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New Results from the Landmark PROactive Trial Found That ACTOS® (pioglitazone HCl) Reduced the Occurrence of Major Adverse Cardiovascular Events

Additional results showed ACTOS delayed the need for insulin use in high-risk patients with type 2 diabetes

Washington, DC, June 12, 2006 – New analyses from the landmark PROactive Study found that ACTOS® (pioglitazone HCl), an oral antidiabetic medication, significantly reduced the occurrence of major adverse cardiovascular events (MACE) such as heart attacks (excluding silent heart attacks), nonfatal stroke, acute coronary syndrome (ACS) and cardiovascular death in high-risk patients with type 2 diabetes. Additionally, results showed that ACTOS significantly decreased the progression to permanent insulin use. These results were presented as three separate abstracts at the American Diabetes Association (ADA) 66th Annual Scientific Sessions.

"What is unique about these new data is that while earlier PROactive results found a combined risk reduction of heart attack stroke and death by 16 percent in high-risk patients treated with ACTOS, we saw a greater risk reduction when we looked at the wider scope of major adverse cardiovascular events, in this high-risk population," said Erland Erdmann, M.D., chairman of the PROactive Executive Committee, and director of the Clinic III for Internal Medicine, University of Cologne, Germany.

"Separate analyses suggest a significant decrease in the amount of insulin needed, as well as a delay in the need for permanent insulin use among patients taking ACTOS," said Robert Spanheimer, M.D., medical director for diabetes and metabolism at Takeda Pharmaceuticals North America, Inc. "As type 2 diabetes is a progressive disease requiring multiple therapies, many patients eventually need supplementary insulin to manage their condition. For patients with type 2 diabetes and established cardiovascular disease, these results could lead to the potential for less dependence on daily insulin use."

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Major Adverse Cardiac Events

Composite endpoints of cardiovascular events are standard measures for comparing treatments in large outcome studies and are referred to as major adverse cardiovascular events (MACE). Patients with type 2 diabetes are at particularly high risk for these events. In this analysis of the PROactive study, there were pre-specified and *post-hoc* MACE endpoints, which looked at a combination of fatal and nonfatal heart attacks, nonfatal strokes, and death.

This analysis demonstrated statistically significant risk reductions with ACTOS compared with placebo for the heart attack endpoint (23 percent, *P*=0.046), major adverse cardiovascular events (MACE1) endpoints of cardiovascular death, nonfatal heart attack or nonfatal stroke (18 percent, *P*=0.020), and MACE2 endpoints of all-cause mortality, nonfatal heart attack, nonfatal stroke or acute coronary syndrome (17 percent, *P*=0.010).

At the end of the study, 339 patients (13 percent) in the ACTOS group had a first event that contributed to the MACE2 endpoint, compared with 409 (15.5 percent) in the placebo group. Additionally, 108 (4.1 percent) ACTOS patients had a myocardial infarction, compared to 140 (5.3 percent) in the placebo group, excluding a silent myocardial infarction.

Insulin Sparing and Insulin Delay

Type 2 diabetes is a progressive disease requiring multiple therapies to achieve blood glucose control; many patients will eventually require insulin. Two additional analyses from the PROactive study examined the effects of ACTOS therapy on insulin use. The results demonstrated that ACTOS reduced the number of patients on insulin and mean daily insulin dose, and delayed need for permanent insulin use.

In one analysis, the one third of patients who were treated with insulin at baseline in the PROactive study (ACTOS = 864, placebo = 896) were evaluated:

- A1C values, a test that measures a person's average blood glucose level over the past two to three months, and mean insulin doses were similar between treatment groups at baseline.
- A rapid and sustained decrease in insulin doses was observed with patients taking ACTOS, as compared to a progressive increase with placebo.
- By study end, the mean insulin dose was lower with ACTOS (42 U/d) than with placebo (55 U/d; *P*<0.0001) and insulin had been discontinued in 9 percent of patients in the ACTOS group vs 2 percent in the placebo group (*P*<0.0001).

