.v. epoprostenol in improving pulmonary hemodynamics was demonstrated in 8 patients with primary pulmonary hypertension who were nonresponders to initial NO treatment and who experienced adverse events with epoprostenol treatment. Combination therapy resulted in significant improvement superior to epoprostenol alone in mean pulmonary arterial pressure, cardiac index, mixed venous oxygen saturation and systemic arterial oxygen pressure. Treatment had no effect on mean systemic arterial pressure or pulmonary capillary wedge pressure (28).

Results from an open, uncontrolled trial involving 2 patients with severe primary pulmonary hypertension and 1 patient with pulmonary hypertension after surgical closure of atrial septal defect (NYHA class II), who were receiving continuous epoprostenol i.v. for 4 years, showed that aerosolized iloprost had only short-term effects and could not substitute for long-term epoprostenol treatment. Doses of epoprostenol were gradually reduced (1 ng/kg/ min steps every 3-10 h) during administration of repeated doses of iloprost (150-300 μg/day with 6-18 inhalations/day). All 3 patients experienced decreases in pulmonary arterial pressure of 49%, 49% and 45%, respectively, and increases in cardiac pressure of 70%, 75% and 41%, respectively, with iloprost treatment, regardless of the epoprostenol dose; these effects lasted for 20 min. However, treatment switch to iloprost was not possible since all patients developed signs of right heart failure. Discontinuation of iloprost resulted in normalization of clinical and hemodynamic parameters (29).

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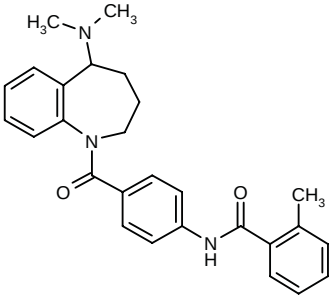
Mozavaptan



Mozavaptan (OPC-31260; Otsuka) is a nonpeptide vasopressin V_2 receptor antagonist with diuretic activity which is in phase II evaluation for the treatment of heart failure. It has also been designated an oprhan drug in Japan for the treatment of hyponatremia in the syndrome of inappropriate secretion of antidiuretic hormone.

An open-label, crossover phase I clinical trial in 12 adult male volunteers determined the efficacy of a combination therapy with furosemide and mozavaptan. Subjects sequentially received 4 treatments consisting of a single dose of placebo, 20 mg furosemide, 30 mg mozavaptan and a combination of 20 mg furosemide and 30 mg mozavaptan; each treatment was separated by a 2-week interval. The mean urine volume excreted during 4 h after administration of the combination was greater than with placebo or either drug alone; this increase was due to the combined effects of higher electrolyte-free water excretion (induced by mozavaptan) and higher urinary sodium excretion (induced by furosemide). The increase in electrolyte-free water excretion found with mozavaptan was associated with an increase in both serum osmolality and serum sodium levels. No significant differences among treatments were found for the blood pressure values, heart rate, serum potassium and calcium levels, or creatinine clearance. The results indicate that the combination of mozavaptan and furosemide might be effective in the treatment of hyponatremia and edema (1).

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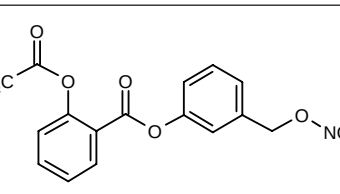
NCX-4016



NCX-4016, a nitric oxide (NO)-donating derivative of aspirin, is in development at NicOx for the treatment of cardiovascular diseases.

Following positive phase I/IIa results, NicOx announced the initiation of a phase II trial in symptomatic peripheral arterial disease. The phase I/IIa data indicated that NCX-4016 inhibits vascular inflammation and platelet activation, and an excellent overall safety was seen in 7 separate phase I trials. NCX-4016 was tested in a human clinical model of vascular inflammation, platelet activation and coagulation induced by lipopolysaccharide (LPS) infusion. NCX-4016 was found to differ from aspirin in the way it reduced platelet activation without affecting parameters related to bleeding risk, and in its broad activity

indicating inhibition of vascular and endothelial inflammation. NCX-4016 was also shown to inhibit cyclooxygensae type 2 (COX-2) enzyme expression, cytokine inflammatory mediators and procoagulant factors, while aspirin was proinflammatory and procoagulant. These results point to the potential of NCX-4016 in the treatment of cardiovascular diseases related to endothelial dysfunction and vascular inflammation, including atherosclerosis, vascular restenosis and cardiovascular complications of diabetes. The results confirm that the compound has a novel pharmacological profile different from aspirin through its NO-donating properties, and support results from animal models in which NCX-4016 was effective in treating endothelial dysfunction and vascular impairment. Its safety was proven in 128 volunteers who received single doses of up to 1600 mg and multiple doses of up to 800 mg twice daily for 7 days (1-3).

The National Cancer Institute (NCI) is funding a trial at the University of Michigan on NCX-4016 as a potential chemopreventive agent for colon cancer. The placebo-controlled study will assess the pharmacokinetics of 2 different doses of NCX-4016 in subjects at risk of colon cancer, at baseline and after 6 months of continuous oral administration. The effect of NCX-4016 on the number and features of aberrant crypt foci in the colon will also be evaluated. The trial will enroll 240 subjects who will receive either high- or low-dose active drug or placebo (4).

Experiments with NO-releasing nonsteroidal antiinflammatory drugs (NO-NSAIDs; nitroaspirin, nitroflurbiprofen, nitroparacetamol) and nitroprednisolone demonstrated the vasorelaxant properties of the agents, although these effects varied widely depending on the agent and blood vessel preparation used (5).

In human monocytes, NCX-4016 (10-300 μmol/ml) concentration-dependently reduced TxB_2 release and it reduced tissue factor activity at a concentration of 300 μmol/ml (6, 7).

An *in vitro* study analyzed the effects of incubating prostatic stromal cells from benign prostatic hyperplasia patients with NO-aspirin and NO-ibuprofen and found that both compounds inhibited cell proliferation in a concentration- and time-dependent manner (8).

In contrast to DETA-NO, aspirin or NCX-4017 (500 μM), NCX-4016 (500 μM) protected human umbilical vein endothelial cells (HUVECs) from staurosporin-induced apoptosis. NCX-4016 did not increase mitochondrial oxidative stress as compared to DETA-NO. The protective effect of NCX-4016 was unrelated to its aspirin moiety. Rather, NCX-4016 protection was associated with its differential ability to both release NO in specific subcellular compartments and prevent caspase 8-dependent Bid cleavage. In conclusion, NCX-4016 penetrated the endothelial cell, caused release of NO at selective membrane areas and protected against cell injury (9).

The effect of NCX-4016 (25, 50 and 100 μM) on responses to vasoconstriction induced by electrical field stimulation (0.5-64 Hz) or exogenous norepinephrine (0.01-10 μM) was assessed in perfused rat tail artery with intact endothelium. Concentration-dependent antagonism of vasoconstriction was observed without the involvement of relaxant factors or NO from endothelial cells. NCX-4016 may have potential for the treatment of disorders linked with vascular smooth muscle hyperactivity to adrenergic stimulation (10).

NCX-4016 and NCX-2216 were shown to concentration-dependently promote scavenging of hydroxyl, but not superoxide, radicals in cultured rat aorta. NCX-4016, but not NCX-2216, aspirin or mannitol, prevented the inhibition of acetylcholine-induced relaxation caused by acute *in vitro* exposure to glucose. In rats with streptozotocin-induced diabetes, chronic treatment with NCX-4016 decreased plasma isoprostanes, normalized the increased NF-κB activity in nuclear extracts from aortic tissue and prevented the development of defective endothelium-dependent relaxation by acetylcholine. It was concluded that NO-NSAIDs may represent a novel therapy to protect diabetic endothelium (11).

An *in vitro* study using rat subcellular fractions (cytosol and microsome) examined the metabolism of NCX-4016 using LC and LC-MS techniques. The agent and its metabolites were detected over the range of 0.25-50 μg/ml and extraction efficiency from liver samples was determined to be 85-95%. The agent was found to undergo rapid metabolism to form salicylic acid and 3-(nitrooxymethyl)phenol (HBN), which was subsequently metabolized to 3-hydroxybenzylalcohol and a new metabolite. Experiments using rat liver cytosol revealed that HBN was metabolized to a thioether adduct within 30 min via glutathione (GSH) transferase activity (12).

NCX-4016 has been compared to aspirin for its cardioprotective effects in hearts isolated from male spontaneously hypertensive rats (SHR). The animals were pretreated with vehicle, NCX-4016 (120 mg/kg) or aspirin (65.2 mg/kg) orally once daily for 5 days before the hearts were isolated and subjected to ischemia/reperfusion. The treatments had no significant effect on mean arterial blood pressure, heart rate or ischemia-induced arrhythmias. NCX-4016 significantly reduced infarct size from 47% to 27% of area at risk and abolished the increase in coronary perfusion pressure following reperfusion, whereas aspirin had no effect. The cardioprotective effect of NCX-4016 in these hearts appeared to be unrelated to cyclooxygenase inhibition, as it had no effect on platelet aggregation or TxB_2 production, in contrast to aspirin (13).

In a model of ischemia/reperfusion in isolated rabbit heart, perfusion with celecoxib, meloxicam, aspirin or DuP-697 (10-100 μM) prior to ischemia, resulted in a concentration-dependent augmentation of left ventricular (LV) end-diastolic pressure, LV strength of contractility, coronary perfusion pressure and creatine kinase activity and a decrease in the release of 6-keto-$PGF_{1\alpha}$ compared to vehicle. In contrast, perfusion of NCX-4016 (10-100 μM) concentration-dependently protected against cardiac dysfunction even at concentrations that inhibit the release of 6-keto-$PGF_{1\alpha}$ and the synthesis of thromboxane. These data suggest that selective

inhibitors of COX-2 have negative effects in experimental myocardial ischemia/reperfusion (14).

In Langendorff-perfused hearts from SHR subjected to ischemia/reperfusion, pretreatment with PEG400 (1 ml/kg/day p.o. x 5 days), NCX-4016 (120 mg/kg/day p.o. x 5 days) or aspirin (65.2 mg/kg/day p.o. x 5 days) did not significantly alter mean arterial blood pressure or heart rate compared to controls, as assessed via standard limb electrode and epicardial echocardiography, respectively. NCX-4016, but not aspirin, reduced coronary perfusion pressure and infarct size, as compared to PEG400-treated animals. Aspirin was the only treatment that significantly reduced TxB_2 levels in carotid artery blood. There were no significant changes in ventricular fibrillation or tachycardia among the groups. The authors concluded that NCX-4016 improves myocardial function in SHR by a mechanism unrelated to cyclooxygenase inhibition (15).

NCX-4016 was compared to aspirin and vehicle treatment in normotensive and hypertensive rats. Compared to aspirin, NCX-4016 significantly reduced blood pressure. The compound also caused a significant drop in mean arterial pressure in hypertensive rats when administered intravenously. The vasorelaxant effects of NCX-4016 were due to its effects on endogenous pressor agents in addition to the vasodilatation due to NO release (16).

In large pigs undergoing experimental ischemia and reperfusion, pretreatment with high-dose NCX-4016 (60 mg/kg p.o. x 7 days), but not low-dose NCX-4016 (18.4 mg/kg p.o. x 7 days) or aspirin (10 mg/kg p.o. x 7 days), significantly reduced the total number of ventricular premature beats and infarct size after artery occlusion as compared to untreated pigs. Both doses of NCX-4016 inhibited collagen-induced platelet aggregation, while both aspirin and the highest dose of NCX-4016 inhibited TxB_2 release from activated platelets. Thus, like aspirin, NCX-4016 is an effective antiplatelet agent but, in contrast to aspirin, NCX-4016 reduces myocardial damage after ischemia/reperfusion in this model (17).

