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New Study Shows Benicar® (olmesartan medoxomil) Reverses Blood Vessel Damage Independent of Blood Pressure Lowering

Data published in the *Journal of the American Society of Hypertension* demonstrate that early blockade of angiotensin II reversed vascular hypertrophy

Parsippany, NJ (June 16, 2008) – A new study published in the current *Journal of the American Society of Hypertension* demonstrates that the hypertension treatment olmesartan medoxomil was effective in reversing the narrowing of the arteries that occurs in patients with hypertension. The study, titled VIOS (**V**ascular **I**mprovement with **O**lmesartan medoxomil **S**tudy) was a one-year, exploratory study that evaluated the effects of an angiotensin receptor blocker (olmesartan medoxomil) vs. a beta-blocker (atenolol) on vascular function and structure in patients with Stage 1 hypertension, independent of the blood pressure lowering effects of these agents.[1]

In the VIOS trial, olmesartan medoxomil, through early blockade of angiotensin II, improved the structure abnormalities of resistance arteries in patients with hypertension as measured by arterial wall to lumen ratio (W/L), returning arterial architecture to normal levels after one year of treatment. This protective effect was not seen with the comparator agent in the study, atenolol.[2] Olmesartan medoxomil is marketed in the United States by Daiichi Sankyo, Inc. as Benicar®. Benicar and Benicar HCT (olmesartan medoxomil/hydrochlorothiazide) are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents. Benicar HCT is not indicated for initial therapy. Benicar and Benicar HCT have not been FDA approved for other indications such as end organ disease or other hypertension related morbidity.

"We believe the VIOS data add to the growing evidence for the role of angiotensin receptor blockers in preventing or reversing vascular damage at many stages during this disease process," said Carlos M. Ferrario, M.D., one of the study's lead investigators and Professor and Director of Hypertension and Vascular Research Center, Wake Forest University School of Medicine.

Angiotensin II has been linked to vascular dysfunction and end-organ damage, including cardiac hypertrophy and renal injury.[3,4,5] Previous studies have demonstrated a beneficial effect of ACE inhibitors or other angiotension II receptor blockers (ARBs) in the reversal of vascular hypertrophy in hypertensive subjects.[6,7,8,9,10,11,12]

Hypertension is one of the most prevalent conditions in the United States, affecting one in three Americans.[13] Long-standing, uncontrolled hypertension can damage the brain, the eyes, the heart and the kidney.[14] Antihypertensive agents that inhibit the renin-angiotensin system, such as angiotensin-converting enzyme inhibitors or ARBs, have demonstrated substantially greater effects on end-organ repair in the kidney and the heart.[15,16,17,18]

VIOS Study Design

The study was a randomized, controlled, open-label, one-year study. The primary endpoint of this study was the change in the morphological characteristics of resistance arteries as determined by differences in the wall (media)/lumen (W/L) ratio. This parameter was measured using a pressurized myograph procedure on arteriole biopsy samples obtained from a sub-group of 49 patients receiving treatment (27 were on olmesartan and 22 were on atenolol) and from 11 normotensive control subjects.[19]

Non-diabetic patients with Stage 1 hypertension (61% male; age 38 to 67 years) were randomized after a 4-week washout period to olmesartan medoximil 20 to 40 mg or atenolol 50 to 100 mg plus additional agents (hydrochlorothiazide 12.5-25 mg , amlodipine 5-10 mg, or hydralazine 50-100 mg twice daily) as needed for a goal BP of <140/90).[20] Stage 1 hypertension is defined by the JNC 7 as systolic blood pressure (SBP) of 140-159 mm Hg or diastolic blood pressure (DBP) of 90-99 mm Hg.[21]

VIOS Study Results

The arteriolar dimensions (W/L Ratios) in the olmesartan medoxomil and atenolol-based treatment groups were similar prior to drug treatment (14.9% and 16% respectively) whereas arteries from the normotensive subjects had significantly smaller W/L ratios (11%). At the end of the study the W/L ratio in the olmesartan medoxomil-based treatment group was significantly reduced (from 14.9% to a mean of 11.1%, $P<0.01$). No significant change was observed in arteries of atenolol-treated patients (from 16.0% to 15.5%; P = NS). The difference between olmesartan medoxomil-treated and atenolol-treated patients at 1 year was significant (11.1% vs. 15.5%, $P < 0.001$). Blood pressure reductions from baseline occurred

within 12 weeks for both treatments and were statistically significant (P<0.05); blood pressure reductions were similar between the two treatments for the remainder of the study.[22]

This study was supported through an unrestricted grant from Daiichi Sankyo, Inc.

