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New Data Shows AZOR[®] (amlodipine and olmesartan medoxomil) Significantly Improves 24-Hour Ambulatory Blood Pressure

AZTEC Trial First to Examine AZOR Using 24-Hour Ambulatory BP Measures

Parsippany, NJ – May 8, 2009 – Daiichi Sankyo, Inc. announced today that data presented at the American Society of Hypertension, Inc. (ASH) Twenty-Fourth Annual Scientific Meeting and Exposition (ASH 2009) in San Francisco from the **AZOR[®] Trial Evaluating Blood Pressure Reductions and Control (AZTEC)** demonstrated that a stepwise amlodipine and olmesartan medoxomil-based titration regimen provided mean 24-hour ambulatory reductions in systolic blood pressure (SBP) of 21.4 mm Hg and diastolic blood pressure (DBP) of 12.7 mm Hg. In addition, 71 percent of patients in the study were able to safely and effectively achieve a 24-hour ambulatory target blood pressure (BP) of <130/80 mm Hg. The study also showed large mean 24-hour ambulatory BP reductions in patients with hypertension from two groups with elevated risk for developing hypertension, Blacks (20.7/11 mm Hg) and patients with type 2 diabetes (21.5/12.6 mm Hg).

AZTEC was the first time researchers have analyzed the effect of AZOR on 24-hour ambulatory BP measurement (ABPM), which provides a 24-hour measurement of patient BP and is generally considered a better indicator of target organ injury than cuff measurement.¹ ABPM can give physicians a clearer picture of 24-hour BP control in patients with hypertension.² According to the Seventh Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7), ABPM patients whose 24-hour BP is >135/85 mm Hg are nearly twice as likely to have a cardiovascular event as those with BP <135/85 mm Hg.³ There are no studies with AZOR demonstrating a reduction in cardiovascular events.

“Analyzing ambulatory BP gives physicians a clear picture of how well a patient’s BP is controlled through a full 24-hour dosing period,” said Dr. Joel Neutel, MD, director, Orange County Heart Institute and Research Center. “Most patients require treatment with at least two antihypertensive agents to achieve their recommended goal BP. The results of this study demonstrated the ability of a stepwise amlodipine and olmesartan medoxomil-based titration regimen to maintain BP reductions over 24 hours. This study also showed that an amlodipine and olmesartan medoxomil-based titration regimen can be an effective tool for treating hypertension in more challenging patient populations, such as patients with type 2 diabetes and Blacks.”

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During the study, AZOR demonstrated significant reductions in seated blood pressure (SeBP), also known as cuff BP. Unlike ABPM, SeBP is only recorded once during the course of a day. AZOR 10/40 mg provided a mean reduction in seated systolic blood pressure (SeSBP) of 24.6 mm Hg and the seated diastolic blood pressure (SeDBP) reading of 12.3 mm Hg.

In AZTEC, the amlodipine and olmesartan medoxomil-based titration regimen was well tolerated, with only three (1 amlodipine patient, 2 AZOR patients) of the 185 patients discontinuing treatment because of drug-related adverse events. In this trial, occurrence of drug-related AEs included: peripheral edema (2.2 percent) and dizziness (1.1 percent).

High blood pressure can cause permanent changes to blood vessels and the heart that may create serious problems elsewhere in the body.⁴ Hypertension is one of the most prevalent conditions in the United States, affecting approximately one in three American adults (about 73 million people age 20 and older) and approximately one billion people worldwide.^{5,6} It is often difficult to control, and of those with high blood pressure, approximately 55 percent do not reach recommended BP levels.⁷ The number of people with high blood pressure is expected to reach about 1.6 billion worldwide by 2025.⁸

Black Patients

In the U.S., the rate of high blood pressure is disproportionately high in the Black community and affects 41 percent of the population.⁹ A further analysis of the AZTEC trial on the basis of race found that treatment with an amlodipine and olmesartan medoxomil-based titration regimen was well tolerated and produced similar 24-hour ambulatory BP reductions from baseline in both Black and non-Black patients. Black patients had a higher mean baseline BP than non-Black patients. The amlodipine and olmesartan medoxomil-based titration regimen produced mean 24-hour ambulatory BP reductions of 20.7/11 mm Hg in Black patients from a baseline of 148.6/85.7 mm Hg. Non-Black patients experienced a mean 24-hour ambulatory BP reduction of 21.5/13 mm Hg from a baseline of 144.2/85.7 mm Hg.

Patients with Diabetes

Seventy five percent of adults diagnosed with diabetes in the U.S. have hypertension.^{10, 11} A further analysis of the AZTEC trial found that treatment with an amlodipine and olmesartan medoxomil-based titration regimen was well tolerated and produced similar 24-hour ambulatory BP reductions from baseline in hypertensive patients with and without diabetes. Patients with diabetes treated with the amlodipine and olmesartan medoxomil-based titration regimen also achieved mean 24-hour ambulatory BP reductions of 21.5/12.6 mm Hg from a baseline of 145.6/83.1 mm Hg. Patients without diabetes experienced a mean 24-hour ambulatory BP reduction of 21.3/12.8 mm Hg from a baseline of 144.6/86.6 mm Hg.