NCX-4016 was compared to aspirin for effects on macrovascular endothelium and kidney function in streptozotocin-diabetic rats. The animals were divided into groups to receive no treatment, vehicle, NCX-4016 100 mg/kg/day or aspirin 54 mg/kg/day orally for 6 weeks. Neither NCX-4016 nor aspirin affected blood glucose levels, but NCX-4016 was able to protect endothelial structure and prevent the increase in blood urea nitrogen. As these protective effects were not seen in aspirin-treated animals, it was concluded that they were due to NO release by NCX-4016 (18).

Preclinical studies demonstrated that celecoxib coadministration was associated with a dose-dependent increase in low-dose aspirin-induced gastric damage in rats, whereas NCX-4016 did not induce significant gastric damage either alone or together with celecoxib (19).

Pretreatment of rats with NCX-4016 (90 mg/kg p.o. x 5 days) significantly inhibited lipopolysaccharide (LPS)-induced tissue factor (TF) and COX-2 mRNA expression in blood-derived monocytes compared to control rats or rats treated with acetylsalicylic acid (ASA; 50 mg/kg p.o.), isosorbide-5-mononitrate (ISMN; 80 mg/kg p.o.) or placebo. NCX-4016 and ISMN reduced surface expression of TF in LPS-induced monocytes, whereas NCX-4016 and ASA prevented the LPS-mediated enhancement of 11-dehydro-TxB_2 urinary excretion. NCX-4016, but not ASA, prevented damage to gastric mucosa and reduced plasma levels of IL-1β and TNF-α. The additive effects of NO release and COX inhibition may underlie the efficacy and tolerability of NCX-4016 (20).

The effect of aspirin (30 mg/kg), NCX-4016 (60 mg/kg), clopidogrel (0.5 mg/kg) and combinations thereof (all orally over 5 days) was evaluated on collagen/epinephrine-induced platelet pulmonary thromboembolism and bleeding in mice. NCX-4016 alone and in combination with clopidogrel significantly increased the survival rate (37% and 41% mortality *vs.* 80% in controls) and alone blocked or reduced arachidonic acid- and U-46619-induced platelet aggregation. NCX-4016 could be a useful adjunctive agent in revascularization therapy with a risk of restenosis (21).

NCX-4016 was compared to an equimolar dose of aspirin and placebo for its chronic effects in hypercholesterolemic LDL receptor-deficient mice. The mice were administered placebo, NCX-4016 30 mg/kg/day or aspirin 18 mg/kg/day for 12 weeks. The results demonstrated a significant reduction in the aortic cumulative lesion area (39.8%) on NCX-4016 compared to aspirin and placebo, as well as significant reductions in plasma LDL oxidation and systemic oxidative stress. NCX-4016 treatment also significantly reduced the expression of oxidation-specific epitopes and macrophage accumulation in arterial wall sections compared to the other groups. Plasma cholesterol and triglyceride levels were similar among all groups of mice. Chronic treatment with NCX-4016 thus appears to attenuate the development of atherosclerosis via antiatherogenic and antioxidant effects (22).

The effects of NCX-4016 (55 mg/kg) and aspirin (30 mg/kg) on restenosis were compared in rats treated 7 days before and 21 days after standard carotid balloon injury. Only NCX-4016 reduced experimental restenosis in elderly rats and only NCX-4016 was well tolerated and did not cause gastric damage in young and old rats (23).

Positive phase I clinical endoscopy results were recently reported for NCX-4016. The data demonstrated that, in contrast to aspirin, NCX-4016 does not induce macroscopic changes in the gastroduodenal mucosa, confirming preclinical data indicating that the drug spares the gastric mucosa. In this study, 40 healthy volunteers were randomized to receive placebo, NCX-4016 400 or 800 mg b.i.d. or aspirin 200 or 425 mg b.i.d. for 7 days. Endoscopic examination showed that NCX-4016 did not induce macroscopic changes in the gastroduodenal mucosa, unlike aspirin which was associated with visible gastric mucosal injury in the majority of volunteers. The extent of gastric damage in subjects treated with NCX-4016 was not different from placebo. Moreover,

NCX-4016 displayed a broader antiplatelet profile than aspirin, indicating significant potential in the treatment of cardiovascular diseases (24).

Positive endoscopic results were reported for NCX-4016, demonstrating gastroprotective effects even when coadministered with celecoxib. In this study, 32 healthy subjects were randomized to receive NCX-4016 (800 mg b.i.d.) alone, NCX-4016 plus celecoxib (400 mg b.i.d.), aspirin (100 mg b.i.d.) alone or aspirin plus celecoxib for 14 days. Whereas celecoxib more than doubled the gastric mucosal injury caused by aspirin, NCX-4016 did not cause gastric damage itself or in combination with celecoxib (25).

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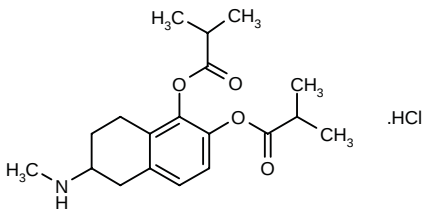
Original monograph - Drugs Fut 1997, 22(11): 1231.

Nolomirole Hydrochloride



Chiesi is conducting phase III clinical trials with the nonselective dopaminergic agent nolomirole hydrochloride (CHF-1035) for heart failure.

In a randomized, double-blind, placebo-controlled study, 59 patients with NYHA class II-III heart failure receiving stable therapy with a diuretic or a diuretic plus an ACE inhibitor were also given nolomirole 2.5, 5 or 10 mg b.i.d. or placebo for 4 weeks. Nolomirole improved the functional class of 32 patients, with patients in the higher dose groups walking significantly further in the 6-min walk test as compared to placebo. Nolomirole also reduced pulmonary congestion and excess water compared with placebo, although the mechanism by which this occurred was not apparent. After 4 weeks of treatment, heart rate remained stable in nolomirole-treated patients, and the reduction in blood pressure was greatest on 5 mg (1-4).

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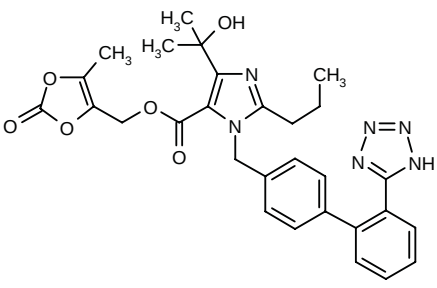
Olmesartan Medoxomil



Sankyo's olmesartan medoxomil (CS-866) was launched last year in the U.S. as Benicar™ and in Germany as Olmetec® for the treatment of high blood pressure, to be used alone or in combination therapy with other antihypertensive agents. Olmesartan is the newest entry to the rapidly growing angiotensin II receptor blocker (ARB) class. Studies have shown that the usual recommended starting dose of 20 mg taken once a day resulted in significant blood pressure reduction, lowering systolic blood pressure by an average of 15 mmHg and diastolic blood pressure by an average of 12 mmHg. Olmesartan also demonstrated superior blood pressure-lowering efficacy over ARB market leader Cozaar® (losartan potassium; Merck & Co.). Forest is Sankyo's long-term copromotion partner for the drug in the U.S. (1).

The effects of olmesartan and temocapril hydrochloride were compared in Otsuka Long-Evans Tokushima fatty (OLETF) rats, a model of type 2 diabetes, for their potential in diabetic nephropathy. High doses of olmesartan and temocapril (0.01% chow, equivalent to approximately 3 mg/day) were associated with significant improvements in proteinuria and urinary beta$_2$-microglobulin excretion, as well as improvements in loss of glomerular anionic sites, glomerular sclerosis and tubulointerstitial injury. Immunohistochemical analysis of glomeruli revealed significant reductions in TGF-β, vascular endothelial growth factor (VEGF) and collagen type IV staining. The authors concluded that olmesartan may be useful for preventing the development and progression of diabetic nephropathy (2, 3). In this animal model, temocapril and olmesartan treatment delayed the onset of diabetes partially by improving insulin sensitivity and secretion. Both agents blunted the development of hypertension and hyperglycemia, suppressed increased serine phosphorylation of IRS-1 in skeletal muscle and increased urine C-peptide levels. The distribution of caveolin-I was shifted to the heavy-density fraction from the light fraction in soleus muscle membrane (4).

A study in monkeys fed a high-cholesterol diet for 6 months investigated the effects of olmesartan (10 mg/kg/day) on vascular function and lipid deposition. Olmesartan significantly reduced the area of lipid deposition on the aortic surface but had no effect on the mean

levels of diet-increased LDL or diet-reduced HDL cholesterol, nor on the mean blood pressure. The accumulation of macrophages in the intimal layer was decreased by olmesartan and levels of vascular ACE increased. Olmesartan also increased serum levels of TGF-β, macrophage colony-stimulating factor (M-CSF) and ICAM-1, and improved vascular relaxation in response to acetylcholine (5, 6).

The organ protective effects of olmesartan (3 or 10 mg/kg/day) alone or in combination with temocapril (10 mg/kg/day) were compared in spontaneously hypertensive rats following 5/6 nephrectomy. The hypertensive effects of the differing therapies were on the order of olmesartan (3 mg) + temocapril > olmesartan (10 mg) = temocapril > olmesartan (3 mg). Urinary protein excretion, glomerular sclerosis index and relative interstitial volume were highly correlated with systolic blood pressure (7).

Olmesartan was administered to Zucker diabetic fatty rats in the chow at doses of approximately 0.6 and 6 mg/kg/day to examine the drug's effects on nephropathy. Olmesartan was started at 12 weeks of age and continued for 19 weeks. The treatment dose-dependently suppressed the development of proteinuria while largely correcting hypoalbuminemia and hyperlipidemia. Olmesartan did not affect plasma glucose or insulin concentrations and its activity in delaying progression of nephropathy was at least partly independent of its effect on blood pressure (8).

Potential drug-drug pharmacokinetic interactions between oral olmesartan medoxomil and warfarin and digoxin (which have narrow therapeutic windows), aluminium magnesium hydroxide (which may affect absorption of olmesartan) and hydrochlorothiazide were investigated. All combination treatments were well tolerated and no clinically significant pharmacokinetic interactions were observed (9).

The effects of age, renal and hepatic impairment on the pharmacokinetic profile of olmesartan medoxomil were evaluated in 4 clinical trials. Patients with mild to moderate or severe renal impairment had steady-state AUC values 1.6-1.8-fold and 2.8-fold higher than healthy subjects, respectively. In subjects with mild to moderate hepatic impairment, C_{max} and AUC_{0-50} were increased by 13% and 65%, respectively. Dose adjustment was considered unnecessary in these patients (10).

Two randomized, double-blind, 12-week, dose-titration trials compared the blood pressure-lowering effects of olmesartan medoxomil, captopril and felodipine. Olmesartan 5-20 mg once daily or captopril 12.5-50 mg b.i.d. was administered to 1,291 patients in the first study, while olmesartan 20-40 mg once daily or felodipine 5-10 mg once daily was administered to 2,381 patients in the second study. Dose doubling was allowed for blood pressure control in both studies. Olmesartan treatment resulted in better blood pressure control than captopril in the first study and similar blood pressure control to felodipine in the second trial (11).

The antihypertensives olmesartan, atenolol, captopril, felodipine and losartan were compared in 5 randomized, double-blind phase III trials. In patients with mild to moderate hypertension, olmesartan 10-20 mg once daily demonstrated similar diastolic blood pressure-reducing efficacy to atenolol 50-100 mg once daily and olmesartan 20-40 mg lowered diastolic blood pressure as well as felodipine 5-10 mg once daily. Also in these patients, olmesartan 5-20 mg once daily was significantly superior to captopril 12.5-50 mg b.i.d. and losartan 50-100 mg once daily (12).

The efficacy and safety of combination therapy with olmesartan medoxomil and hydrochlorothiazide (HCTZ) were assessed in a multicenter, double-blind clinical trial that included 502 patients with mild to moderate hypertension. The patients were randomized to receive placebo, olmesartan medoxomil monotherapy (10, 20 or 40 mg/day), HCTZ monotherapy (12.5 or 25 mg/day) or different olmesartan medoxomil/HCTZ combinations for 8 weeks. All the combination therapies were more effective than either drug alone or placebo in reducing the seated systolic and diastolic blood pressures of the patients. No significant differences were found in the incidence of adverse events in all study groups (13).

