CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-073/S023

Trade Name: Actos Tablets
15 mg, 30 mg and 45 mg

Generic Name: pioglitazone HCl

Sponsor: Takeda Global Research and Development Center, Inc

Approval Date: July 3, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-073/S023

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-073/S023

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-073/S-023

Takeda Global Research & Development Center, Inc.
Attention: Mary Jo Pritza, MPH, PharmD
Manager, Regulatory Affairs
475 Half Day Road, Suite 500
Lincolnshire, IL 60069

Dear Ms. Pritza:

Please refer to your supplemental new drug application dated June 16, 2004, received July 21, 2004, submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act for Actos® (pioglitazone HCl) Tablets, 15 mg, 30 mg, and 45 mg.

We acknowledge receipt of your submissions dated June 23 and 28 and July 20, 2004.

This supplemental new drug application proposes to add the following new heading and two paragraphs to the **WARNINGS** section, **Cardiac Failure and Other Cardiac Effects** subsection of the package insert:

> *"In type 2 diabetes and congestive heart failure (systolic dysfunction)*
>
> A 24-week post-marketing safety study was performed to compare ACTOS (n=262) to glyburide (n=256) in uncontrolled diabetic patients (mean HbA_{1C} 8.8% at baseline) with NYHA Class II and III heart failure and ejection fraction less than 40% (mean EF 30% at baseline). Over the course of the study, overnight hospitalization for congestive heart failure was reported in 9.9% of patients on ACTOS compared to 4.7% of patients on glyburide with a treatment difference observed from 6 weeks. This adverse event associated with ACTOS was more marked in patients using insulin at baseline and in patients over 64 years of age. No difference in cardiovascular mortality between the treatment groups was observed.
>
> ACTOS should be initiated at the lowest approved dose if it is prescribed for patients with type 2 diabetes and systolic heart failure (NYHA Class II). If subsequent dose escalation is necessary, the dose should be increased gradually only after several months of treatment with careful monitoring for weight gain, edema, or signs and symptoms of CHF exacerbation."

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) submitted on July 20, 2004.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-073/S-023." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-827-6422.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mary Parks
8/3/04 04:19:06 PM
for Dr. Orloff

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-073/S023

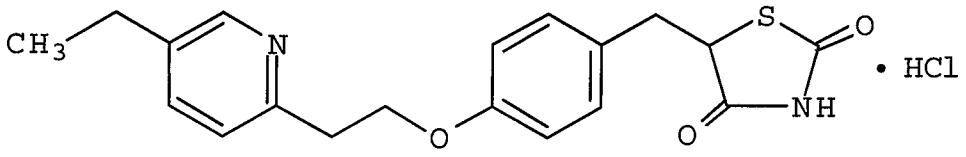
LABELING

ACTOS®
(pioglitazone hydrochloride) Tablets

DESCRIPTION

ACTOS (pioglitazone hydrochloride) is an oral antidiabetic agent that acts primarily by decreasing insulin resistance. ACTOS is used in the management of type 2 diabetes mellitus (also known as non-insulin-dependent diabetes mellitus [NIDDM] or adult-onset diabetes). Pharmacological studies indicate that ACTOS improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. ACTOS improves glycemic control while reducing circulating insulin levels.

Pioglitazone [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-] thiazolidine-dione monohydrochloride belongs to a different chemical class and has a different pharmacological action than the sulfonylureas, metformin, or the α-glucosidase inhibi-tors. The molecule contains one asymmetric carbon, and the compound is synthesized and used as the racemic mixture. The two enantiomers of pioglitazone interconvert in vivo. No differences were found in the pharmacologic activity between the two enan-tiomers. The structural formula is as shown:



Pioglitazone hydrochloride is an odorless white crystalline powder that has a molecular formula of $C_{19}H_{20}N_2O_3S$•HCl and a molecular weight of 392.90 daltons. It is soluble in N,N-dimethylformamide, slightly soluble in anhydrous ethanol, very slightly soluble in acetone and acetonitrile, practically insoluble in water, and insoluble in ether.

ACTOS is available as a tablet for oral administration containing 15 mg, 30 mg, or 45 mg of pioglitazone (as the base) formulated with the following excipients: lactose monohydrate NF, hydroxypropylcellulose NF, carboxymethylcellulose calcium NF, and magnesium stearate NF.

CLINICAL PHARMACOLOGY

Mechanism of Action

ACTOS is a thiazolidinedione antidiabetic agent that depends on the presence of insulin for its mechanism of action. ACTOS decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased he-patic glucose output. Unlike sulfonylureas, pioglitazone is not an insulin secretagogue. Pioglitazone is a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism.

In animal models of diabetes, pioglitazone reduces the hyperglycemia, hyperinsulin-emia, and hypertriglyceridemia characteristic of insulin-resistant states such as type 2 diabetes. The metabolic changes produced by pioglitazone result in increased respon-siveness of insulin-dependent tissues and are observed in numerous animal models of insulin resistance.

Since pioglitazone enhances the effects of circulating insulin (by decreasing insulin resistance), it does not lower blood glucose in animal models that lack endogenous insulin.

Pharmacokinetics and Drug Metabolism

Serum concentrations of total pioglitazone (pioglitazone plus active metabolites) remain elevated 24 hours after once daily dosing. Steady-state serum concentrations of both pioglitazone and total pioglitazone are achieved within 7 days. At steady-state, two of the pharmacologically active metabolites of pioglitazone, Metabolites III (M-III) and IV (M-IV), reach serum concentrations equal to or greater than pioglitazone. In both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approx-imately 30% to 50% of the peak total pioglitazone serum concentrations and 20% to 25% of the total area under the serum concentration-time curve (AUC).

Maximum serum concentration (C_{max}), AUC, and trough serum concentrations (C_{min}) for both pioglitazone and total pioglitazone increase proportionally at doses of 15 mg and 30 mg per day. There is a slightly less than proportional increase for pioglitazone and total pioglitazone at a dose of 60 mg per day.

Absorption: Following oral administration, in the fasting state, pioglitazone is first measurable in serum within 30 minutes, with peak concentrations observed within 2 hours. Food slightly delays the time to peak serum concentration to 3 to 4 hours, but does not alter the extent of absorption.

Distribution: The mean apparent volume of distribution (Vd/F) of pioglitazone following single-dose administration is 0.63 ± 0.41 (mean ± SD) L/kg of body weight. Pioglita-zone is extensively protein bound (> 99%) in human serum, principally to serum albu-min. Pioglitazone also binds to other serum proteins, but with lower affinity. Metabolites M-III and M-IV also are extensively bound (> 98%) to serum albumin.

