Takeda Diabetes Lilly

ADVANCING CARE TOGETHER℠

Dear Colleague,

Takeda Pharmaceuticals North America, Inc. and Eli Lilly and Company would like to provide you information regarding recent changes to the prescribing information for Actos® (pioglitazone HCl), an oral agent approved for the treatment of type 2 diabetes. The updated information reflects adverse event experience gained from U.S. controlled clinical trials, as well as from post-marketing experience. The changes are discussed below. A copy of the revised package insert is enclosed.

Actos is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes as:

- Monotherapy
  and in combination with:
- Sulfonylureas, or
- Metformin, or
- Insulin

Changes to the package insert:

A new **"WARNINGS"** section has been added to further emphasize the importance of cardiac safety concerns with Actos, particularly fluid retention which may contribute to heart failure, as well as specific concerns when Actos is used in combination with insulin:

Actos, like other thiazolidinediones, 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. Actos should be discontinued if any deterioration in cardiac status occurs. Actos is not recommended in patients with New York Heart Association (NYHA) Class III and IV cardiac status.

In a 16-week, double-blind, placebo-controlled trial involving 566 patients with type 2 diabetes and a high prevalence of pre-existing cardiovascular disease, there were four episodes of CHF among patients treated with Actos plus insulin (two each in the 15 mg and 30 mg Actos groups, respectively) for a rate of 1.1% compared to no episodes of CHF in the group treated with insulin plus placebo. All four of these patients had previous histories of cardiovascular conditions including coronary artery disease, previous CABG, and previous MI. However, analysis of these data did not identify specific risk factors that could predict increased risk of CHF on combination therapy with insulin.

The **"PRECAUTIONS"** section has been modified to include additional information about Actos monotherapy and combination therapy:

The incidence of serious cardiac adverse events (e.g., CHF) related to intravascular volume expansion has not been shown to be increased in patients treated with Actos as monotherapy or in combination with sulfonylureas or metformin compared to placebo-treated patients. In insulin combination studies, a small number of patients with a history of previously existing cardiac disease developed CHF when treated with Actos in combination with insulin.

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In post-marketing experience with Actos, cases of CHF have been reported in patients both with and without previously known heart disease.

Dose related weight gain was seen with Actos alone and in combination with other hypoglycemic agents. Weight changes from baseline during clinical trials with Actos are presented in tabular form (see Table 6).

Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on Actos should immediately report these symptoms to their physician.

The **"ADVERSE REACTIONS"** section has been modified to include additional information about adverse events observed with Actos and insulin in combination:

In the 16-week trial of Actos plus insulin versus insulin plus placebo,10 patients treated with combination therapy developed dyspnea and also, at some point during their therapy, developed either weight change or edema. Seven of the 10 patients received diuretics to treat these symptoms. These events were not reported in the insulin plus placebo group.

In combination therapy studies, edema was reported for 7.2% of patients treated with Actos and sulfonylureas compared to 2.1% of patients on sulfonylureas alone. In combination therapy studies with metformin, edema was reported in 6.0% of patients on combination therapy compared to 2.5% of patients on metformin alone. In combination therapy studies with insulin, edema was reported to 15.3% of patients on combination therapy compared to 7.0% of patients on insulin alone.

The ongoing incorporation of updated information into the labeling for Actos is appropriate for continued safe and effective use of this agent in the clinical setting. Takeda and Lilly will continue to closely monitor patient experiences.

It is important that any adverse event information associated with the use of Actos or any questions be forwarded to Takeda Pharmaceuticals North America, Inc. at (877) Takeda-7.

Sincerely yours,

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