The pooled results of 3 clinical trials were used to determine the effects of dose titration with olmesartan medoxomil in hypertensive patients. The administration of an initial dose of 20 mg/day of the drug induced a clinical response (defined as achieving a seated diastolic blood pressure [SeDBP] of < 90 mmHg or an SeDBP reduction from baseline of at least 10 mmHg) in 404 patients of an original population of 791 subjects. The remaining 397 patients did not respond to the treatment and were titrated to receive a dose of 40 mg/day, which further reduced the SeDBP values of the patients and resulted in a response rate of 50%. These results suggested a dose-response effect for olmesartan medoxomil, and that a better blood pressure control might be achieved at higher drug doses (14).

The efficacy of olmesartan was evaluated in 334 patients with moderate to severe essential hypertension in a randomized, double-blind, placebo-controlled trial. Olmesartan doses were 5, 20 or 80 mg once daily or 2.5, 10 or 40 mg b.i.d. Significant reductions in mean 24-h diastolic blood pressure were seen with once- and twice-daily dosing, and the drug provided 24-h blood pressure control. Safety was similar with olmesartan and placebo (15).

The efficacy of olmesartan medoxomil as an antihypertensive drug was confirmed by the pooled results of 7 double-blind, placebo-controlled clinical trials that enrolled a total of 2,693 patients with mild to moderate hypertension. The patients were randomized to receive drug doses that ranged from 2.5 mg to 80 mg once daily for 6-12 weeks. At the end of the treatment, the administration of the drug at daily doses of 20 and 40 mg reduced the systolic/diastolic blood pressure values of the patients by 15.1/12.2 mmHg and 17.6/13.1 mmHg, respectively. The effects of the drug were greatest among the

subgroup of 1,415 patients with a wide baseline pulse pressure > 55 mmHg, with SBP/DBP reductions of 17.7/10.8 mmHg and 22.0/12.9 mmHg being reported for daily doses of 20 and 40 mg, respectively; significant pulse pressure reductions were also found for the drug in this subgroup of patients. Olmesartan proved to be equally safe and effective in men and women (16, 17).

Olmesartan was compared to other angiotensin II antagonists in 2 multicenter, randomized, double-blind studies in patients with essential hypertension. Olmesartan 10-20 mg once daily or losartan 50-100 mg once daily was assigned to 1,316 patients for as long as 12 weeks in the first study, while in a second study 588 patients were given olmesartan 20 mg, losartan 50 mg, valsartan 80 mg or irbesartan 150 mg, all once daily for 8 weeks. Greater changes in diastolic and systolic blood pressure were seen with olmesartan than with losartan in study 1, and in study 2 the decrease by week 8 in cuff diastolic blood pressure was greater with olmesartan than with the other agents (18).

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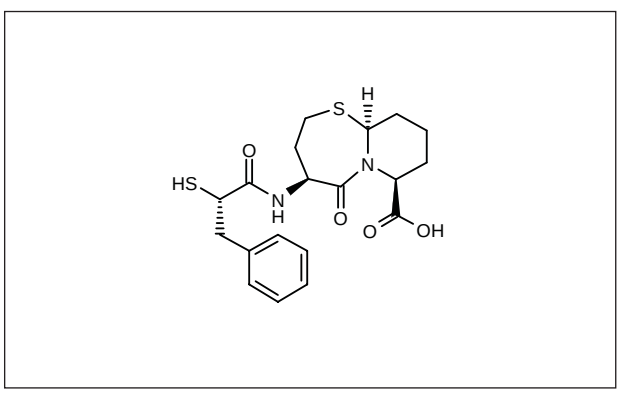
Original monograph - Drugs Fut 1997, 22(11): 1205.

Omapatrilat



Bristol-Myers Squibb received an approvable letter last year from the FDA for the antihypertensive agent Vanlev™ (omapatrilat), a dual ACE and neutral endopeptidase (NEP, neprilysin), or vasopeptidase, inhibitor. Among other issues that must be addressed before full approval can be given, the FDA requested that Bristol-Myers Squibb conduct at least one additional clinical trial to demonstrate a superior antihypertensive effect of VanlevTM in patients who have been unequivocally shown to be resistant to multiple other antihypertensives used in combination at their highest doses. The company is reportedly reviewing its options (1-3).

Data from two major clinical trials of the vasopeptidase inhibitor were also released last year: the OCTAVE (Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril) study in 25,000 hypertensive patients and the OVERTURE (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events) study in

5,770 patients with heart failure. The OCTAVE study assessed multiple treatment strategies with omapatrilat versus the ACE inhibitor enalapril, including patients initiating therapy, replacing current therapy or adding on therapy to other antihypertensive drugs. The design allowed physicians to electively increase the dose of study drug or add other antihypertensive therapies as needed to control blood pressure. At the end of the study, more patients treated with enalapril required an increase in dose or the addition of other antihypertensive therapies to reach target blood pressure. The study also demonstrated consistently greater systolic blood pressure reductions on omapatrilat in all patient groups (average of 3 mmHg), whether used alone or in combination with existing antihypertensive therapies. The proportion of patients who reached blood pressure goals of < 140 mmHg systolic and < 90 mmHg diastolic was consistently about 9% higher on omapatrilat than on enalapril. However, a higher risk of angioedema was seen in omapatrilat-treated patients. The overall incidence of angioedema over 24 weeks was 2.17% on omapatrilat *versus* 0.68% on enalapril. The risk of developing angioedema was higher in black patients on both drugs (5.54% on omapatrilat, 1.62% on enalapril) than in nonblack patients (1.78% on omapatrilat, 0.55% on enalapril). The most common manifestation of angioedema was swelling of the face or lips. Over half of all cases required no treatment or treatment with antihistamines only, while the remaining cases were treated with epinephrine or steroids. Two cases of airways compromise occurred on omapatrilat, one of whom experienced an anaphylactic reaction that responded to treatment with epinephrine and did not require mechanical airways protection, and the other requiring mechanical airways protection prior to resolution. Preliminary results from the OVERTURE trial were presented during a late-breaking clinical trials session at the American College of Cardiology meeting. OVERTURE, an international, double-blind, randomized trial in patients with moderate to severe heart failure comparing omapatrilat 10-40 mg once daily and enalapril 2.5-10 mg twice daily for a minimum of 8 months, demonstrated a similar benefit for omapatrilat and enalapril in the treatment of heart failure. Specifically, preliminary data showed that the primary endpoint – the incidence of death or hospitalization due to worsening heart failure – was 31.7% on omapatrilat and 33.7% on enalapril. Both treatments were generally safe and well tolerated, with a similar incidence of angioedema (0.8% on omapatrilat *vs.* 0.5% on enalapril) and no cases of airways compromise (4).

In experiments in cultured endothelial cells, brain natriuretic peptide (BNP) prevented increases in endothelial cell permeability induced by thrombin. Additionally, endothelial cell impermeability was maintained with long-term omapatrilat treatment in a rabbit model of atherosclerosis. Omapatrilat also attenuated atheroma formation in these animals (5).

The effects of omapatrilat on the expression of NEP and ACE in rat tissues were assessed *in vivo* by *in vitro* autoradiography. Rats received 40 mg/kg/day omapatrilat orally for 3 days and were then killed 1 h after the final dose. Using inhibitor radioligands for NEP and ACE, it was found that omapatrilat inhibited tissue ACE by 70-95% and tissue NEP by percentages ranging from 20-40% to 87% in different tissues. Omapatrilat did not inhibit either ACE in brain or NEP in brain, ventricle or spleen (6).

Treatment with omapatrilat alone and omapatrilat plus a diuretic was compared with administration of an ACE inhibitor plus a diuretic in dogs with pacing-induced congestive heart failure. Acute administration of omapatrilat with or without a diuretic demonstrated better cardiorenal and humoral responses than ACE inhibition plus a diuretic (7).

The mechanism of action of omapatrilat was investigated in a canine model of hypertension. Omapatrilat 30 μM/kg i.v. led to marked decreases in preload. Decreased left ventricular systolic pressure was also associated with a decrease in BNP. It was concluded that the antihypertensive effect of omapatrilat was in part due to treatment-induced increases in adrenomedullin (8).

The effects of candesartan and omapatrilat on the development and progression of atherosclerosis were assessed in male apolipoprotein E-deficient (ApoE-/-) mice. Both drugs decreased systolic blood pressure and inhibited fatty streak formation in early atherogenesis, but candesartan was more effective than omapatrilat in preventing the further development of lesions in the presence of angiotensin II. The lack of beneficial changes in plasma lipid, glucose or insulin levels induced by either candesartan or omapatrilat suggested that these drugs had a direct effect on the cells in the atherosclerotic lesion (9).

The effects of omapatrilat (4 or 20 mg/kg/day for 3 months) on blood pressure, oxidative stress and atherogenesis were investigated in atherosclerotic ApoE-/- mice. Omapatrilat (20 mg/kg) reduced systolic and diastolic blood pressure by 33% and 25%, respectively. The agent also reduced serum susceptibility to lipid peroxidation by 16%, increased serum paraoxanase activity by 22% and dose-dependently reduced the area of atherosclerotic lesions. Isolated peritoneal macrophages demonstrated reduced oxidative stress (10).

A study revealed that omapatrilat 100 μg/kg/day for 30 consecutive days improved systemic hemodynamics and left ventricular contractility and relaxation in male rats with heart failure induced by ligation of the left coronary artery (11).

Spontaneously hypertensive rats received 100 mg/kg/day omapatrilat, 10-20 mg/kg/day benazepril or 10-20 mg/kg/day benazepril plus 16-32 mg/kg/day furosemide for 12 weeks. Treatment with omapatrilat was associated with a greater blood pressure decrease, better improvement in systemic hemodynamics and better effects on left ventricular weight and fibrosis (12).

Using hypertensive 1-kidney, 1-clip rats subjected to dietary sodium restriction for several days before treatment, it was found that omapatrilat 30 mg/kg had the same effects on mean arterial pressure as enalapril 10

mg/kg, but was associated with fewer deleterious effects on glomerular filtration (13).

When given to SHR for 6 months, omapatrilat decreased systolic blood pressure and mean blood pressure values, improved cardiac function and decreased plasma levels of brain natriuretic peptide BNP, a marker of left ventricular hypertrophy and dysfunction, to a greater degree than the ACE inhibitor fosinopril (14).

Salt-induced hypertensive rats received a 4-week treatment with equipotent doses of either omapatrilat or enalapril. High dietary salt intake increased both systolic blood pressure and myocardial fibrosis. Both enalapril and omapatrilat inhibited this increase in systolic blood pressure; however, only omapatrilat decreased salt-induced myocardial fibrosis (15).

Administration of omapatrilat (10 mg/kg once daily) to Zucker fatty rats 7 days prior to and 38 days after induction of myocardial infarction (MI), resulted in reduced numbers of large MI and increased survival rates 24 h post-MI as compared to untreated animals. Omapatrilat normalized glucose levels and reduced left ventricular systolic and diastolic circumferences by echocardiography in treated animals with large MI. Reactive hypertrophy and pulmonary congestion were also decreased by omapatrilat treatment. Thus, omapatrilat improved left ventricular remodeling and hemodynamics in this experimental system (16).

Researchers found that omapatrilat and CGS-25462, but not enalapril (100, 10 and 40 mg/kg/day for 3 weeks, respectively), lowered systolic blood pressure, improved vascular structure and endothelial function and reduced collagen deposition of small arteries in DOCA-salt hypertensive rats. These results indicate that NEP but not ACE inhibition improves blood vessel structure/function and reduces blood pressure in this hypertensive model (17).