Metabolism: Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-II and M-IV (hydroxy derivatives of pioglitazone) and M-III (keto derivative of pioglita-zone) are pharmacologically active in animal models of type 2 diabetes. In addition to pioglitazone, M-III and M-IV are the principal drug-related species found in human serum following multiple dosing. At steady-state, in both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the total peak serum concentrations and 20% to 25% of the total AUC.

In vitro data demonstrate that multiple CYP isoforms are involved in the metabolism of pioglitazone. The cytochrome P450 isoforms involved are CYP2C8 and, to a lesser degree, CYP3A4 with additional contributions from a variety of other isoforms including the mainly extrahepatic CYP1A1. In vivo studies of pioglitazone in combination with P450 inhibitors and substrates have been performed (see Drug Interactions). Urinary 6ß-hydroxycortisol/cortisol ratios measured in patients treated with ACTOS showed that pioglitazone is not a strong CYP3A4 enzyme inducer.

Excretion and Elimination: Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible, and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces.

The mean serum half-life of pioglitazone and total pioglitazone ranges from 3 to 7 hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be 5 to 7 L/hr.

Special Populations

Renal Insufficiency: The serum elimination half-life of pioglitazone, M-III, and M-IV remains unchanged in patients with moderate (creatinine clearance 30 to 60 mL/min) to severe (creatinine clearance < 30 mL/min) renal impairment when compared to normal subjects. No dose adjustment in patients with renal dysfunction is recommended (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: Compared with normal controls, subjects with impaired hepatic function (Child-Pugh Grade B/C) have an approximate 45% reduction in pioglitazone and total pioglitazone mean peak concentrations but no change in the mean AUC values.

ACTOS therapy should not be initiated if the patient exhibits clinical evidence of active liver disease or serum transaminase levels (ALT) exceed 2.5 times the upper limit of normal (see PRECAUTIONS, Hepatic Effects).

Elderly: In healthy elderly subjects, peak serum concentrations of pioglitazone and total pioglitazone are not significantly different, but AUC values are slightly higher and the terminal half-life values slightly longer than for younger subjects. These changes were not of a magnitude that would be considered clinically relevant.

Pediatrics: Pharmacokinetic data in the pediatric population are not available.

Gender: The mean C_{max} and AUC values were increased 20% to 60% in females. As monotherapy and in combination with sulfonylurea, metformin, or insulin, ACTOS im-proved glycemic control in both males and females. In controlled clinical trials, hemo-globin A_{1c} (HbA_{1c}) decreases from baseline were generally greater for females than for males (average mean difference in HbA_{1c} 0.5%). Since therapy should be individual-ized for each patient to achieve glycemic control, no dose adjustment is recommended based on gender alone.

Ethnicity: Pharmacokinetic data among various ethnic groups are not available.

Drug-Drug Interactions

The following drugs were studied in healthy volunteers with a co-administration of ACTOS 45 mg once daily. Listed below are the results:

Oral Contraceptives: Co-administration of ACTOS (45 mg once daily) and an oral contraceptive (1 mg norethindrone plus 0.035 mg ethinyl estradiol once daily) for 21 days, resulted in 11% and 11-14% decrease in ethinyl estradiol AUC (0-24h) and C_{max} respectively. There were no significant changes in norethindrone AUC (0-24h) and C_{max}. In view of the high variability of ethinyl estradiol pharmacokinetics, the clinical significance of this finding is unknown.

Fexofenadine HCl: Co-administration of ACTOS for 7 days with 60 mg fexofenadine administered orally twice daily resulted in no significant effect on pioglitazone pharmacokinetics. ACTOS had no significant effect on fexofenadine pharmacokinetics.

Glipizide: Co-administration of ACTOS and 5 mg glipizide administered orally once daily for 7 days did not alter the steady-state pharmacokinetics of glipizide.

Digoxin: Co-administration of ACTOS with 0.25 mg digoxin administered orally once daily for 7 days did not alter the steady-state pharmacokinetics of digoxin.

Warfarin: Co-administration of ACTOS for 7 days with warfarin did not alter the steady-state pharmacokinetics of warfarin. ACTOS has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

Metformin: Co-administration of a single dose of metformin (1000 mg) and ACTOS after 7 days of ACTOS did not alter the pharmacokinetics of the single dose of metformin.

Midazolam: Administration of ACTOS for 15 days followed by a single 7.5 mg dose of midazolam syrup resulted in a 26% reduction in midazolam C_{max} and AUC.

Ranitidine HCl: Co-administration of ACTOS for 7 days with ranitidine administered orally twice daily for either 4 or 7 days resulted in no significant effect on pioglitazone pharmacokinetics. ACTOS showed no significant effect on ranitidine pharmacokinetics.

Nifedipine ER: Co-administration of ACTOS for 7 days with 30 mg nifedipine ER administered orally once daily for 4 days to male and female volunteers resulted in least square mean (90% CI) values for unchanged nifedipine of 0.83 (0.73 - 0.95) for C_{max} and 0.88 (0.80 - 0.96) for AUC. In view of the high variability of nifedipine pharmaco-kinetics, the clinical significance of this finding is unknown.

Ketoconazole: Co-administration of ACTOS for 7 days with ketoconazole 200 mg administered twice daily resulted in least square mean (90% CI) values for unchanged pioglitazone of 1.14 (1.06 - 1.23) for C_{max}, 1.34 (1.26 - 1.41) for AUC and 1.87 (1.71 - 2.04) for C_{min}.

Atorvastatin Calcium: Co-administration of ACTOS for 7 days with atorvastatin calcium (LIPITOR®) 80 mg once daily resulted in least square mean (90% CI) values for un-changed pioglitazone of 0.69 (0.57 - 0.85) for C_{max}, 0.76 (0.65 - 0.88) for AUC and 0.96 (0.87 - 1.05) for C_{min}. For unchanged atorvastatin the least square mean (90% CI) values were 0.77 (0.66 - 0.90) for C_{max}, 0.86 (0.78 - 0.94) for AUC and 0.92 (0.82 - 1.02) for C_{min}.

