actos®
pioglitazone HCl

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PROactive Study Shows Takeda's ACTOS® (pioglitazone HCl) Reduced Heart Attacks, Strokes and Deaths in Patients with Type 2 Diabetes

LINCOLNSHIRE, Ill., September 12, 2005 – Landmark data from the PROactive Study, presented today at the 41st meeting of the European Association for the Study of Diabetes (EASD) demonstrated that ACTOS® (pioglitazone HCl) significantly reduced the combined risk of heart attacks, strokes and death by 16% in high–risk patients with type 2 diabetes.

"The PROactive study is the first in the world to prospectively show that a specific oral glucose lowering medication, namely pioglitazone, can significantly improve cardiovascular outcomes by helping to delay or reduce heart attacks, strokes and death in high–risk patients," said John Dormandy, M.D., professor of Vascular Sciences at St. George's Hospital, London, UK, and chairman of the PROactive Study Steering Committee. "This groundbreaking study gives new hope to people with type 2 diabetes who, despite their attempts to control blood glucose and take medications, fear these life–threatening events."

PROactive (PROspective PioglitAzone Clinical Trial In MacroVascular Events) was a randomized, double blind, placebo–controlled outcome study to determine the effects of ACTOS on mortality and morbidity associated with cardiovascular disease progression in more than 5,000 high risk patients

with type 2 diabetes when added to standard of care treatment.

Standard of care included 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.

Compelling Study Results

This study focused on two key endpoints: a primary combination endpoint of seven different macrovascular events of varying clinical importance; and a principal secondary combination endpoint of life–threatening events including death, heart attack and stroke.

The primary endpoint was reduced by 10% but had not reached statistical significance by study end ($p=0.095$). The principal secondary endpoint of life–threatening events showed that pioglitazone significantly reduced the risk of heart attacks, strokes and death by 16% ($p=0.027$).

According to Professor Dormandy, these results predict that 10 heart attacks, strokes or deaths will be prevented for every 500 high–risk patients treated with ACTOS® (pioglitazone HCl) over three years. Additional PROactive study results of ACTOS showed:

- HbA1c levels (a measurement of long–term blood glucose control) were significantly reduced as compared to placebo ($p<0.001$).
- Lipid profiles significantly improved by increasing HDL cholesterol (“good” cholesterol) by 9% more than placebo ($p<0.001$), and reducing triglycerides (a known cardiovascular risk factor) by 13% more than placebo ($p<0.001$).
- The LDL/HDL cholesterol ratio (“bad” to “good” cholesterol) was significantly improved ($p<0.001$). A 2% increase in LDL cholesterol (“bad” cholesterol) was observed compared to placebo ($p=0.003$).
- Systolic blood pressure was significantly decreased ($p=0.03$); median change of 3 mmHg more than produced by placebo.
- The number of patients needing to have insulin added permanently to their treatment was 50% less than placebo ($p<0.001$).

The PROactive Study was also designed to further examine the safety of ACTOS in this high–risk

patient group. The results demonstrated that adverse events reported in this study were consistent with the known safety profile. Known side effects of ACTOS, including weight gain, edema, non–serious hypoglycemia and heart failure were observed more frequently compared to placebo. However, the benefits of ACTOS in the study outweighed the risks. In addition, there were no reports of acute liver toxicity.

“ACTOS has demonstrated a unique profile in earlier comparative clinical studies by providing benefits beyond glycemic control on markers of cardiovascular risk,” commented Dr. Kitazawa, a member of the board of Takeda Pharmaceutical Company, Osaka, Japan. “However, the clinical significance of these effects of pioglitazone was unknown until we knew the exciting news from the PROactive Study. Additional clinical studies are being funded by Takeda to further improve our understanding of how ACTOS enables the results we have seen in the PROactive study, specifically the reduction in risk of heart attacks, strokes and deaths.”

Professor Dormandy added, “Until we know how pioglitazone works to provide these life–saving benefits, the beneficial results of PROactive should not be generalized to any other glucose–lowering medication.”

The PROactive Study was funded by Takeda Pharmaceutical Company Limited, the makers of pioglitazone (marketed under the trade name ACTOS®) and Eli Lilly and Company.

The results in slide format and other information on the PROactive Study are available on the global PROactive website, www.proactive–results.com. *(This independent website is supported by an unrestricted educational grant by Takeda Pharmaceutical Company and Eli Lilly and Company.)*

ACTOS, an insulin sensitizer belonging to the thiazolidinedione (TZD) class of oral anti–diabetic medications, directly targets 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 in type 2 diabetes as monotherapy to lower blood glucose and in combination therapy with insulin, sulfonylureas or metformin.

Important Product 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.

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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 and cholesterol–lowering 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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