The cardioprotective effects of omapatrilat were assessed in mice with chronic heart failure due to myocardial infarction. The animals received 50 mg/kg/day omapatrilat, 20 mg/kg/day candoxatril or 2.5 mg/kg/day ramipril for 5 months, and omapatrilat was found to be more effective than the other two treatments in improving cardiac function and remodeling. The cardioprotective effects of all treatments were lower in knockout mice that do not express the bradykinin B_2 receptor, suggesting that kinins play an important role in the cardioprotective effects of these drugs (18).

In hypertensive uremic rats, vascular and renal ET-1 and TGF-β1 expression decreased further after treatment with omapatrilat than with enalapril, suggesting that omapatrilat possesses strong renoprotective effects (19).

A study in rats, dogs and humans compared the metabolism of [^{14}C]-omapatrilat and [$^{13}C_2$]-omapatrilat after single oral doses. The major metabolites identified in human, rat and dog plasma were *S*-methylomapatrilat and (*S*)-2-thiomethyl-3-phenylpropionic acid; only a small amount of the extractable radioactivity detected in plasma was attributable to unchanged drug. Some of the radioactivity in plasma was unextractable and was identified as omapatrilat and (*S*)-2-thiomethyl-3-phenylpropionic acid. Amine hydrolysis products, the diastereomeric sulfoxide of (*S*)-2-thiomethyl-3-phenylpropionic acid, the acyl glucuronide of *S*-methylomapatrilat and *S*-methylomapatrilat were the major metabolites detected in human urine while the acyl glucuronide of (*S*)-2-thiomethyl-3-phenylpropionic acid, the L-cysteine mixed disulfide of omapatrilat, diastereomers of the *S*-methyl sulfoxide of omapatrilat and the *S*-methylomapatrilat ring sulfoxide were minor metabolites. Similar metabolites were identified in dog urine, while the metabolites identified in rat urine were mainly formed after hydrolysis of the agent. Omapatrilat was concluded to be extensively metabolized in all species since unchanged compound was not found in any urine samples (20).

The pharmacodynamic effects of omapatrilat (40 and 80 mg) and fosinopril (20 mg) during salt depletion and salt repletion were assessed in a double-blind, placebo-controlled, randomized, crossover study. Twenty-four normotensive subjects were randomized to receive a single oral dose of each study drug, either after a low-sodium diet for 36 h or after a high-sodium diet for 6 days. Administration of either omapatrilat dose resulted in a strong and long-lasting inhibitory effect on plasma ACE activity. The dose of 40 mg omapatrilat resulted in maximal hormonal and blood pressure effects and was more effective than 20 mg fosinopril in increasing plasma active renin levels and decreasing mean arterial pressure (21).

Results from a double-blind, randomized, 12-week trial in 167 patients with moderate systolic hypertension (systolic blood pressure [SBP] = 160 mmHg or greater) showed that omapatrilat 80 mg/day was more effective than enalapril 40 mg/day in reducing pulse pressure and proximal aortic stiffness. Greater, more significant reductions in peripheral (–8.2 ± 12.2 mmHg *vs.* –4 ± 12.2 mmHg) and central (–10.2 ± 16.2 mmHg *vs.* –3.2 ± 16.9 mmHg) pulse pressures and characteristic impedance were seen in patients treated with omapatrilat as compared to enalapril. Adverse events were similar in both groups (22).

A total of 321 patients enrolled in the echo substudy of the OVERTURE trial were randomized to enalapril 10 mg b.i.d. or omapatrilat 40 mg once daily and echocardiograms were performed at baseline and 1 year. Left ventricular size decreased and ejection fraction increased significantly with either treatment, with no difference seen between treatment groups (23).

Short- and long-term hemodynamic benefits were observed in symptomatic heart failure patients treated with omapatrilat in a randomized, double-blind study. In the trial, the first 190 patients received omapatrilat 2.5, 5 or 10 mg while the next 179 patients were given 2.5, 20 or 40 mg once daily for 12 weeks. The higher doses (20 and 40 mg) produced greater increases in vasodilator and natriuretic peptides and greater declines in pulmonary capillary wedge pressure and systolic blood pressure than the lowest dose (24).

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Pexelizumab

The complement inhibitor pexelizumab (5G1.1-SC) is under joint development by Alexion and Procter & Gamble. The drug is in phase II clinical trials for myocardial infarction and phase III trials for cardiopulmonary bypass surgery

Enrollment has been completed in the phase III PRIMO-CABG (Pexelizumab for Reduction in Infarction and MOrtality in Coronary Artery Bypass Graft surgery) trial of in approximately 3,000 patients undergoing CABG surgery with cardiopulmonary bypass. Results are expected in the second half of the year. In the trial, patients enrolled at over 200 sites received either placebo or pexelizumab by bolus followed by a continuous infusion over 24 h. The trial aims to assess the safety and efficacy of pexelizumab in reducing the incidence of death or myocardial infarction in this patient population. Pexelizumab has also been studied in 2 large phase II trials in approximately 900 acute MI patients each – the COMMA (COMplement inhibition in MyocArdial infarction treated with PTCA) trial and the COMPLY (COMPlement inhibition in myocardial infarction treated with thromboLYtics) trial (1, 2).

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2. *Enrollment complete in second phase II trial of pexelizumab in acute myocardial infarction*. DailyDrugNews.com (Daily Essentials) April 11, 2002.

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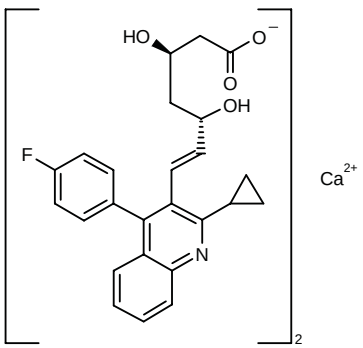
Pitavastatin Calcium



Pitavastatin calcium (itavastatin, nisvastatin, NK-104, NKS-104) is a lipid-lowering statin developed by Kowa and Nissan Chemical which was recently granted approval in Japan for the treatment of hypercholesterolemia. The product, known as Ribar®, will be manufactured by Nissan and Kowa and marketed by Kowa and Sankyo. Kowa also has a manufacturing agreement with SkyePharma for the drug, as well as copromotion agreements with Sankyo for the U.S. and with Novartis for Europe, where it is in phase II.

The inhibitory activity of pitavastatin was evaluated on the migration and proliferation of rat vascular smooth muscle cells. Pitavastatin significantly inhibited angiotensin II-induced migration at 0.01 and 0.1 μmol/l and inhibited platelet-derived growth factor-induced migration at 1-10 nmol/l in a relatively concentration-dependent manner. The induction of DNA synthesis and cell number increase were also significantly inhibited, without affecting cell viability. Pitavastatin may produce antiatherogenic activity via these mechanisms of action (1).

The analysis of different variants of the 5' region of the apolipoprotein A-I gene using the luciferase assay revealed that the lipid-lowering drugs pitavastatin and fenofibrate increased the expression of this gene through an interaction with promoter elements located at positions –27 and/or –75 (2).

In human liver Hep G2 cells, pitavastatin concentration-dependently increased the expression of several genes involved in the catabolism of cholesterol, such as the farnesoid X receptor (FXR), the peroxisome proliferator-activated receptor-α (PPARα) and the liver X receptor (LXRα) (3).

A flow cytometry analysis conducted in human umbilical vein endothelial cells (HUVEC) established that pitavastatin increased the surface expression of the zinc metalloprotease aminopeptidase N (membrane alanine aminopeptidase) and reduced the increase in IL-6 production induced by thrombin, and may therefore protect against vascular endothelial damage (4).

The incubation of PLC/PRF/5 human hepatic cells with pitavastatin 18 mcM for 24 h significantly decreased the IL-6-induced synthesis of C-reactive protein, which is both a marker for inflammation and a risk factor for cardiovascular disease (5).

According to recent findings, pitavastatin may have beneficial effects in the treatment of vascular diabetic complications. The statin reduced the expression of osteopontin in cultured rat aorta smooth muscle cells via inhibition of protein geranylgeranylation. Furthermore, in diabetic rats, it normalized the elevated expression of osteopontin in aorta and kidney following oral administration (6).

In rabbits, atherosclerosis induced by a high-cholesterol diet was inhibited by treatment with pitavastatin (0.1 mg/kg/day) via enhancement of NO bioavailability (7).

The potential use of pitavastatin for the prevention of restenosis was suggested by the finding that a daily oral dose of 40 mg administered to pigs for 7 days before stent implantation was more effective than placebo in reducing neointimal hyperplasia and microvessel area density of stent-injured arteries (8).

In dogs with tachycardia, heart failure impaired the increase in femoral blood flow induced by acetylcholine, reduced the expression of endothelial nitric oxide synthase (eNOS) mRNA and increased the production of superoxide in the aorta, all of which were suggestive of endothelial dysfunction. The administration of pitavastatin at a daily dose of 0.3 mg/kg for 4 weeks improved peripheral blood flow by reducing the aortic synthesis of superoxide and upregulating the expression of eNOS (9).

A murine model of hindlimb ischemia was used to assess the angiogenic effects of pitavastatin. Control mice with hindlimb ischemia treated with saline showed autoamputation of the ischemic toe, whereas mice treated with pitavastatin (1 mg/kg p.o.) displayed increased blood flow to the ischemic limb and no autoamputation, and significantly increased angiogenesis, apparently via upregulation of NO and VEGF production. High doses of pitavastatin (10 mg/kg), however, suppressed angiogenesis and were associated with enhanced apoptosis (10).

A new genetic rat model of non-insulin-dependent diabetes mellitus was used to assess the apoptotic effects of pitavastatin and olmesartan (both 3 mg/kg/day) over a period of 12 weeks. Neither drug significantly altered plasma glucose or cholesterol levels in Otsuka Long-Evans Tokushima fatty (OLETF) rats, but pitavastatin significantly inhibited interstitial cardiac fibrosis via suppression of TGF-β1 mRNA and caspase 3 expression (11).

Postprandial effects of pitavastatin were examined using a rat model of postprandial lipemia. Chylomicron triglyceride secretion was attenuated by 40% in the lymph and plasma triglyceride levels were decreased by 53% (at 6 h) in animals treated with pitavastatin (1 mg/kg). Animals treated with pitavastatin at 0.5 mg/kg

demonstrated a 56% reduction in the AUC_{0-12h} and reduced activity of intestinal microsomal triglyceride transfer protein. Atorvastatin demonstrated similar but less pronounced effects (12).

Pitavastatin was safe and effective and reduced LDL cholesterol levels in a dose-dependent manner in patients with hypercholesterolemia (13).

Pitavastatin 2 mg/day was administered for 8 weeks to 25 patients with heterozygous familial hypercholesterolemia. The dose was then doubled and given for 68-96 weeks. The drug significantly reduced total and LDL cholesterol from baseline in a dose-dependent manner. The treatment was safe, with adverse reactions seen in 1 case (14).

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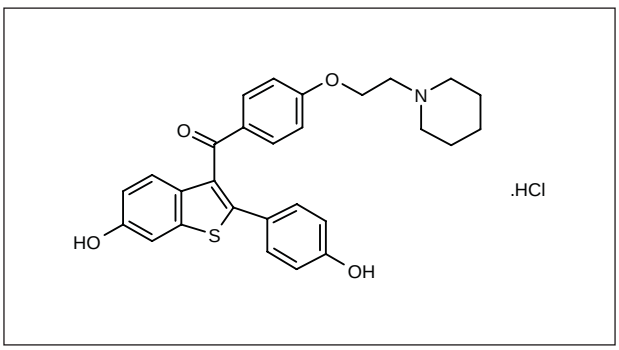
Raloxifene



A selective estrogen receptor modulator (SERM), raloxifene hydrochloride (Evista®; Lilly) is currently used for the treatment and prevention of osteoporosis and fractures in postmenopausal women. It is also being assessed for use for preventing cardiovascular events in postmenopausal women.

The effect of raloxifene on coronary arteries was investigated in 48 aged ewes randomized to undergo either sham surgery, ovariectomy, ovariectomy with estradiol supplementation or ovariectomy with raloxifene (0.02 or 0.10 mg/kg/day) supplementation. Results indicated that raloxifene allowed greater dilation and was more protective of coronary arteries than estrogen (1).