Theophylline: Co-administration of ACTOS for 7 days with theophylline 400 mg admin-istered twice daily resulted in no change in the pharmacokinetics of either drug.
Cytochrome P450: See **PRECAUTIONS**

Pharmacodynamics and Clinical Effects
Clinical studies demonstrate that ACTOS improves insulin sensitivity in insulin-resistant patients. ACTOS enhances cellular responsiveness to insulin, increases insulin-dependent glucose disposal, improves hepatic sensitivity to insulin, and improves dysfunctional glucose homeostasis. In patients with type 2 diabetes, the decreased insulin resistance produced by ACTOS results in lower plasma glucose concentrations, lower plasma insulin levels, and lower HbA_{1c} values. Based on results from an open-label extension study, the glucose lowering effects of ACTOS appear to persist for at least one year. In controlled clinical trials, ACTOS in combination with sulfonylurea, metformin, or insulin had an additive effect on glycemic control.

Patients with lipid abnormalities were included in clinical trials with ACTOS. Overall, patients treated with ACTOS had mean decreases in triglycerides, mean increases in HDL cholesterol, and no consistent mean changes in LDL and total cholesterol.

In a 26-week, placebo-controlled, dose-ranging study, mean triglyceride levels de-creased in the 15 mg, 30 mg, and 45 mg ACTOS dose groups compared to a mean in-crease in the placebo group. Mean HDL levels increased to a greater extent in patients treated with ACTOS than in the placebo-treated patients. There were no consistent differences for LDL and total cholesterol in patients treated with ACTOS compared to placebo (Table 1).

Table 1 ***Lipids in a 26-Week Placebo-Controlled Monotherapy Dose-Ranging Study***

	Placebo	***ACTOS 15 mg Once Daily***	***ACTOS 30 mg Once Daily***	***ACTOS 45 mg Once Daily***
Triglycerides (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	262.8	283.8	261.1	259.7
Percent change from baseline (mean)	4.8%	-9.0%	-9.6%	-9.3%
HDL Cholesterol (mg/dL)	N=79	N=79	N=83	N=77
Baseline (mean)	41.7	40.4	40.8	40.7
Percent change from baseline (mean)	8.1%	14.1%	12.2%	19.1%
LDL Cholesterol (mg/dL)	N=65	N=63	N=74	N=62
Baseline (mean)	138.8	131.9	135.6	126.8
Percent change from baseline (mean)	4.8%	7.2%	5.2%	6.0%
Total Cholesterol (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	224.6	220.0	222.7	213.7
Percent change from baseline (mean)	4.4%	4.6%	3.3%	6.4%

In the two other monotherapy studies (24 weeks and 16 weeks) and in combination therapy studies with sulfonylurea (24 weeks and 16 weeks) and metformin (24 weeks and 16 weeks), the results were generally consistent with the data above. In placebo-controlled trials, the placebo-corrected mean changes from baseline decreased 5% to 26% for triglycerides and increased 6% to 13% for HDL in patients treated with ACTOS. A similar pattern of results was seen in 24-week combination therapy studies of ACTOS with sulfonylurea or metformin.

In a combination therapy study with insulin (16 weeks), the placebo-corrected mean percent change from baseline in triglyceride values for patients treated with ACTOS was also decreased. A placebo-corrected mean change from baseline in LDL cholesterol of 7% was observed for the 15 mg dose group. Similar results to those noted above for HDL and total cholesterol were observed. A similar pattern of results was seen in a 24-week combination therapy study with ACTOS with insulin.

Clinical Studies
Monotherapy
In the U.S., three randomized, double-blind, placebo-controlled trials with durations from 16 to 26 weeks were conducted to evaluate the use of ACTOS as monotherapy in patients with type 2 diabetes. These studies examined ACTOS at doses up to 45 mg or placebo once daily in 865 patients.

In a 26-week dose-ranging study, 408 patients with type 2 diabetes were random-ized to receive 7.5 mg, 15 mg, 30 mg, or 45 mg of ACTOS, or placebo once daily. Therapy with any previous antidiabetic agent was discontinued 8 weeks prior to the double-blind period. Treatment with 15 mg, 30 mg, and 45 mg of ACTOS produced statistically significant improvements in HbA_{1c} and fasting plasma glucose (FPG) at endpoint compared to placebo (see Figure 1, Table 2).

Figure 1 shows the time course for changes in FPG and HbA_{1c} for the entire study population in this 26-week study.

FIGURE 1 MEAN CHANGE FROM BASELINE FOR FPG AND HBA_{1c} IN A 26-WEEK PLACEBO-CONTROLLED DOSE-RANGING STUDY

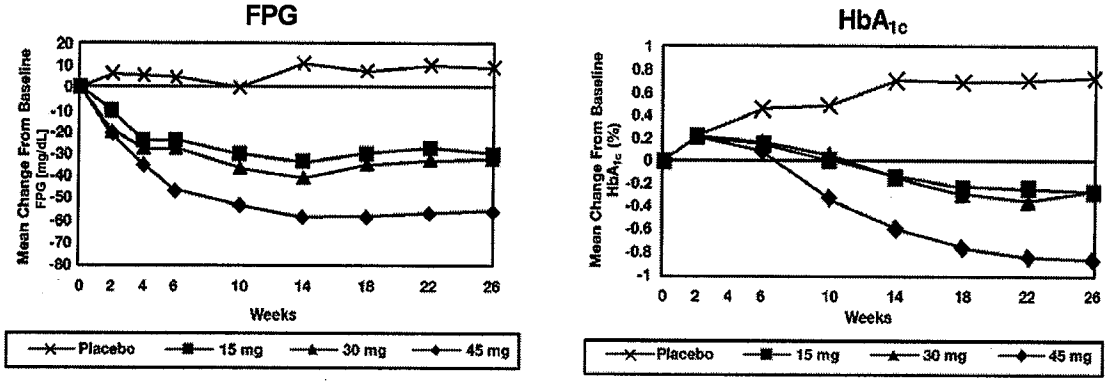


Table 2 shows HbA_{1c} and FPG values for the entire study population.