Ongoing Studies with Olmesartan Medoxomil

Olmestartan medoxomil is currently being reviewed in several outcomes trials, including the landmark "**R**andomized **O**lmesartan **A**nd **D**iabetes **M**icro**A**lbuminuria **P**revention Study" or ROADMAP trial. This is a Phase IV multinational clinical study to investigate the drug's effectiveness in preventing early stage kidney disease in patients with Type 2 diabetes. The trial is being conducted at 200 sites in 20 countries involving 4,400 patients. Another study, titled "**O**lmesartan **R**educing **I**ncidence of **E**nd stage renal stage in diabetic **N**ephropathy **T**rial," or ORIENT, targeting Japanese and Hong Kong Chinese patients, is investigating the suppressive effects of the drug against the progression of diabetic nephropathy.

About Benicar and Benicar HCT

Angiotensin II is a hormone that interacts with a receptor on arterial blood vessels, which results in constriction and increasing blood pressure. In addition, angiotensin II stimulates the release of another hormone that causes enhanced sodium and chloride (salt) retention, with a resultant increase in vascular water retention and blood volume that also contributes to an elevation in blood pressure. BENICAR is a member of the ARB class of antihypertensive medications that help lower blood pressure by blocking the angiotensin II receptor on the blood vessels and antagonizing the release of the hormone which causes salt retention and increased blood volume. BENICAR HCT combines BENICAR with the diuretic hydrochlorothiazide.

BENICAR and BENICAR HCT are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents. BENICAR HCT is not indicated for initial therapy.

Important Safety Information

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, BENICAR or BENICAR HCT should be discontinued as soon as possible**. See WARNINGS, Fetal/Neonatal Morbidity and Mortality** in the prescribing information**.**

Hypotension in Volume- or Salt-Depleted Patients

In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (eg,

those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of treatment with BENICAR. Treatment should start under close medical supervision. If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

Impaired Renal Function
In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been no long-term use of olmesartan medoxomil in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.

The prescribing information for BENICAR HCT also includes the following warnings regarding its hydrochlorothiazide component:
BENICAR HCT is not recommended in patients with severe renal impairment and is contraindicated in patients with anuria or hypersensitivity to other sulfonamide derived drugs

Fetal/Neonatal Morbidity and Mortality
Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Hepatic Impairment
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Hypersensitivity Reaction
Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Systemic Lupus Erythematosus
Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Lithium Interaction
Lithium generally should not be given with thiazides.

Adverse Events
● The withdrawal rates due to adverse events (AEs) were similar with BENICAR and BENICAR HCT to placebo: BENICAR (2.4% vs 2.7%); BENICAR HCT (2.0% vs 2.0%)
● The incidence of AEs with BENICAR and BENICAR HCT was similar to placebo
— The only AE that occurred in >1% of patients treated with BENICAR and more frequently than placebo was dizziness (3% vs 1%)
— AEs reported in >2% of patients taking BENICAR HCT and more frequently than placebo included nausea (3% vs 0%), hyperuricemia (4% vs 2%), dizziness (9% vs 2%), and upper respiratory tract infection (7% vs 0%)

Dosing and Administration

● No initial dosage adjustments are recommended with BENICAR in elderly or in moderate to marked renal impairment*/hepatic dysfunction

— In patients with possible depletion of intravascular volume (eg, patients on diuretics, particularly with impaired renal function), BENICAR should be initiated under close medical supervision and consideration given to use of a lower starting dose

● For BENICAR HCT, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosage range

*Creatinine clearance <40 mL/min.

Please see full prescribing information for BENICAR and BENICAR HCT.

About Daiichi Sankyo, Inc.

Daiichi Sankyo, Inc., headquartered in Parsippany, New Jersey, is the U.S. subsidiary of Daiichi Sankyo Co., Ltd., Japan's second largest pharmaceutical company and a global leader in pharmaceutical innovation since 1899. The company is dedicated to the discovery, development and commercialization of innovative medicines that improve the lives of patients throughout the world.

The primary focus of Daiichi Sankyo's research and development is cardiovascular disease, including therapies for dyslipidemia, hypertension, diabetes, and acute coronary syndrome. The company is also pursuing the discovery of new medicines in the areas of glucose metabolic disorders, infectious diseases, cancer, bone and joint diseases, and immune disorders. For more information, please visit www.dsus.com.

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