The *in vitro* antioxidant effects of raloxifene, tamoxifen and estradiol on low-density lipoproteins (LDL) were assessed in blood samples from 12 healthy untreated postmenopausal women. Evaluation of the AUC revealed that raloxifene had an antioxidant effect on LDL that was at least 7 times greater than estradiol or tamoxifen. This effect, together with the other favorable actions of raloxifene on cardiovascular risk factors, may establish a cardioprotective effect of this drug (2).

A secondary analysis of data from the Multiple Outcomes of Raloxifene Evaluation (MORE) trial in terms of the effects of raloxifene on cardiovascular events in postmenopausal women with osteoporosis was recently reported. Raloxifene was previously reported to reduce

the risk of osteoporotic vertebral fractures and newly diagnosed breast cancer in this double-blind, placebo-controlled trial enrolling 7,705 postmenopausal women with osteoporosis, without increasing the risk of endometrial cancer. The patients were randomized to receive raloxifene 60 or 120 mg/day or placebo for 4 years. In this secondary analysis, no significant differences were seen among treatment groups in the overall cohort as regards the number of combined coronary and cerebrovascular events, with relative risk ratios of 0.86 and 0.98 for raloxifene 60 and 120 mg/day, respectively, and similar findings were obtained following analysis of coronary and cerebrovascular events separately. However, in a subset of over 1,000 women with an increased risk for cardiovascular events at baseline, raloxifene was associated with a significantly lower risk of cardiovascular events compared to placebo, with a relative risk of 0.60 for both raloxifene groups. Moreover, no evidence for an early increase in the risk of cardiovascular events was found in the overall cohort or subsets of women at increased cardiovascular risk or established coronary heart disease (3).

Raloxifene 60 mg/day was compared to simvastatin 20 mg/day in a randomized, double-blind, crossover study in 12 postmenopausal women with hypercholesterolemia and coronary artery disease. Treatment periods lasted for 8 weeks and were separated by a 4-week washout period. Raloxifene decreased ICAM-1 and VCAM-1 significantly more than simvastatin, while simvastatin lowered total and LDL cholesterol significantly more than raloxifene (4).

The lipid-lowering effects of a combination of raloxifene 60 mg/day and simvastatin 10 mg/day were compared with those of either drug alone or placebo in a randomized trial conducted in 94 postmenopausal women with moderately increased serum LDL levels. Compared to baseline, the combination induced significantly larger decreases in mean LDL cholesterol, apolipoprotein B and total cholesterol levels than raloxifene or simvastatin alone, effects which were observed within 1 month of beginning therapy and sustained throughout the study. The safety profile of all study treatments was good and no adverse effects were reported on triglycerides, HDL or liver function tests (5).

A prospective, open study evaluated the effect of raloxifene therapy (60 mg/day) on the lipid pattern of 29 postmenopausal women with densitometric osteopenia or osteoporosis over 1 year. Results indicated that total cholesterol levels decreased significantly compared to baseline levels, but levels of HDL and LDL cholesterol did not change significantly. Changes in triglyceride levels also did not reach significance when compared to baseline levels (6).

The RUTH (Raloxifene Use for The Heart) trial assessed the effects of raloxifene in women from 26 countries at high risk for cardiovascular disease. The percentage of women who attained desirable LDL levels after being treated with raloxifene varied depending on factors such as the region, risk status, body mass index, statin administration, vigorous activity and, among diabetics, HbA1c levels below 7 (7).

A total of 70 healthy menopausal women were recruited into a randomized study to evaluate the effects of a 6-month regimen of raloxifene (60 mg/day) on serum lipid profiles. Results for the 68 evaluable subjects (34 in the active treatment group, 34 in the control group) revealed no significant changes in the serum concentrations of total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides with raloxifene (8).

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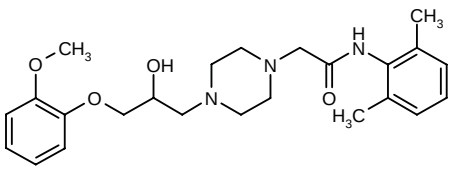
Ranolazine



Ranolazine (Ranexa™) is the first in a new class of compounds known as partial fatty acid oxidation (pFOX) inhibitors. CV Therapeutics submitted an NDA for ranolazine for the treatment of chronic angina to the FDA in December 2002, which is scheduled for review by the Cardiovascular and Renal Drugs Advisory Committee at its meeting on September 15-16, 2003. The NDA contains data from more than 3,000 patients with angina and healthy volunteers and includes over 25,000 electrocardiograms. If approved by the FDA, ranolazine would represent the first new class of antianginal agents in over 20 years (1-3).

Results from the CARISA (Combination Assessment of Ranolazine in Stable Angina) trial demonstrated that treatment with ranolazine (750 or 1000 mg b.i.d.) for 12 weeks increased exercise duration, time to angina and time to 1-mm S-T segment depression in patients with and without a history of heart failure. However, the improvement in exercise parameters at trough on the 750-mg dose of ranolazine was smaller in heart failure patients. Also, the incidence of adverse events was lower in heart failure patients than in those with no previous heart failure. Age was seen to affect the safety, but not the efficacy, of ranolazine. Treatment with the drug resulted in similar increases in exercise duration, time to angina onset and time to 1-mm S-T segment depression in patients aged below 65 years and in those aged 65 years or over. Adverse effects (especially nausea, dizziness and constipation) were more frequent in the older patients (at least 65 years of age) treated with ranolazine (42% *vs.* 24% on 1000 mg b.i.d., 36% *vs.* 26% on 750 mg b.i.d. and 27% *vs.* 26% on placebo) (4, 5).

In a preclinical study, ranolazine both terminated and suppressed ventricular tachycardias. In an isolated guinea pig heart model, the naturally occurring toxin ATX-II elicits early afterdepolarizations (EADs) and ventricular tachycardia (VT) by selective activation of the late sodium channel in the heart. In this study, EADs and VT could not be induced with ranolazine (5-30 μM) alone or in combination with ATX-II (10 nM). In the absence of ranolazine, ATX-II induced EADs and VT in 4 of 5 hearts. These arrhythmias were terminated by subsequent application of ranolazine (6-8).

The effect on hemodynamic abnormalities following partial inhibition of fatty acids with ranolazine was assessed in a dog heart failure model. The agent significantly increased the left ventricular ejection fraction (27 ± 1% *vs.* 32 ± 2%), peak left ventricular dysfunction +dP/dt (1712 ± 122 mmHg/s *vs.* 1900 ± 112 mmHg/s) and stroke volume (20 ± 1 ml *vs.* 26 ± 1 ml). The agent was without effect on the hemodynamics of normal dogs (9).

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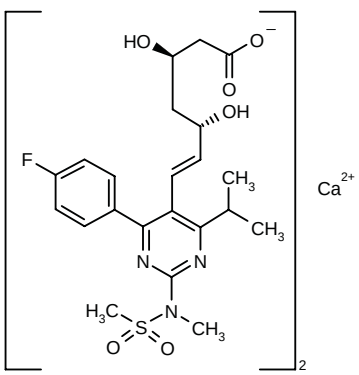
Rosuvastatin Calcium



The long-acting HMG-CoA reductase inhibitor (statin) rosuvastatin calcium (Crestor®) has been introduced by AstraZeneca in The Netherlands, its first market, Canada and the U.K. for the treatment of primary hypercholesterolemia and mixed dyslipidemia as an adjunct to diet when response to diet and exercise is inadequate. It is also indicated for monotherapy or as an adjunct to diet and other lipid-lowering agents in homozygous familial hypercholesterolemia. It has been approved in Singapore and through the mutual recognition procedure in most E.U. countries, and filings are also under review in Japan and the U.S., among other markets. AstraZeneca licensed worldwide rights to the drug from Shionogi in 1998 and the companies subsequently agreed to comarket rosuvastatin in Japan (1-10).

AstraZeneca has initiated a long-term phase III study to assess whether rosuvastatin can reduce the risk of major cardiovascular events in patients. The JUPITER (Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin) study will evaluate the effect of statin therapy on the reduction of cardiovascular morbidity and mortality among some 15,000 individuals with average or normal LDL cholesterol levels and elevated C-reactive protein (CRP) levels. The primary objective of the multicenter, randomized, double-blind, placebo-controlled study is to investigate whether long-term treatment with rosuvastatin will decrease the rate of major cardiovascular events among individuals with LDL cholesterol and elevated levels of CRP who may be at vascular risk on the basis of an enhanced inflammatory response. The JUPITER study is part of the GALAXY program in which several other studies are already under way. The METEOR (Measuring Effects on intima media Thickness: an Evaluation Of Rosuvastatin) study is evaluating the effect of rosuvastatin on the progression of carotid atherosclerosis by measuring intima media thickness in low-risk, asymptomatic hypercholesterolemic subjects with subclinical evidence of atherosclerosis as determined by thickened carotid artery walls. More than 800 patients will be enrolled worldwide in this randomized, double-blind, placebo-controlled study which began in August 2002. The ASTEROID (A Study To evaluate the Effect of Rosuvastatin On Intravascular ultrasound-Derived coronary atheroma burden) study is designed to assess the effects of rosuvastatin on the regression of coronary atherosclerosis in patients with coronary artery disease who require coronary angiography. The open-label, noncomparative study began in November 2002 and will enroll more than 400 patients worldwide. A third study, AURORA (A study to evaluate the Use of Rosuvastatin in subjects On Regular hemodialysis: an Assessment of survival and cardiovascular events) has also started. The randomized, placebo-controlled study will examine the role of statin therapy in patients with end-stage renal disease undergoing chronic hemodialysis (11).

Transgenic ApoE*3 Leiden mice fed a high-cholesterol diet plus rosuvastatin for 24 weeks showed significantly lower plasma cholesterol and triglyceride levels than mice given the high-cholesterol diet alone. Progression of the aortic root total lesion area was also slower in rosuvastatin-treated mice than in mice fed either a high- or low-cholesterol diet, suggesting that the reduction in the progression of aortic atherosclerotic lesions induced by rosuvastatin is independent of its cholesterol-lowering effect (12).

In other studies in ApoE*3 Leiden transgenic mice, administration of different doses of rosuvastatin confirmed the beneficial effects of this drug on plasma cholesterol and triglyceride levels, and indicated that these effects involved a decrease in hepatic VLDL production and promotion of hepatobiliary removal of cholesterol, bile acids and phospholipids (13).

The nonlipophilic effects of rosuvastatin were tested in cultured bovine aortic endothelial cells and 129/SV wild-type mice. Concentration- and time-dependent upregulation of endothelial nitric oxide synthase (eNOS) mRNA and protein expression was observed in endothelial cells. In aortas of 129/SV mice, rosuvastatin (0.2, 2 and 20 mg/kg s.c. for 10 days) significantly upregulated eNOS mRNA by 50%, 142% and 205%, respectively, and NOS activity by 75%, 145% and 320%, respectively, and reduced stroke volume by 27%, 56% and 50%, respectively. No changes in serum cholesterol and TAG levels were observed. Results were equivalent or superior to those with simvastatin and atorvastatin in this model (14, 15).

Rosuvastatin enhanced the fluidity of apolipoprotein B (apo B)-containing lipoproteins in both the surface phospholipid monolayer and the hydrophobic lipid core. These changes were consistent with the cholesterol-lowering

effect of rosuvastatin, and may play an important role in the control of metabolic processes involved in the etiology of atherosclerosis (16).

The results from an open-label, crossover trial indicated that the pharmacodynamics, pharmacokinetics and efficacy of rosuvastatin (10 mg) are unaffected by the time of dosing. Following morning and evening dosing, C_{max} and AUC_{0-24} were 4.58 ng/ml *vs.* 4.54 ng/ml and 40.1 ng·ml/h *vs.* 42.7 ng·ml/h, respectively. Similarly, no significant differences were observed in the reduction in serum concentrations of LDL cholesterol (–41.3% *vs.* –44.2%), total cholesterol (–30.9% *vs.* –31.8%), triglycerides (–17.1% *vs.* –22.7%) or apo B (–32.4% *vs.* –35.3%) following morning and evening administration, respectively (17).