Table 2 Glycemic Parameters in a 26-Week Placebo-Controlled Dose-Ranging Study

	Placebo	ACTOS 15 mg Once Daily	ACTOS 30 mg Once Daily	ACTOS 45 mg Once Daily
Total Population				
HbA_{1c} (%)	N=79	N=79	N=85	N=76
Baseline (mean)	10.4	10.2	10.2	10.3
Change from baseline (adjusted mean[+])	0.7	-0.3	-0.3	-0.9
Difference from placebo (adjusted mean[+])		-1.0*	-1.0*	-1.6*
FPG (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	268	267	269	276
Change from baseline (adjusted mean[+])	9	-30	-32	-56
Difference from placebo (adjusted mean[+])		-39*	-41*	-65*

[+] Adjusted for baseline, pooled center, and pooled center by treatment interaction

* $p \leq 0.050$ vs. placebo

The study population included patients not previously treated with antidiabetic medication (naïve; 31%) and patients who were receiving antidiabetic medication at the time of study enrollment (previously treated; 69%). The data for the naïve and previously treated patient subsets are shown in Table 3. All patients entered an 8 week washout/run-in period prior to double-blind treatment. This run-in period was associated with little change in HbA_{1c} and FPG values from screening to baseline for the naïve patients; however, for the previously-treated group, washout from previous antidiabetic medication resulted in deterioration of glycemic control and increases in HbA_{1c} and FPG. Although most patients in the previously-treated group had a decrease from baseline in HbA_{1c} and FPG with ACTOS, in many cases the values did not return to screening levels by the end of the study. The study design did not permit the evaluation of patients who switched directly to ACTOS from another antidiabetic agent.

Table 3 **Glycemic Parameters in a 26-Week Placebo-Controlled Dose-Ranging Study**

	Placebo	ACTOS 15 mg Once Daily	ACTOS 30 mg Once Daily	ACTOS 45 mg Once Daily
Naïve to Therapy				
HbA_{1c} (%)	N=25	N=26	N=26	N=21
Screening (mean)	9.3	10.0	9.5	9.8
Baseline (mean)	9.0	9.9	9.3	10.0
Change from baseline (adjusted mean*)	0.6	-0.8	-0.6	-1.9
Difference from placebo (adjusted mean*)		-1.4	-1.3	-2.6
FPG (mg/dL)	N=25	N=26	N=26	N=21
Screening (mean)	223	245	239	239
Baseline (mean)	229	251	225	235
Change from baseline (adjusted mean*)	16	-37	-41	-64
Difference from placebo (adjusted mean*)		-52	-56	-80
Previously Treated				
HbA_{1c} (%)	N=54	N=53	N=59	N=55
Screening (mean)	9.3	9.0	9.1	9.0
Baseline (mean)	10.9	10.4	10.4	10.6
Change from baseline (adjusted mean*)	0.8	-0.1	-0.0	-0.6
Difference from placebo (adjusted mean*)		-1.0	-0.9	-1.4
FPG (mg/dL)	N=54	N=53	N=58	N=56
Screening (mean)	222	209	230	215
Baseline (mean)	285	275	286	292
Change from baseline (adjusted mean*)	4	-32	-27	-55
Difference from placebo (adjusted mean*)		-36	-31	-59

* Adjusted for baseline and pooled center

In a 24-week placebo-controlled study, 260 patients with type 2 diabetes were randomized to one of two forced-titration ACTOS treatment groups or a mock titration placebo group. Therapy with any previous antidiabetic agent was discontinued 6 weeks prior to the double-blind period. In one ACTOS treatment group, patients received an initial dose of 7.5 mg once daily. After four weeks, the dose was increased to 15 mg once daily and after another four weeks, the dose was increased to 30 mg once daily for the remainder of the study (16 weeks). In the second ACTOS treatment group, patients received an initial dose of 15 mg once daily and were titrated to 30 mg once daily and 45 mg once daily in a similar manner. Treatment with ACTOS, as described, produced statistically significant improvements in HbA_{1c} and FPG at endpoint compared to placebo (see Table 4).

Table 4 **Glycemic Parameters in a 24-Week Placebo-Controlled Forced-Titration Study**

	Placebo	ACTOS 30 mg[+] Once Daily	ACTOS 45 mg[+] Once Daily
Total Population			
HbA_{1c} (%)	N=83	N=85	N=85
Baseline (mean)	10.8	10.3	10.8
Change from baseline (adjusted mean[++])	0.9	-0.6	-0.6
Difference from placebo (adjusted mean[++])		-1.5*	-1.5*
FPG (mg/dL)	N=78	N=82	N=85
Baseline (mean)	279	268	281
Change from baseline (adjusted mean[++])	18	-44	-50
Difference from placebo (adjusted mean[++])		-62*	-68*

[+] Final dose in forced titration

[++] Adjusted for baseline, pooled center, and pooled center by treatment interaction

* $p \leq 0.050$ vs. placebo

For patients who had not been previously treated with antidiabetic medication (24%), mean values at screening were 10.1% for HbA_{1c} and 238 mg/dL for FPG. At baseline, mean HbA_{1c} was 10.2% and mean FPG was 243 mg/dL. Compared with placebo, treat-ment with ACTOS titrated to a final dose of 30 mg and 45 mg resulted in reductions from baseline in mean HbA_{1c} of 2.3% and 2.6% and mean FPG of 63 mg/dL and 95 mg/dL, respectively. For patients who had been previously treated with antidiabetic medication (76%), this medication was discontinued at screening. Mean values at screening were 9.4% for HbA_{1c} and 216 mg/dL for FPG. At baseline, mean HbA_{1c} was 10.7% and mean FPG was 290 mg/dL. Compared with placebo, treatment with ACTOS titrated to a final dose of 30 mg and 45 mg resulted in reductions from baseline in mean HbA_{1c} of 1.3% and 1.4% and mean FPG of 55 mg/dL and 60 mg/dL, respectively. For many previously-treated patients, HbA_{1c} and FPG had not returned to screening levels by the end of the study.

In a 16-week study, 197 patients with type 2 diabetes were randomized to treatment with 30 mg of ACTOS or placebo once daily. Therapy with any previous antidiabetic agent was discontinued 6 weeks prior to the double-blind period. Treatment with 30 mg of ACTOS produced statistically significant improvements in HbA_{1c} and FPG at endpoint compared to placebo (see Table 5).

Table 5 **Glycemic Parameters in a 16-Week Placebo-Controlled Study**

	Placebo	ACTOS 30 mg Once Daily
Total Population		
HbA_{1c} (%)	N=93	N=100
Baseline (mean)	10.3	10.5
Change from baseline (adjusted mean[+])	0.8	-0.6
Difference from placebo (adjusted mean[+])		-1.4*
FPG (mg/dL)	N=91	N=99
Baseline (mean)	270	273
Change from baseline (adjusted mean[+])	8	-50
Difference from placebo (adjusted mean[+])		-58*

[+] Adjusted for baseline, pooled center, and pooled center by treatment interaction

* $p \leq 0.050$ vs. placebo

For patients who had not been previously treated with antidiabetic medication (40%), mean values at screening were 10.3% for HbA_{1c} and 240 mg/dL for FPG. At baseline, mean HbA_{1c} was 10.4% and mean FPG was 254 mg/dL. Compared with placebo, treatment with ACTOS 30 mg resulted in reductions from baseline in mean HbA_{1c} of 1.0% and mean FPG of 62 mg/dL. For patients who had been previously treated with antidiabetic medication (60%), this medication was discontinued at screening. Mean values at screening were 9.4% for HbA_{1c} and 216 mg/dL for FPG. At baseline, mean HbA_{1c} was 10.6% and mean FPG was 287 mg/dL. Compared with placebo, treatment with ACTOS 30 mg resulted in reductions from baseline in mean HbA_{1c} of 1.3% and mean FPG of 46 mg/dL. For many previously-treated patients, HbA_{1c} and FPG had not returned to screening levels by the end of the study.

