March 2007

Re: Observation of an Increased Incidence of Fractures in Female Patients Who Received Long-Term Treatment with ACTOS® (pioglitazone HCl) Tablets for Type 2 Diabetes Mellitus

Dear Healthcare Provider:

As part of our continuing efforts to provide appropriate safety information to healthcare providers, Takeda Pharmaceuticals North America, Inc., is informing you of recent safety data concerning pioglitazone-containing products, i.e., ACTOS Tablets, ACTO*plus* met® (pioglitazone HCl and metformin hydrochloride) Tablets, and *duet*act™ (pioglitazone HCl and glimepiride) Tablets. These products are used to treat type 2 diabetes mellitus.

To date, cumulative worldwide postmarketing exposure is more than 7 million patient-years for ACTOS and nearly 40,000 patient-years for ACTO*plus* met.

As part of our ongoing evaluation of all safety information, Takeda has recently undertaken an analysis of its clinical trial database of pioglitazone with a special focus on fractures, comparing patients treated with pioglitazone or a comparator (either placebo or active). The maximum duration of pioglitazone treatment was up to 3.5 years. There were more than 8100 patients in the pioglitazone-treated groups and over 7400 patients in the comparator-treated groups, corresponding to just under 12,000 patient-years exposure per group.

There was no increased risk of fracture identified in men.

However, there were more reports of fractures in female patients taking pioglitazone than those taking a comparator.

The majority of fractures observed in female patients who received pioglitazone were in the distal upper limb (forearm, hand and wrist) or distal lower limb (foot, ankle, fibula and tibia). The fracture incidence calculated was 1.9 fractures per 100 patient-years in the pioglitazone-treated group and 1.1 fractures per 100 patient-years in the comparator-treated group. The observed excess risk of fractures for women in this data set on pioglitazone is therefore 0.8 fractures per 100 patient-years of use.

The explanation for this finding is currently not known. It should also be noted that none of the pioglitazone studies in the database addressed, or were designed to study, the effect on bone, but fractures were collected as adverse events. Due to the limitations of the existing data set, multiple known risk factors for fractures cannot be excluded as confounding variables. Further evaluation of these findings is ongoing.

The risk of fracture should be considered in the care of female patients with type 2 diabetes mellitus who are currently being treated with pioglitazone, or when initiation of pioglitazone treatment is being considered.

TAKEDA PHARMACEUTICALS NORTH AMERICA, INC.
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Takeda Pharmaceuticals North America, Inc. is committed to providing healthcare providers and patients with up-to-date and accurate information regarding our products. You can assist Takeda in monitoring the safety of our products by reporting adverse reactions to Takeda at 1-877-TAKEDA7 or to the FDA MedWatch program (telephone 1-800-332-1088, fax 1-800-332-0178, online at www.fda.gov/medwatch, or by mail to MedWatch, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852-9787).

Should you have any questions or require additional information, please contact Takeda Pharmaceuticals North America, Inc., information line at 1-877-TAKEDA7.

Sincerely,

Robert Spanheimer, MD
Senior Director, Diabetes, Metabolism
Medical and Scientific Affairs
Takeda Pharmaceuticals North America, Inc.

ACTOS is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. ACTOS is approved for use as monotherapy and in combination with sulfonylureas, metformin, or insulin when diet and exercise plus a single agent do not result in glycemic control.

Important Safety Information

Like other thiazolidinediones (TZDs), pioglitazone can cause fluid retention when used alone or in combination with other antidiabetic agents, including insulin. Fluid retention may lead to or exacerbate heart failure. Patients should be observed for signs and symptoms of heart failure. • In clinical trials, a small number of patients with a history of previously existing cardiac disease were reported to develop congestive heart failure (CHF) when treated with pioglitazone in combination with insulin. Reports of CHF have been received in postmarketing experience in patients with and without previously known heart disease. • Patients with NYHA Class III and IV cardiac status were not studied in pioglitazone clinical trials; therefore, ACTOS is not indicated in these patients. • Patients with systolic heart failure (NYHA Class II) naïve to pioglitazone therapy should be initiated at the lowest approved dose. Patients should be monitored for signs and symptoms of CHF exacerbation.

Reports of hepatitis and of hepatic enzyme elevations to three or more times the upper limit of normal (ULN) have been received in postmarketing experience with pioglitazone. Very rarely, these reports have involved hepatic failure with or without fatal outcome, although causality has not been established. • Liver enzymes, including serum ALT, should be evaluated in all patients at initiation of therapy with ACTOS, and periodically thereafter per the clinical judgment of the healthcare professional. If ALT >2.5X ULN at baseline or if the patient exhibits clinical evidence of active liver disease, do not initiate therapy with ACTOS.

ACTOS may also be associated with hypoglycemia, edema, anemia, weight gain, and/or ovulation in premenopausal, anovulatory women. Adequate contraception should be recommended for premenopausal women. Macular edema has been reported in some diabetic patients receiving TZD therapy, although a causal relationship is unknown. Persons with diabetes should have routine eye exams, and be instructed to immediately report any visual changes to their healthcare provider.

In US placebo-controlled ACTOS monotherapy clinical trials, the most common adverse events (≥5%) were upper respiratory tract infection, headache, sinusitis, myalgia, tooth disorder, aggravated diabetes mellitus, and pharyngitis.

ACTOS should not be used in patients with type 1 diabetes. Management of type 2 diabetes should also include nutritional counseling, weight reduction as needed, and exercise.

Please see accompanying Complete Prescribing Information.