No significant differences were observed in the pharmacokinetics of digoxin when administered concomitantly with rosuvastatin to healthy volunteers in a double-blind, randomized, crossover trial. The mean AUC and C_{max} of digoxin were increased by 4% when coadministered with rosuvastatin as compared with coadministration with placebo; the 90% confidence intervals for both treatment regimens were within the prespecified margin. Urine excretion and renal clearance of digoxin were similar for both regimens (18).

The effect of fluconazole on the pharmacokinetics of rosuvastatin was evaluated in a randomized, double-blind, crossover trial in 14 healthy male volunteers. Subjects were dosed with fluconazole (200 mg) or placebo for 11 days and rosuvastatin (80 mg) was coadministered on day 8. There were small increases in the AUC and C_{max} when rosuvastatin was coadministered with fluconazole, but these increases were not considered to be clinically relevant (19).

Pooled data from several clinical trials reported that the number of Western patients who achieved the LDL cholesterol target established by the Japanese Atherosclerosis Society was higher after treatment with rosuvastatin than with atorvastatin. Rosuvastatin was particularly effective in high-risk patients suffering from coronary artery disorders (20, 21). A higher percentage of patients treated with rosuvastatin also reached the Joint European Societies LDL cholesterol goal than patients treated with atorvastatin, pravastatin or simvastatin for the same period of time (22, 23). The analysis of pooled data from 3 multicenter, double-blind trials revealed that rosuvastatin 5-10 mg for 12 weeks was more effective than atorvastatin 10 mg for 12 weeks in reducing LDL cholesterol levels, increasing HDL cholesterol levels and increasing the number of patients achieving LDL cholesterol goals established by the U.S. National Cholesterol Education Program Adult Treatment Panel (24).

A randomized, double-blind, placebo-controlled study assessed the effects and safety of rosuvastatin in 113 Japanese hypercholesterolemic patients. Doses ranging from 2.5-40 mg administered for 6 weeks induced a dose-dependent decrease in LDL cholesterol, total cholesterol and apo B levels (25).

A 6-week, double-blind, randomized clinical trial assessed the lipid-lowering effects of rosuvastatin (5, 10, 20, 40 or 80 mg once daily) and atorvastatin (10, 20, 40 or 80 mg once daily) in 374 hypercholesterolemic patients. Both drugs were well tolerated and induced dose-dependent reductions in plasma LDL cholesterol levels. Rosuvastatin was more effective than atorvastatin in reducing the plasma levels of total cholesterol, non-HDL cholesterol, LDL cholesterol and apo B, and increasing those of HDL cholesterol (26).

In a 6-week, double-blind, randomized trial in dyslipidemic men and women, conducted in the U.S. and Canada, an additional 8.4% mean reduction in LDL cholesterol levels was achieved on rosuvastatin compared to atorvastatin, more than the 6% additional lowering in LDL cholesterol levels generally observed when the dose of a statin is doubled. Rosuvastatin also had beneficial effects on total cholesterol, non-HDL cholesterol, apo B, lipoprotein ratios and HDL cholesterol compared to atorvastatin (27).

A total of 477 patients with hypercholesterolemia were included in a double-blind clinical trial to compare the lipid-lowering efficacy and safety of rosuvastatin calcium, pravastatin sodium and simvastatin. The patients were randomized to receive fixed oral doses of rosuvastatin (5 or 10 mg), pravastatin (20 mg) or simvastatin (20 mg) once daily for 12 weeks, followed by an extension period of 40 weeks where the dose could be increased if the LDL cholesterol treatment goals established by the Adult Treatment Panel II (ATP II) had not been reached. After 12 weeks of treatment, rosuvastatin was found to be more effective than either simvastatin or pravastatin in reducing the levels of LDL cholesterol, triglycerides, total cholesterol, non-HDL cholesterol and apo B, and increasing those of HDL cholesterol. The percentages of patients who had reached the ATP II treatment goals were 80.2% with rosuvastatin 5 mg, 89.6% with rosuvastatin 10 mg, 53.4% with pravastatin and 68.9% with simvastatin. At the end of the 40-week extension period, these percentages had increased to 88.1%, 87.5%, 60.0% and 72.5%, respectively, but most patients in the rosuvastatin groups were still receiving their initial dose and had not required any dose escalation. All treatments were well tolerated and showed no significant differences in their safety profiles (28).

In a randomized study, a combination of 10-40 mg rosuvastatin and 0.5-2 g extended-release niacin decreased plasma LDL cholesterol levels as much as rosuvastatin alone and promoted an increase in HDL cholesterol levels (+24% compared to +11% with rosuvastatin alone) (29).

In a randomized, double-blind, placebo-controlled trial, 135 postmenopausal women received placebo, 5 mg rosuvastatin or 10 mg rosuvastatin for 12 weeks. Both rosuvastatin doses were well tolerated, significantly decreased LDL cholesterol, total cholesterol, triglycerides, apo B levels and lipid ratios in plasma, and also increased plasma HDL cholesterol and apo A-I levels (30).

The international MERCURY I trial compared the lipid-lowering effects of rosuvastatin calcium and other statins in a population of 3,161 adult patients with hypercholesterolemia. The patients were randomized to receive rosuvastatin (10 mg), atorvastatin (10 or 20 mg), simvastatin (20 mg) or pravastatin (40 mg) for 8 weeks, after which they either remained on the same treatments or were switched to receive rosuvastatin (10 or 20 mg) for another 8 weeks. Compared to the other statins, rosuvastatin was found to be associated with greater reductions in the plasma levels of LDL cholesterol and non-HDL cholesterol, and with higher percentages of patients who reached the European LDL-C goals and those established by the Adult Treatment Panel III. All study treatments were well tolerated and showed similar safety profiles (31).

An open-label study found that 20, 40 and 80 mg of rosuvastatin administered to 44 patients with homozygous familial hypercholesterolemia for a total of 18 weeks decreased LDL cholesterol and total cholesterol levels by 21% and 20%, respectively, compared to baseline values. The drug had variable effects on other lipid endpoints and was well tolerated (32).

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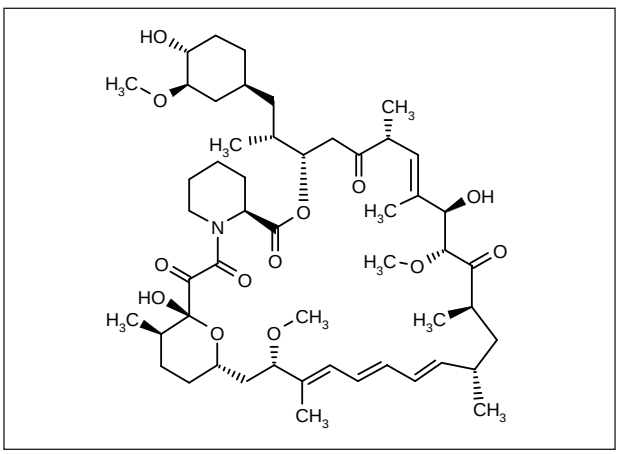
Original monograph - Drugs Fut 1999, 24(5): 511.

Sirolimus



Cordis, a Johnson & Johnson company, has received approval from the FDA to market its Cypher™ sirolimus-eluting coronary stent for the reduction of restenosis of a treated coronary artery.

The FDA approved the Cypher™ stent under an expedited review for use in native coronary arteries with reference diameters of 2.5-3.5 mm and lengths of 8, 13, 18, 23, 28 and 33 mm, covering the majority of stent cases performed. The stent's action is controlled by a polymer coating that gradually releases sirolimus into the vessel lining to prevent scar tissue growth. Cordis has an exclusive worldwide license agreement with Wyeth for the localized delivery of sirolimus in certain fields of use. The stent's efficacy is supported by data from 2 large randomized, double-blind, controlled trials in 1,400 patients. Data from the 2-year follow-up to the pivotal European RAVEL trial and the 1-year follow-up to the U.S. SIRIUS trial showed sustained reductions in the incidence of reblockage of more than 90% as compared to a conventional bare metal stent, with a greater than 95% chance that patients can avoid retreatment. The Cypher™ stent was first introduced by Cordis in April 2002 and is now available in Europe, the Middle East, Canada, the Asia-Pacific region and Latin America. The FDA is requiring the company to conduct a 2,000-patient postapproval study and continue to evaluate patients from ongoing clinical trials to assess the long-term safety and efficacy of the stent and to look for rare adverse events that may result from the use of the product (1).

The efficacy and safety of sirolimus-eluting stents was evaluated in 40 patients with in-stent restenosis. Preliminary examination of 22 patients revealed no angiographic restenosis, few cardiac events and a low incidence of intravascular ultrasound in-stent obstruction (2).

Intravascular ultrasound was used to provide morphological analysis of 238 patients enrolled in the multicenter, randomized, double-blind RAVEL (RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with *de novo* native coronary artery Lesions) study comparing the sirolimus-eluting Bx Velocity™ stent with the uncoated Bx Velocity™ stent. At 6 months, the sirolimus stent prevented neointimal hyperplasia and the late lumen loss, regardless of vessel size. In addition, the sirolimus-eluting stent did not create an edge effect and did not affect plaque volume outside the stent structure. Furthermore, the incidence of incomplete stent apposition was significantly higher in patients with the sirolimus-eluting stent. The outcomes of side branches in 128 patients were not significantly different between stent groups, although a trend towards reopening was seen in the group receiving the sirolimus-eluting stent (3-9).

Intimal hyperplasia with sirolimus-coated and uncoated stents was assessed in 45 patients undergoing single-vessel coronary stenting. At 4 and 12 months, patients with both the fast- and slow-release formulations of the sirolimus-coated stent had almost no late lumen loss or intimal hyperplasia (10).

1. *Cypher stent approved by FDA*. DailyDrugNews.com (Daily Essentials) April 28, 2003.

2. Serruys, P.W., Abizaid, A., Foley, D. et al. *Sirolimus-eluting stents abolish neointimal hyperplasia in patients with in-stent restenosis: Late angio-*

graphic and intravascular ultrasound results. J Am Coll Cardiol 2002, 39(5, Suppl. A): 37A.

3. Fajadet, J., Perin, M., Ban Hayashi, E., Colombo, A., Schuler, G., Barragan, P., Bode, C., Sousa, J.E., Morice, M.C., Serruys, P.W. *210-Day follow-up of the RAVEL study: A randomized study with the sirolimus-eluting Bx Velocity™ balloon-expandable stent in the treatment of patients with de novo native coronary artery lesions*. J Am Coll Cardiol 2002, 39(5, Suppl. A): 20A.

4. Sousa, J.E.E., Tanake, K., Degertekin, M., Fajadet, J., Perin, M., Ban Hayashi, E., Colombo, A., Morice, M.C., Serruys, P.W., Demeyere, C. *Is there an edge effect with the sirolimus-eluting stent?* J Am Coll Cardiol 2002, 39(5, Suppl. A): 37A.

5. Serruys, P.W., Degertekin, M., Tanabe, K. et al. *Intravascular ultrasound findings in the multicenter, randomized, double-blind RAVEL (RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) trial*. Circulation 2002, 106(7): 798.

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7. Tanabe, K., Degertekin, M., Sousa, J.E., Fajadet, J., Perin, M., Ban Hayashi, E., Colombo, A., Morice, M.C., Serruys, P.W., Wulfert, E. *Fate of side branches after sirolimus-eluting stent implantation*. J Am Coll Cardiol 2002, 39(5, Suppl. A): 51A.

8. Regar, E., Laarman, G., Blanchard, D., Eltchaninoff, H., Sousa, J.E., Fajadet, J., Perin, M., Ban Hayashi, E., Morice, M.C., Serruys, P.W. *Sirolimus inhibits restenosis irrespective of the vessel size: A subanalysis of the multicenter RAVEL trial*. J Am Coll Cardiol 2002, 39(5, Suppl. A): 58A.