Combination Therapy
Three 16-week, randomized, double-blind, placebo-controlled clinical studies and three 24-week randomized, double-blind, dose-controlled clinical studies were conducted to evaluate the effects of ACTOS on glycemic control in patients with type 2 diabetes who were inadequately controlled ($HbA_{1c} \geq 8\%$) despite current therapy with a sulfonylurea, metformin, or insulin. Previous diabetes treatment may have been monotherapy or combination therapy.

ACTOS Plus Sulfonylurea Studies
Two clinical studies were conducted with ACTOS in combination with a sulfonylurea. Both studies included patients with type 2 diabetes on a sulfonylurea, either alone or in combination with another antidiabetic agent. All other antidiabetic agents were withdrawn prior to starting study treatment. In the first study, 560 patients were randomized to receive 15 mg or 30 mg of ACTOS or placebo once daily for 16 weeks in addition to their current sulfonylurea regimen. When compared to placebo at Week 16, the addition of ACTOS to the sulfonylurea significantly reduced the mean HbA_{1c} by 0.9% and 1.3% and mean FPG by 39 mg/dL and 58 mg/dL for the 15 mg and 30 mg doses, respectively.

In the second study, 702 patients were randomized to receive 30 mg or 45 mg of ACTOS once daily for 24 weeks in addition to their current sulfonylurea regimen. The mean reductions from baseline at Week 24 in HbA_{1c} were 1.55% and 1.67% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 51.5 mg/dL and 56.1 mg/dL.

The therapeutic effect of ACTOS in combination with sulfonylurea was observed in patients regardless of whether the patients were receiving low, medium, or high doses of sulfonylurea.

ACTOS Plus Metformin Studies
Two clinical studies were conducted with ACTOS in combination with metformin. Both studies included patients with type 2 diabetes on metformin, either alone or in combination with another diabetic agent. All other antidiabetic agents were withdrawn prior to starting study treatment. In the first study, 328 patients were randomized to receive either 30 mg of ACTOS or placebo once daily for 16 weeks in addition to their current metformin regimen. When compared to placebo at Week 16, the addition of ACTOS to metformin significantly reduced the mean HbA_{1c} by 0.8% and decreased the mean FPG by 38 mg/dL.

In the second study, 827 patients were randomized to receive either 30 mg or 45 mg of ACTOS once daily for 24 weeks in addition to their current metformin regimen.

The mean reductions from baseline at Week 24 in HbA_{1c} were 0.80% and 1.01% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 38.2 mg/dL and 50.7 mg/dL.

The therapeutic effect of ACTOS in combination with metformin was observed in patients regardless of whether the patients were receiving lower or higher doses of metformin.

ACTOS Plus Insulin Studies

Two clinical studies were conducted with ACTOS in combination with insulin. Both studies included patients with type 2 diabetes on insulin, either alone or in combination with another antidiabetic agent. All other antidiabetic agents were withdrawn prior to starting study treatment. In the first study, 566 patients receiving a median of 60.5 units per day of insulin were randomized to receive either 15 mg or 30 mg of ACTOS or placebo once daily for 16 weeks in addition to their insulin regimen. When compared to placebo at Week 16, the addition of ACTOS to insulin significantly reduced both HbA_{1c} by 0.7% and 1.0% and FPG by 35 mg/dL and 49 mg/dL for the 15 mg and 30 mg dose, respectively.

In the second study, 690 patients receiving a median of 60.0 units per day of insulin received either 30 mg or 45 mg of ACTOS once daily for 24 weeks in addition to their current insulin regimen. The mean reductions from baseline at Week 24 in HbA_{1c} were 1.17% and 1.46% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 31.9 mg/dL and 45.8 mg/dL. Improved glycemic control was accompanied by mean decreases from baseline in insulin dose requirements of 6.0% and 9.4% per day for the 30 mg and 45 mg dose, respectively.

The therapeutic effect of ACTOS in combination with insulin was observed in patients regardless of whether the patients were receiving lower or higher doses of insulin.

INDICATIONS AND USAGE

ACTOS is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes (non-insulin-dependent diabetes mellitus, NIDDM). ACTOS is indicated for monotherapy. ACTOS is also indicated for use in combination with a sulfonylurea, metformin, or insulin when diet and exercise plus the single agent does not result in adequate glycemic control.

Management of type 2 diabetes should also include nutritional counseling, weight reduction as needed, and exercise. These efforts are important not only in the primary treatment of type 2 diabetes, but also to maintain the efficacy of drug therapy.

CONTRAINDICATIONS

ACTOS is contraindicated in patients with known hypersensitivity to this product or any of its components.

WARNINGS

Cardiac Failure and Other Cardiac Effects

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. Patients should be observed for signs and symptoms of heart failure (see Information for Patients). ACTOS should be discontinued if any deterioration in cardiac status occurs. Patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during pre-approval clinical trials; ACTOS is not recommended in these patients (see PRECAUTIONS, Cardiovascular).

In one 16-week U.S. double-blind, placebo-controlled clinical trial involving 566 patients with type 2 diabetes, ACTOS at doses of 15 mg and 30 mg in combination with insulin was compared to insulin therapy alone. This trial included patients with long-standing diabetes and a high prevalence of pre-existing medical conditions as follows: arterial hypertension (57.2%), peripheral neuropathy (22.6%), coronary heart disease (19.6%), retinopathy (13.1%), myocardial infarction (8.8%), vascular disease (6.4%), angina pectoris (4.4%), stroke and/or transient ischemic attack (4.1%), and congestive heart failure (2.3%).