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Study Design

AZTEC was a 15-16-week (3- to 4-week placebo run-in and 12-week active treatment periods), open label, prospective, single-arm, titrate-to-goal study, conducted in 185 patients with mild to moderate (Stage 1) and challenging (Stage 2) hypertension. The study evaluated the safety and efficacy of an amlodipine and olmesartan medoxomil-based titration algorithm. Of the total study population, 26 patients were Black and 43 patients were diagnosed as having type 2 diabetes (populations are not mutually exclusive). The primary endpoint was change in mean systolic blood pressure (SBP) from baseline after 12 weeks of treatment as measured by 24-hour ABPM. Secondary endpoints included change from baseline in mean 24-hour DBP as measured by ABPM; change from baseline in mean daytime, nighttime, and last 2, 4, and 6 hours ambulatory SBP and DBP; achievement of ABPM prespecified BP targets; change from baseline mean SeSBP and SeDBP at each titration step; and achievement of BP goals.

Following placebo run-in, patients were started on amlodipine (AML) 5 mg, and were up-titrated at three week intervals if mean cuff BP was $\geq 120/80$ mm Hg to AML/olmesartan medoxomil (OM) 5/20 mg, AML/OM 5/40 mg then AML/OM 10/40 mg. If BP was $< 120/80$ mm Hg, patients were not up-titrated to the next dose level and remained at the assigned dose (maintenance dose). Patients on maintenance doses were up-titrated if BP subsequently became uncontrolled (SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg). Twenty-four hour ABPM was performed at baseline and end of study (Week 12). One hundred seventy two patients had ABPM values for baseline and end of study. A total of 134 patients (72.4%) were titrated to AML/OM 10/40 mg.

About AZOR[®]

AZOR is a convenient, once daily, single tablet combination of amlodipine, the most prescribed CCB on the market¹², which inhibits the entrance of calcium into the blood vessel walls, with olmesartan medoxomil, the active ingredient in Benicar[®], which blocks angiotensin II receptors. Angiotensin II is a hormone that causes blood vessels to tighten and narrow. Together the two medicines relax the blood vessels so that blood can flow more easily. Benicar (olmesartan medoxomil), Daiichi Sankyo's flagship ARB product, is the fastest growing medication in the fastest growing class of blood pressure-lowering drugs.¹³

The U.S. Food and Drug Administration (FDA) granted marketing approval for AZOR in September 2007. AZOR is indicated for the treatment of hypertension, alone or with other antihypertensive agents. AZOR is not indicated for the initial therapy of hypertension. AZOR may be substituted for its individually titrated components. AZOR may also be used to provide additional blood pressure lowering for patients not adequately controlled with any calcium channel blocker or any angiotensin receptor blocker alone. In the pivotal registrational trial, AZOR demonstrated that eight weeks of double-blind treatment with combination therapy resulted in larger mean reductions in seated blood pressure and brought more patients to goal in comparison to the corresponding monotherapies.

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IMPORTANT SAFETY INFORMATION ABOUT AZOR®

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, AZOR should be discontinued as soon as possible. See **WARNINGS AND PRECAUTIONS, Fetal/Neonatal Morbidity and Mortality.**

Hypotension in Volume- or Salt-Depleted Patients

In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients, symptomatic hypotension due particularly to the olmesartan component may occur after initiation of treatment with AZOR. Treatment should start under close medical supervision.

Vasodilation

Since the vasodilation attributable to amlodipine in AZOR is gradual in onset, acute hypotension has rarely been reported after oral administration. Nonetheless, caution, as with any other peripheral vasodilator, should be exercised when administering AZOR, particularly in patients with severe aortic stenosis.

Severe Obstructive Coronary Artery Disease

Patients, particularly those with severe obstructive coronary artery disease, may develop increased frequency, duration, or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase.

Congestive Heart Failure

In general, calcium channel blockers should be used with caution in patients with heart failure.

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 effects would be expected with AZOR because of the olmesartan medoxomil component.

Hepatic Impairment

Since amlodipine is extensively metabolized by the liver and the plasma elimination half-life ($t_{1/2}$) is 56 hours in patients with severely impaired hepatic function, caution should be exercised when administering AZOR to patients with severe hepatic impairment.

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Laboratory Tests

There was a greater decrease in hemoglobin and hematocrit in the combination product compared to either component alone.

Adverse Reactions

The only adverse reaction that occurred in greater than or equal to 3 percent of patients treated with AZOR and more frequently than placebo was edema. The placebo-subtracted incidence was 5.7 percent (5/20 mg), 6.2 percent (5/40 mg), 13.3 percent (10/20 mg), and 11.2 percent (10/40 mg). The edema incidence for placebo was 12.3 percent.

Adverse reactions seen at lower rates but at about the same or greater incidence as in patients receiving placebo included hypotension, orthostatic hypotension, rash, pruritus, palpitation, urinary frequency, and nocturia.

In individual clinical trials of amlodipine and olmesartan medoxomil, other commonly reported adverse reactions included headache, dizziness, and flushing.

For more information on AZOR[®], call 877-4-DSPROD (877-437-7763) or go to the web site www.azor.com.

About Daiichi Sankyo

A global pharma innovator, Daiichi Sankyo Co., Ltd., was established in 2005 through the merger of two leading Japanese pharmaceutical companies. This integration created a more robust organization that allows for continuous development of novel drugs that enrich the quality of life for patients around the world. A central focus of Daiichi Sankyo's research and development are thrombotic disorders, malignant neoplasm, diabetes mellitus, and autoimmune disorders. Equally important to the company are hypertension, hyperlipidemia or atherosclerosis and bacterial infections. For more information, visit www.daiichisankyo.com.

Daiichi Sankyo, Inc., headquartered in Parsippany, New Jersey, is the U.S. subsidiary of Daiichi Sankyo Co., Ltd. For more information on Daiichi Sankyo, Inc., please visit www.dsi.com.

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