9. Degertekin, M., Tanabe, K., Regar, E., Sousa, J.E., Colombo, A., Guagliumi, G., Guermonperez, J.L., Morice, M.C., Serruys, P.W. *Are sirolimus-eluting stents inducing vascular remodeling? A subgroup analysis of 3D-intravascular ultrasound in the RAVEL trial*. J Am Coll Cardiol 2002, 39(5, Suppl. A): 59A.

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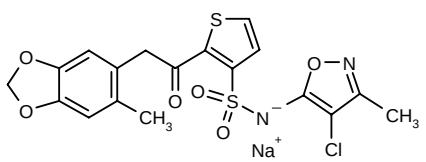
Original monograph - Drugs Fut 1977, 2(10): 692.

Sitaxsentan Sodium



Sitaxsentan sodium (TBC-11251) is small-molecule endothelin antagonist in late-stage clinical development at Encysive Pharmaceuticals (the former Texas Biotechnology) for the treatment of pulmonary hypertension. In April Encysive acquired Icos's 50% interest in the Icos-Texas Biotechnology joint venture, thereby regaining full ownership rights to the endothelin receptor antagonist program, including sitaxsentan sodium. The company expects to license certain rights to the drug, retaining North American rights.

Encysive recently received a special protocol assessment (SPA) from the FDA, creating a binding agreement for the basis of sitaxsentan regulatory review. The agreement confirms that STRIDE 2 (Sitaxsentan To Relieve ImpaireD Exercise in pulmonary hypertension), which will be initiated imminently, together with the results from STRIDE 1 and planned supportive trials, will be sufficient for an NDA. STRIDE 2 was designed to confirm the benefits seen in STRIDE 1 and the company anticipates enrollment to be completed in the spring of 2004. NDA submission is anticipated for between the end of 2004 and the first quarter of 2005. STRIDE 2 will be an 18-week double-blind, placebo-controlled trial, which will evaluate doses of sitaxsentan of 50 and 100 mg, and in addition, it will include a randomized bosentan (Tracleer®) arm. The primary efficacy variable will be the 6-min walk distance and secondary variables will include change in functional class, occurrence of clinical events and shortness of breath as measured by the Borg dyspnea scale. STRIDE 2 will also have a long-term extension phase allowing patients administered the highest dose of sitaxsentan and bosentan to continue treatment if they respond adequately during the first 18-week period. Those patients administered the 50-mg dose of sitaxsentan or placebo experiencing clinical deterioration will have the opportunity to take part in the extension. There will also be a trial enrolling patients who have failed bosentan due to hepatic toxicity or lack of efficacy. Other trials, primarily focused on collecting safety data, will be conducted in parallel (1-5).

An open-label trial of sitaxsentan enrolled 6 children and 4 adults with primary pulmonary hypertension or pulmonary arterial hypertension associated with either congenital systemic-to-pulmonary shunts or collagen vascular disease. The drug was administered for 12 weeks at doses of 100-500 mg b.i.d. p.o. Exercise capacity was significantly improved by sitaxsentan and mean pulmonary arterial pressure and pulmonary vascular resistance were also improved (6).

The first phase IIb/III STRIDE study determined the effects of sitaxsentan sodium on the hemodynamics of patients with NYHA class II-IV pulmonary arterial hypertension. A total of 178 patients were randomized to receive placebo or oral doses of 100 or 300 mg of sitaxsentan every day for 12 weeks. Compared with placebo, the drug dose-dependently reduced mean pulmonary arterial pressure, mean systemic arterial pressure and mean right atrial pressure. Both doses were equally effective in improving the cardiac index and pulmonary and systemic vascular resistance, but the lower dose was better tolerated The primary endpoint of

change in percent of peak VO_2 was significantly improved with sitaxsentan 300 mg as compared with placebo, and both sitaxsentan doses improved 6-min walk tests and NYHA class. Liver abnormalities, considered a complication related to the endothelin antagonist class of drugs, were defined in the STRIDE trial as elevated aminotransferase values more than 3 times normal. The incidence of liver abnormalities, which were reversible in all cases, was 2% for the placebo group, 0% for sitaxsentan 100 mg group and 10% for the sitaxsentan 300 mg group. When STRIDE data were combined with data from the subsequent extension trial, the incidence of reversible liver abnormalities was 5% for the sitaxsentan 100 mg group and 21% for the sitaxsentan 300 mg group (7-9).

1. *Texas Biotechnology acquires Icos interest in partnership*. DailyDrugNews.com (Daily Essentials) April 25, 2003.

2. *Texas Biotechnology renamed*. DailyDrugNews.com (Daily Essentials) May 21, 2003.

3. *Encysive receives SPA from the FDA for sitaxsentan*. DailyDrugNews.com (Daily Essentials) June 20, 2003.

4. *Sitaxsentan phase IIb/III trial completes enrollment, extension study stopped*. DailyDrugNews.com (Daily Essentials) July 24, 2002.

5. *Texas Biotechnology to reacquire full sitaxsentan rights*. DailyDrugNews.com (Daily Essentials) Feb 3, 2003.

6. Barst, R.J., Rich, S., Widlitz, A., Horn, E.M., McLaughlin, V., McFarlin, J. *Clinical efficacy of sitaxsentan, an endothelin-A receptor antagonist, in patients with pulmonary arterial hypertension: Open-label pilot study*. Chest 2002, 121(6): 1860.

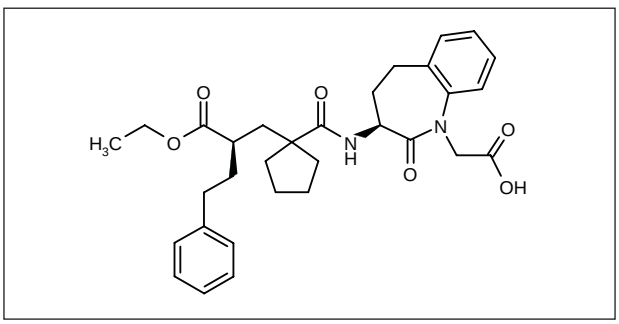
7. Barst, R.J., Langleben, D., Frost, A. et al. *Sitaxsentan, a selective ETA receptor antagonist, improves exercise capacity and NYHA functional class in pulmonary arterial hypertension (PAH)*. 99th Int Conf Am Thorac Soc (May 16-21, Seattle) 2003, A440.

8. Barst, R.J., Langleben, D., Frost, A. et al. *Sitaxsentan, a selective ETA antagonist, improves cardiopulmonary hemodynamics in pulmonary arterial hypertension (PAH)*. 99th Int Conf Am Thorac Soc (May 16-21, Seattle) 2003, A273.

9. *Top-line results from phase IIb/III sitaxsentan trial*. DailyDrugNews.com (Daily Essentials) Oct 23, 2002.

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

SLV-306



Solvay's SLV-306, a dual neutral endopeptidase (NEP, neprilysin) and endothelin-converting enzyme (ECE) inhibitor, is in phase II clinical trials for the treatment of arterial hypertension and heart failure.

Thirteen healthy male subjects were included in a clinical trial in order to establish whether the dual inhibitory action of SLV-306 on NEP and ECE was present in humans. The subjects were randomized to receive a single dose of either placebo or different doses of SLV-306 established to obtain plasma levels of 75, 300 or 1200 ng/ml of its active metabolite, KC-12615, followed 3 h later by two 20-min infusions of big ET-1 (8 and 12 pmol/kg/min). After the second big ET-1 infusion, respective increases in systolic and diastolic blood pressure values (mmHg) were: 19.4 and 16.2 (placebo), 16.5 and 14.3 (75 ng/ml), 14.6 and 12.0 (300 ng/ml), and 12.9 and 11.4 (1200 ng/ml). The drug dose-dependently increased the plasma levels of atrial natriuretic peptide (ANP) and big ET-1, and decreased those of ET-1. These results confirm that SLV-306 inhibits both ECE and NEP in humans (1, 2).

The potential therapeutic effects of SLV-306 were assessed in a double-blind, placebo-controlled clinical trial that randomized 75 patients with NYHA class II-III congestive heart failure to receive either placebo or SLV-306 at dose levels of 200, 400 or 800 mg. Compared to placebo, the drug significantly reduced the pulmonary blood pressure parameters of the patients, including the pulmonary systolic and diastolic blood pressure and the pulmonary capillary wedge pressure. SLV-306 also reduced the mean systemic arterial pressure and the systemic vascular resistance, although the differences compared to placebo were not statistically significant. The authors concluded that the reduction in the left ventricular filling pressure induced by dual inhibitors of both NEP and ECE might be useful in the treatment of congestive heart failure (3).

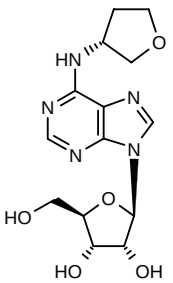
1. Seed, A., Kuc, R., Davenport, A., Hillier, C., Essers, H., McMurray, J.J.V. *Novel, systemic neutral endopeptidase and endothelin converting enzyme inhibition in humans using orally active, SLV 306*. Eur Heart J 2002, 23(Suppl.): Abst P1740.

2. Seed, A., Kuc, R., Davenport, A., Ashby, M., Hillier, C., de Voogd, H., Essers, H., McMurray, J. *First demonstration in humans of systemic neutral endopeptidase and endothelin converting enzyme inhibition using a new orally active dual metalloprotease inhibitor SLV 306*. J Am Coll Cardiol 2003, 41(6, Suppl. A): 265A.

3. Dickstein, K., de Voogd, H., Miric, M., Willenbrock, R., Mitrovic, V., Pacher, R., Bambasek, G., Koopman, P. *Inhibition of both neutral endopeptidase and endothelin converting enzyme lowers pulmonary pressures in congestive heart failure*. J Am Coll Cardiol 2003, 41(6, Suppl. A): 266A.

Original monograph - Drugs Fut 2002, 27(1): 27.

Tecadenoson



Tecadenoson (CVT-510; CV Therapeutics) is a novel compound that selectively stimulates the adenosine A_1 receptor. In preclinical trials, tecadenoson selectively stimulated the adenosine A1 receptor in the atrioventricular (AV) node and slowed the speed of electrical conduction across the AV node, reducing the number of electrical impulses that reached the ventricle.

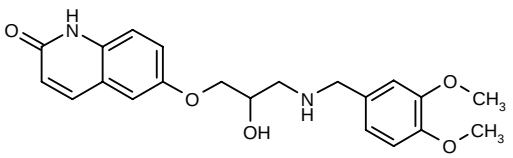
Clinical studies with intravenous tecadenoson suggest that it may slow the speed of AV nodal conduction by selectively stimulating the A_1 receptor, and may avoid blood pressure lowering by not stimulating the adenosine A_2 receptor. The phase III trial of tecadenoson in patients with paroxysmal supraventricular tachycardia (PSVT) was reported to meet its primary endpoint, specifically, the conversion of PSVT to a normal sinus heart rhythm without second- or third-degree AV block. Five doses of tecadenoson were evaluated in 181 patients in the multicenter, randomized, double-blind, placebo-controlled trial. Tecadenoson has also been investigated in a phase IIb program for use in patients with atrial fibrillation or atrial flutter. Additional studies will be conducted to identify a potential commercial dosing regimen in this patient population (1, 2).

1. *Enrollment complete in tecadenoson phase III trial*. DailyDrugNews.com (Daily Essentials) July 31, 2002.

2. *Phase III trial of tecadenoson in PSVT meets primary endpoint*. DailyDrugNews.com (Daily Essentials) Oct 25, 2002.

Original monograph - Drugs Fut 2002, 27(9): 846.

Toborinone



Toborinone (OPC-18790) is a positive inotropic agent from Otsuka that acts by inhibiting phosphodiesterase type 3 (PDE3) and is in late-stage clinical evaluation for the treatment of heart failure.