In this study two of the 191 patients receiving 15 mg ACTOS plus insulin (1.1%) and two of the 188 patients receiving 30 mg ACTOS plus insulin (1.1%) developed congestive heart failure compared with none of the 187 patients on insulin therapy alone. All four of these patients had previous histories of cardiovascular conditions including coronary artery disease, previous CABG procedures, and myocardial infarction. In a 24-week dose-controlled study in which ACTOS was coadministered with insulin, 0.3% of patients (1/345) on 30 mg and 0.9% (3/345) of patients on 45 mg reported CHF as a serious adverse event.

Analysis of data from these studies did not identify specific factors that predict increased risk of congestive heart failure on combination therapy with insulin.

In type 2 diabetes and congestive heart failure (systolic dysfunction)

A 24-week post-marketing safety study was performed to compare ACTOS (n=262) to glyburide (n=256) in uncontrolled diabetic patients (mean HbA_{1C} 8.8% at baseline) with NYHA Class II and III heart failure and ejection fraction less than 40% (mean EF 30% at baseline). Over the course of the study, overnight hospitalization for congestive heart failure was reported in 9.9% of patients on ACTOS compared to 4.7% of patients on glyburide with a treatment difference observed from 6 weeks. This adverse event associated with ACTOS was more marked in patients using insulin at baseline and in patients over 64 years of age. No difference in cardiovascular mortality between the treatment groups was observed.

ACTOS should be initiated at the lowest approved dose if it is prescribed for patients with type 2 diabetes and systolic heart failure (NYHA Class II). If subsequent dose escalation is necessary, the dose should be increased gradually only after several months of treatment with careful monitoring for weight gain, edema, or signs and symptoms of CHF exacerbation.

PRECAUTIONS

General

ACTOS exerts its antihyperglycemic effect only in the presence of insulin. Therefore, ACTOS should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Hypoglycemia: Patients receiving ACTOS in combination with insulin or oral hypogly-cemic agents may be at risk for hypoglycemia, and a reduction in the dose of the con-comitant agent may be necessary.

Cardiovascular: In U.S. placebo-controlled clinical trials that excluded patients with New York Heart Association (NYHA) Class III and IV cardiac status, the incidence of serious cardiac adverse events related to volume expansion was not increased in patients treated with ACTOS as monotherapy or in combination with sulfonylureas or metformin vs. placebo-treated patients.

In insulin combination studies, a small number of patients with a history of previously existing cardiac disease developed congestive heart failure when treated with ACTOS in combination with insulin (see WARNINGS). Patients with NYHA Class III and IV cardiac status were not studied in these ACTOS clinical trials. ACTOS is not indicated in patients with NYHA Class III or IV cardiac status.

In postmarketing experience with ACTOS, cases of congestive heart failure have been reported in patients both with and without previously known heart disease.

Edema: ACTOS should be used with caution in patients with edema. In all U.S. clinical trials, edema was reported more frequently in patients treated with ACTOS than in placebo-treated patients and appears to be dose related (see ADVERSE REACTIONS). In postmarketing experience, reports of initiation or worsening of edema have been received.

Weight Gain: Dose related weight gain was seen with ACTOS alone and in combination with other hypoglycemic agents (Table 6). The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Table 6 **Weight Changes (kg) from Baseline during Double-Blind Clinical Trials with ACTOS**

		Control Group (Placebo)	ACTOS 15 mg	ACTOS 30 mg	ACTOS 45 mg
		Median ($25^{th}/75^{th}$ percentile)	Median ($25^{th}/75^{th}$ percentile)	Median ($25^{th}/75^{th}$ percentile)	Median ($25^{th}/75^{th}$ percentile)
Monotherapy		-1.4 (-2.7/0.0) n=256	0.9(-0.5/3.4) n = 79	1.0(-0.9/3.4) n=188	2.6 (0.2/5.4) n = 79
Combination Therapy	Sulfonylurea	-0.5 (-1.8/0.7) n=187	2.0 (0.2/3.2) n=183	3.1 (1.1/5.4) n=528	4.1 (1.8/7.3) N=333
	Metformin	-1.4 (-3.2/0.3) n=160	N/A	0.9(-0.3/3.2) n=567	1.8(-0.9/5.0) N=407
	Insulin	0.2 (-1.4/1.4) n=182	2.3 (0.5/4.3) n=190	3.3 (0.9/6.3) n=522	4.1 (1.4/6.8) N=338

Note: Trial durations of 16 to 26 weeks

Ovulation: Therapy with ACTOS, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking ACTOS. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been investigated in clinical studies so the frequency of this occurrence is not known.

Hematologic: ACTOS may cause decreases in hemoglobin and hematocrit. Across all clinical studies, mean hemoglobin values declined by 2% to 4% in patients treated with ACTOS. These changes primarily occurred within the first 4 to 12 weeks of therapy and remained relatively constant thereafter. These changes may be related to increased plasma volume and have rarely been associated with any significant hematologic clinical effects (see ADVERSE REACTIONS, Laboratory Abnormalities).

Hepatic Effects: In pre-approval clinical studies worldwide, over 4500 subjects were treated with ACTOS. In U.S. clinical studies, over 4700 patients with type 2 diabetes received ACTOS. There was no evidence of drug-induced hepatotoxicity or elevation of ALT levels in the clinical studies.

During pre-approval placebo-controlled clinical trials in the U.S., a total of 4 of 1526 (0.26%) patients treated with ACTOS and 2 of 793 (0.25%) placebo-treated patients had ALT values ≥ 3 times the upper limit of normal. The ALT elevations in patients treated with ACTOS were reversible and were not clearly related to therapy with ACTOS.

In postmarketing experience with ACTOS, reports of hepatitis and of hepatic enzyme elevations to 3 or more times the upper limit of normal have been received. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established.

Pioglitazone is structurally related to troglitazone, a thiazolidinedione no longer marketed in the United States, which was associated with idiosyncratic hepatotoxicity and cases of liver failure, liver transplants and death during postmarketing clinical use. In pre-approval controlled clinical trials in patients with type 2 diabetes, troglitazone was more frequently associated with clinically significant elevations of hepatic enzymes (ALT > 3 times the upper limit of normal) compared to placebo, and cases of reversible jaundice were reported.

Pending the availability of the results of additional large, long-term controlled clinical trials and additional postmarketing safety data, it is recommended that patients treated with ACTOS undergo periodic monitoring of liver enzymes.