In the second analysis, the two thirds of PROactive patients (ACTOS = 1741 and placebo = 1737) who were not on insulin at baseline were evaluated. The study demonstrated that ACTOS delayed the need for permanent insulin use – defined as daily use for greater than or equal to ninety days, or ongoing use at

death/final visit. In fact, twice as many placebo patients progressed to permanent insulin use, as compared to ACTOS patients (N=362 and N=183, respectively) with projected rates for time to permanent insulin use 11 percent and 21 percent for the ACTOS and placebo groups, respectively (*P*<0.0001).

In addition, ACTOS patients not on insulin at baseline showed improved A1C values compared with placebo patients at final visit (6.97 percent vs 7.49 percent, *P*<0.0001). Overall, progression to permanent insulin use was reduced by 50 percent at three years with ACTOS vs placebo, and better glycemic control was seen with ACTOS. The incidence of hypoglycemia was higher in the ACTOS-treated group than in the placebo group.

About the PROactive Study

PROactive (**PRO**spective Pioglit**A**zone **C**linical **T**rial **I**n Macro**V**ascular **E**vents) was the first study to prospectively look at the reduction in total mortality and macrovascular morbidity using a glucose-lowering agent. It was a randomized, double-blind, placebo-controlled outcome study of 5,238 patients with type 2 diabetes and macrovascular disease. Patients were randomized to receive either ACTOS or placebo in addition to other blood glucose medications and on top of standard of care treatment (including the routine use of anti-hypertensives such as ACE inhibitors and beta blockers; glucose-lowering agents such as metformin, sulfonylureas and insulin; antiplatelet drugs such as aspirin, and lipid-modifying medicines such as statins and fibrates).

This study focused on two key endpoints: a primary combination endpoint of seven different macrovascular events including both disease and procedural endpoints; and a principal secondary combination of disease endpoints including death, heart attack and stroke.

As reported at the European Association for the Study of Diabetes (EASD) Annual Meeting in September 2005, the primary endpoint was reduced by 10 percent but had not reached statistical significance by study end (*P*=0.095). The principal secondary endpoint showed that ACTOS significantly reduced the combined risk of heart attacks, strokes and death by 16 percent (*P*=0.027) in high-risk patients with type 2 diabetes.

For more information, visit www.proactive-results.com. (*This independent website is supported by an unrestricted educational grant by Takeda Pharmaceutical Company Limited and Eli Lilly and Company*.)

About ACTOS

ACTOS works by directly targeting insulin resistance, a condition in which the body does not efficiently use the insulin it produces to control blood glucose levels. ACTOS is taken once daily as an adjunct to diet and exercise, and is approved for use for type 2 diabetes as monotherapy to lower blood glucose and in combination therapy with insulin, sulfonylureas or metformin.

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Additional Information

ACTOS is not for everyone. ACTOS can cause fluid retention that may lead to or worsen heart failure, so tell your doctor if you have a history of these conditions. Talk to your doctor immediately if you experience rapid weight gain, fluid retention, or shortness of breath while taking ACTOS. If you have moderate to severe heart failure, ACTOS is not recommended. Your doctor should perform a blood test to check for liver problems before you start ACTOS and periodically thereafter.

Do not take ACTOS if you have active liver disease. Talk to your doctor immediately if you experience nausea, vomiting, stomach pain, tiredness, loss of appetite, dark urine, or yellowing of the skin. If you are of childbearing age, talk to your doctor before taking ACTOS as it could increase your chance of becoming pregnant. Some people taking ACTOS may experience flu-like symptoms, mild to moderate swelling of legs and ankles, and anemia. When taking ACTOS with insulin or sulfonylureas, you may be at risk for low blood glucose.

Takeda Pharmaceuticals North America, Inc.

Based in Lincolnshire, Ill., Takeda Pharmaceuticals North America, Inc., is a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, the largest pharmaceutical company in Japan. In the United States, Takeda currently markets oral diabetes, insomnia, cholesterol-lowering and gastroenterology treatments, and through the Takeda Global Research & Development Center, Inc., the company has a robust pipeline with compounds in development for diabetes, cardiovascular disease and other conditions. Takeda is committed to striving toward better health for individuals and progress in medicine by developing superior pharmaceutical products. To learn more about the company and its products, visit www.tpna.com.

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