Results from a series of studies indicate that inhibition of the delayed rectifier potassium current (I_K) contributes to the positive inotropic effects of toborinone. Toborinone (1-10 μM) simultaneously increased the Q-T interval and contractility in isolated perfused rabbit hearts, the latter to a greater extent than in the presence of E-4031 (10-100 nM); contractility, but not the Q-T interval, increased in the presence of milrinone (1-10 μM). In anesthetized rabbits treated with methoxamine, toborinone (0.1-10 mg/kg i.v.), E-4031 (3-300 μg/kg) and MS-551 (0.003-3 mg/kg) induced torsade de pointes in 1, 8 and 8 of 10 animals, respectively. The results indicate that the proarrythmic potential of toborinone is lower than pure class III antiarrhythmic agents (1).

The pharmacokinetic profile of toborinone (1.0 mg/kg/min x 4 h) was evaluated in 32 patients with congestive heart failure and concomitant renal and/or hepatic impairment. Pharmacokinetic analysis revealed no significant differences among the four study groups, and a positive correlation between toborinone clearance and indices of renal and hepatic function was observed (2).

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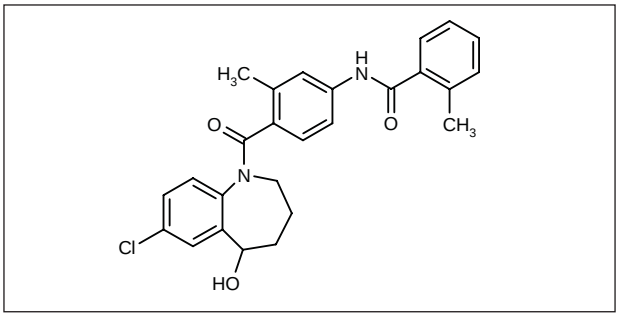
2. Tammara, B., Trang, J.M., Kitani, M., Miyamoto, G., Bramer, S.L. *The pharmacokinetics of toborinone in subjects with congestive heart failure and concomitant renal impairment and/or concomitant hepatic impairment*. J Clin Pharmacol 2002, 42(12): 1318.

Original monograph - Drugs Fut 1993, 18(12): 1114.

Tolvaptan



Otsuka is currently conducting phase II clinical studies with the vasopressin V_2 receptor antagonist tolvaptan (OPC-41061) as a diuretic for use in heart failure.

Tolvaptan normalized serum sodium in heart failure patients with hyponatremia enrolled in a randomized, placebo-controlled study. In the trial, patients with signs of congestion were treated with furosemide plus tolvaptan 30, 45 or 60 mg/day for 25 days. Body weight and edema were reduced in all patients by tolvaptan, which also significantly and dose-dependently increased urine volume on day 1 (1, 2).

In a double-blind trial, 254 chronic heart failure patients were randomized to tolvaptan 30, 45 or 60 mg or placebo once daily for 25 days. Decreases in body weight were seen in all tolvaptan dose groups, while body weight increased in the placebo group. Only patients in the tolvaptan groups experienced decreases in edema; hyponatremic patients in these groups had normalized serum sodium (3).

A study in 22 patients with a history of cardiac arrhythmia examined the interaction between tolvaptan and amiodarone, a CPY3A4 substrate. The subjects received amiodarone at a daily dose of 200 mg for at least 28 days and plasma levels were determined on day 2 when they received amiodarone alone, day 3 when they were administered amiodarone + 30 mg tolvaptan and day 4 when they received amiodarone + 90 mg tolvaptan. The results showed no significant effect for tolvaptan on the steady-state pharmacokinetic profile of amiodarone (4).

Healthy volunteers (n=21) were entered into a randomized, placebo-controlled, crossover study to receive warfarin as a single dose of 25 mg and tolvaptan 60 mg/day or placebo for 14 days. No significant pharmacokinetic or pharmacodynamic interaction was detected for these drugs (5).

Treatment of patients with heart failure and signs of congestion (n=83) with tolvaptan 30 mg was compared to treatment with placebo, furosemide 80 mg or both tolvaptan and furosemide in a randomized trial. Treatments were given once daily for 7 days, after which time body weight was reduced by 1.37 ± 1.61, 0.54 ± 1.59 and 1.13 ± 1.49 kg in patients given tolvaptan, furosemide and tolvaptan plus furosemide, respectively. Tolvaptan monotherapy also reduced edema compared with placebo and was well tolerated (6).

1. Gheorghiade, M., Konstam, M.A., Udelson, J.E., Ouyang, J., Orlandi, C. *Vasopressin receptor blockade with tolvaptan in chronic heart failure: Differential effects in normonatremic and hyponatremic patients*. J Am Coll Cardiol 2002, 39(5, Suppl. A): 171A.

2. Orlandi, C., Ouyang, J., Kambayashi, J., Konstam, M.A., Gheorghiade, M. *Beneficial effects of chronic therapy with tolvaptan, a novel vasopressin receptor blocker, in patients with congestive heart failure*. Circ J 2002, 66(Suppl. 1): Abst OE-360.

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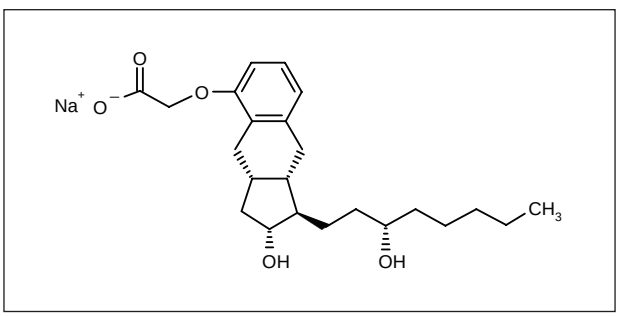
4. Shoaf, S.E., Wang, Z., Sekar, K., Orlandi, C., Bramer, S.L. *Tolvaptan has no effect on steady state amiodarone concentrations*. Clin Pharmacol Ther 2003, 73(2): Abst PII-60.

5. Wang, Z., Shoaf, S., Kumara, S., Mallikaarjun, S., Orlandi, C., Bramer, S. *Lack of effect of tolvaptan on pharmacokinetics (PK) and pharmacodynamics (PD) of warfarin*. Clin Pharmacol Ther 2003, 73(2): Abst PII-61.

6. Udelson, J.E., Orlandi, C., O'Brien, T., Sequeira, R., Ouyang, J., Konstam, M.A. *Vasopressin receptor blockade in patients with congestive heart failure: Results from a placebo controlled, randomized study comparing the effects of tolvaptan, furosemide, and their combination*. J Am Coll Cardiol 2002, 39(5, Suppl. A): 156A.

Original monograph - Drugs Fut 2002, 27(4): 350.

Treprostinil Sodium



The prostacyclin analogue treprostinil sodium (Remodulin™) was approved and launched in the U.S. about a year ago as a continuous s.c. infusion for the treatment of pulmonary hypertension.

Treprostinil was subsequently introduced in Canada, where it is distributed by Paladin, and approved in Israel. Developed and marketed by United Therapeutics,

treprostinil was approved specifically for the treatment of pulmonary arterial hypertension (PAH) in patients with NYHA class II-IV symptoms to reduce symptoms associated with exercise. Regulatory submissions are also under review in France, Switzerland and Australia. As a condition of U.S. approval, United Therapeutics will conduct a phase IV controlled trial involving a randomized transition of patients receiving Flolan®, a synthetic form of prostacyclin delivered intravenously, to either s.c. treprostinil or placebo. Clinical deterioration, pulmonary arterial hypertension symptoms and exercise performance will be measured (1-6).

An *in vitro* study using human pulmonary arterial smooth muscle cells examined the antiproliferative activity of iloprost, UT-15, cicaprost and beraprost. All agents significantly inhibited proliferation, with a 10-fold difference in potency for each agent (UT-15 > iloprost > cicaprost > beraprost). The antiproliferative effects were reversed by 2,5'-dideoxyadenosine (ddA) but not by SQ-22536. All agents increased intracellular cAMP, with UT-15 having the most potent effect and iloprost the least; ddA inhibited the increase in cAMP while inhibitory effects with SQ-22536 were variable. It was concluded that inhibition of human pulmonary arterial smooth muscle cell proliferation observed with these agents may be via a cAMP-dependent pathway (7).

Experiments were conducted to test the effects of treprostinil, known to exert vasodilating and antiplatelet effects, on alveolar macrophage cytokine production using lipopolysaccharide (LPS)-stimulated macrophages from healthy volunteers. At concentrations not affecting cell adherence or viability (2-200 ng/ml), treprostinil concentration-dependently reduced IL-6 release from these macrophages, as well as IL-1β and granulocyte-macrophage colony-stimulating factor (GM-CSF) release. The compound appeared to affect cytokine production at the transcriptional level. These findings suggest that treprostinil may exert its beneficial effects in pulmonary hypertension at least in part via its ability to downregulate cytokines (8).

In a double-blind, randomized, placebo-controlled study in patients with pulmonary arterial hypertension (PAH), treprostinil sodium produced a median improvement of 17 m in the 6-min walk distance at 12 weeks. Although dose escalation in this study was hampered by local reactions at the infusion site, the possibility that the effects of treprostinil might be dose-related was examined. When the 202 patients randomized to active drug and completing the 12-week 6-min walk test were divided into groups according to dose, it was seen that the effect on exercise tolerance was indeed dose-dependent, ranging from -4 m in patients given doses of < 5.0 ng/kg/min to +36 m in those receiving doses of > 13.8 ng/kg/min (9).

Results from a multicenter open trial involving 8 patients with PAH (most of whom were NYHA class II) treated with continuous i.v. epoprostenol (3.5-75 ng/kg/min; mean = 27 ng/kg/min) and suffering from life-threatening complications demonstrated that patients could be safely transitioned to s.c. treprostinil (3-65 ng/kg/min; mean = 22 ng/kg/min). The transition was completed within 21-96 h without major adverse events or changes in clinical status (including NYHA status and 6-min walk distance) in the majority of patients. Only 1 patient deteriorated, although worsening was noted in this patient during epoprostenol. Patients continued to show clinical improvement at 4-11 months posttransition. Mild to moderate pain at the infusion site was seen with s.c. treprostinil, although patients reported improved comfort and well-being (10).

Patients with PAH (n=470) were given placebo or s.c. treprostinil (begun at 1.25 ng/kg/min and increased to a maximum dose of 22.5 ng/kg/min) for 12 weeks in a multicenter, randomized, double-blind trial. The active treatment significantly improved exercise capacity compared with placebo, and such improvements were dose-related and greater in patients who were more compromised at baseline. Drug-related side effects included infusion-site pain (85% of patients) and gastrointestinal hemorrhage in 3 patients (11).

Subcutaneous treprostinil was administered to 3 patients with HIV infection and pulmonary hypertension. An initial dose of 2 ng/kg/min was administered and was increased according to tolerance. At 1 year, NYHA functional class and 6-min walk tests improved in all patients, and no serious adverse events were seen (12).

1. *Approvable letter issued by FDA for Remodulin in pulmonary arterial hypertension*. DailyDrugNews.com (Daily Essentials) Feb 13, 2002.

2. *Remodulin approved for pulmonary arterial hypertension in Israel*. DailyDrugNews.com (Daily Essentials) Nov 7, 2002.

3. *Remodulin approved in Canada*. DailyDrugNews.com (Daily Essentials) Oct 8, 2002.

4. *Remodulin filing accepted, granted priority review in Canada*. DailyDrugNews.com (Daily Essentials) Feb 20, 2002.

5. *Launch of Remodulin expands treatment options for pulmonary hypertension*. DailyDrugNews.com (Daily Essentials) June 7, 2002.

6. *Remodulin approved for pulmonary arterial hypertension*. DailyDrugNews.com (Daily Essentials) May 24, 2002.

7. Clapp, L.H., Finney, P., Turcato, S., Tran, S., Rubin, L.J., Tinker, A. *Differential effects of stable prostacyclin analogs on smooth muscle proliferation and cyclic AMP generation in human pulmonary artery*. Am J Respir Cell Mol Biol 2002, 26(2): 194.

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