Serum ALT (alanine aminotransferase) levels should be evaluated prior to the initiation of therapy with ACTOS in all patients and periodically thereafter per the clinical judgment of the health care professional. Liver function tests should also be obtained for patients if symptoms suggestive of hepatic dysfunction occur, e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine. The decision whether to continue the patient on therapy with ACTOS should be guided by clinical judgment pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

Therapy with ACTOS should not be initiated if the patient exhibits clinical evidence of active liver disease or the ALT levels exceed 2.5 times the upper limit of normal. Patients with mildly elevated liver enzymes (ALT levels at 1 to 2.5 times the upper limit of normal) at baseline or any time during therapy with ACTOS should be evaluated to determine the cause of the liver enzyme elevation. Initiation or continuation of therapy with ACTOS in patients with mildly elevated liver enzymes should proceed with caution and include appropriate clinical follow-up which may include more frequent liver enzyme monitoring. If serum transaminase levels are increased (ALT > 2.5 times the upper limit of normal), liver function tests should be evaluated more frequently until the levels return to normal or pretreatment values. If ALT levels exceed 3 times the upper limit of normal, the test should be repeated as soon as possible. If ALT levels remain > 3 times the upper limit of normal or if the patient is jaundiced, ACTOS therapy should be discontinued.

There are no data available to evaluate the safety of ACTOS in patients who experienced liver abnormalities, hepatic dysfunction, or jaundice while on troglitazone. ACTOS should not be used in patients who experienced jaundice while taking troglitazone.

Laboratory Tests
FPG and HbA_{1c} measurements should be performed periodically to monitor glycemic control and the therapeutic response to ACTOS.

Liver enzyme monitoring is recommended prior to initiation of therapy with ACTOS in all patients and periodically thereafter per the clinical judgment of the health care professional (see PRECAUTIONS, General, Hepatic Effects and ADVERSE REACTIONS, Serum Transaminase Levels).

Information for Patients
It is important to instruct patients to adhere to dietary instructions and to have blood glucose and glycosylated hemoglobin tested regularly. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be reminded to seek medical advice promptly.

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.

Patients should be told that blood tests for liver function will be performed prior to the start of therapy and periodically thereafter per the clinical judgment of the health care professional. Patients should be told to seek immediate medical advice for unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine.

Patients should be told to take ACTOS once daily. ACTOS can be taken with or without meals. If a dose is missed on one day, the dose should not be doubled the following day.

When using combination therapy with insulin or oral hypoglycemic agents, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.

Therapy with ACTOS, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking ACTOS. Thus, adequate contraception in premeno-pausal women should be recommended. This possible effect has not been investigated in clinical studies so the frequency of this occurrence is not known.

Drug Interactions
In vivo drug-drug interaction studies have suggested that pioglitazone may be a weak inducer of CYP 450 isoform 3A4 substrate (see CLINICAL PHARMACOLOGY, Metabolism and Drug-Drug Interactions).

Carcinogenesis, Mutagenesis, Impairment of Fertility
A two-year carcinogenicity study was conducted in male and female rats at oral doses up to 63 mg/kg (approximately 14 times the maximum recommended human oral dose of 45 mg based on mg/m^2). Drug-induced tumors were not observed in any organ ex-cept for the urinary bladder. Benign and/or malignant transitional cell neoplasms were observed in male rats at 4 mg/kg/day and above (approximately equal to the maximum recommended human oral dose based on mg/m^2). A two-year carcinogenicity study was conducted in male and female mice at oral doses up to 100 mg/kg/day (approximately 11 times the maximum recommended human oral dose based on mg/m^2). No drug-induced tumors were observed in any organ. Urinary tract tumors have been reported in rodents taking experimental drugs with dual PPAR α/γ activity; however ACTOS is a selective agonist for PPAR γ.

During prospective evaluation of urinary cytology involving more than 1800 patients receiving ACTOS in clinical trials up to one year in duration, no new cases of bladder tumors

were identified. Occasionally, abnormal urinary cytology results indicating possible malignancy were observed in both patients treated with ACTOS (0.72%) and patients treated with placebo (0.88%).

Pioglitazone HCl was not mutagenic in a battery of genetic toxicology studies, including the Ames bacterial assay, a mammalian cell forward gene mutation assay (CHO/HPRT and AS52/XPRT), an in vitro cytogenetics assay using CHL cells, an unscheduled DNA synthesis assay, and an in vivo micronucleus assay.

No adverse effects upon fertility were observed in male and female rats at oral doses up to 40 mg/kg pioglitazone HCl daily prior to and throughout mating and gestation (approximately 9 times the maximum recommended human oral dose based on mg/m^2).

Animal Toxicology

Heart enlargement has been observed in mice (100 mg/kg), rats (4 mg/kg and above) and dogs (3 mg/kg) treated orally with pioglitazone HCl (approximately 11, 1, and 2 times the maximum recommended human oral dose for mice, rats, and dogs, respec-tively, based on mg/m^2). In a one-year rat study, drug-related early death due to apparent heart dysfunction occurred at an oral dose of 160 mg/kg/day (approximately 35 times the maximum recommended human oral dose based on mg/m^2). Heart enlargement was seen in a 13-week study in monkeys at oral doses of 8.9 mg/kg and above (approximately 4 times the maximum recommended human oral dose based on mg/m^2), but not in a 52-week study at oral doses up to 32 mg/kg (approximately 13 times the maximum recommended human oral dose based on mg/m^2).

Pregnancy

Pregnancy Category C. Pioglitazone was not teratogenic in rats at oral doses up to 80 mg/kg or in rabbits given up to 160 mg/kg during organogenesis (approximately 17 and 40 times the maximum recommended human oral dose based on mg/m^2, respectively). Delayed parturition and embryotoxicity (as evidenced by increased postimplantation losses, delayed development and reduced fetal weights) were observed in rats at oral doses of 40 mg/kg/day and above (approximately 10 times the maximum recommended human oral dose based on mg/m^2). No functional or behavioral toxicity was observed in offspring of rats. In rabbits, embryotoxicity was observed at an oral dose of 160 mg/kg (approximately 40 times the maximum recommended human oral dose based on mg/m^2). Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats at oral doses of 10 mg/kg and above during late gestation and lactation periods (approximately 2 times the maximum recommended human oral dose based on mg/m^2).

There are no adequate and well-controlled studies in pregnant women. ACTOS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies, as well as increased neonatal morbidity and mortality, most experts recommend that insu-lin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers

Pioglitazone is secreted in the milk of lactating rats. It is not known whether ACTOS is secreted in human milk. Because many drugs are excreted in human milk, ACTOS should not be administered to a breastfeeding woman.

Pediatric Use
Safety and effectiveness of ACTOS in pediatric patients have not been established.

Elderly Use
Approximately 500 patients in placebo-controlled clinical trials of ACTOS were 65 and over. No significant differences in effectiveness and safety were observed between these patients and younger patients.

ADVERSE REACTIONS
In worldwide clinical trials, over 5900 patients with type 2 diabetes have been treated with ACTOS. In U.S. clinical trials, over 4700 patients have received ACTOS, over 3300 patients have been treated for 6 months or longer, and over 450 patients for one year or longer.

The overall incidence and types of adverse events reported in placebo-controlled clinical trials of ACTOS monotherapy at doses of 7.5 mg, 15 mg, 30 mg, or 45 mg once daily are shown in Table 7.

Table 7

Placebo-Controlled Clinical Studies of ACTOS Monotherapy: Adverse Events Reported at a Frequency ≥ 5% of Patients Treated with ACTOS

(% of Patients)		
	Placebo N=259	ACTOS N=606
Upper Respiratory Tract Infection	8.5	13.2
Headache	6.9	9.1
Sinusitis	4.6	6.3
Myalgia	2.7	5.4
Tooth Disorder	2.3	5.3
Diabetes Mellitus Aggravated	8.1	5.1
Pharyngitis	0.8	5.1

For most clinical adverse events the incidence was similar for groups treated with ACTOS monotherapy and those treated in combination with sulfonylureas, metformin, and insulin. There was an increase in the occurrence of edema in the patients treated with ACTOS and insulin compared to insulin alone.

In a 16-week, placebo-controlled ACTOS plus insulin trial (n=379), 10 patients treated with ACTOS plus insulin developed dyspnea and also, at some point during their therapy, developed either weight change or edema. Seven of these 10 patients received diuretics to treat these symptoms. This was not reported in the insulin plus placebo group.

The incidence of withdrawals from placebo-controlled clinical trials due to an adverse event other than hyperglycemia was similar for patients treated with placebo (2.8%) or ACTOS (3.3%).

In controlled combination therapy studies with either a sulfonylurea or insulin, mild to moderate hypoglycemia, which appears to be dose related, was reported (see PRECAUTIONS, General, Hypoglycemia and DOSAGE and ADMINISTRATION, Combination Therapy).

In U.S. double-blind studies, anemia was reported in ≤ 2% of patients treated with ACTOS plus sulfonylurea, metformin or insulin (see PRECAUTIONS, General, Hematologic).

In monotherapy studies, edema was reported for 4.8% of patients treated with ACTOS versus 1.2% of placebo-treated patients. In combination therapy studies, edema was reported for 7.2% of patients treated with ACTOS and sulfonylureas com-pared 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 in 15.3% of patients on combination therapy compared to 7.0% of patients on insulin alone. Most of these events were considered mild or moderate in intensity (see PRECAUTIONS, General, Edema).

In one 16-week clinical trial of insulin plus ACTOS combination therapy, more patients developed congestive heart failure on combination therapy (1.1%) compared to none on insulin alone (see WARNINGS, Cardiac Failure and Other Cardiac Effects).

Laboratory Abnormalities

Hematologic: ACTOS may cause decreases in hemoglobin and hematocrit. The fall in hemoglobin and hematocrit with ACTOS appears to be dose related. Across all clinical studies, mean hemoglobin values declined by 2% to 4% in patients treated with ACTOS. These changes generally occurred within the first 4 to 12 weeks of therapy and remained relatively stable thereafter. These changes may be related to increased plasma volume associated with ACTOS therapy and have rarely been associated with any significant hematologic clinical effects.

Serum Transaminase Levels: During all clinical studies in the U.S., 14 of 4780 (0.30%) patients treated with ACTOS had ALT values ≥ 3 times the upper limit of normal during treatment. All patients with follow-up values had reversible elevations in ALT. In the population of patients treated with ACTOS, mean values for bilirubin, AST, ALT, alkaline phosphatase, and GGT were decreased at the final visit compared with baseline. Fewer than 0.9% of patients treated with ACTOS were withdrawn from clinical trials in the U.S. due to abnormal liver function tests.

In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure (see PRECAUTIONS, Hepatic Effects).

CPK Levels: During required laboratory testing in clinical trials, sporadic, transient elevations in creatine phosphokinase levels (CPK) were observed. An isolated elevation to greater than 10 times the upper limit of normal was noted in 9 patients (values of 2150 to 11400 IU/L). Six of these patients continued to receive ACTOS, two patients had completed receiving study medication at the time of the elevated value and one patient discontinued study medication due to the elevation. These elevations resolved without any apparent clinical sequelae. The relationship of these events to ACTOS therapy is unknown.

OVERDOSAGE

During controlled clinical trials, one case of overdose with ACTOS was reported. A male patient took 120 mg per day for four days, then 180 mg per day for seven days. The patient denied any clinical symptoms during this period.

In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

DOSAGE AND ADMINISTRATION

ACTOS should be taken once daily without regard to meals.

The management of antidiabetic therapy should be individualized. Ideally, the response to therapy should be evaluated using HbA_{1c} which is a better indicator of long-term glycemic control than FPG alone. HbA_{1c} reflects glycemia over the past two to three months. In clinical use, it is recommended that patients be treated with ACTOS for a period of time adequate to evaluate change in HbA_{1c} (three months) unless glycemic control deteriorates.

Monotherapy

ACTOS monotherapy in patients not adequately controlled with diet and exercise may be initiated at 15 mg or 30 mg once daily. For patients who respond inadequately to the initial dose of ACTOS, the dose can be increased in increments up to 45 mg once daily. For patients not responding adequately to monotherapy, combination therapy should be considered.

Combination Therapy

Sulfonylureas: ACTOS in combination with a sulfonylurea may be initiated at 15 mg or 30 mg once daily. The current sulfonylurea dose can be continued upon initiation of ACTOS therapy. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased.

Metformin: ACTOS in combination with metformin may be initiated at 15 mg or 30 mg once daily. The current metformin dose can be continued upon initiation of ACTOS therapy. It is unlikely that the dose of metformin will require adjustment due to hypo-glycemia during combination therapy with ACTOS.

Insulin: ACTOS in combination with insulin may be initiated at 15 mg or 30 mg once daily. The current insulin dose can be continued upon initiation of ACTOS therapy. In patients receiving ACTOS and insulin, the insulin dose can be decreased by 10% to 25% if the patient reports hypoglycemia or if plasma glucose concentrations decrease to less than 100 mg/dL. Further adjustments should be individualized based on glucose-lowering response.

Maximum Recommended Dose

The dose of ACTOS should not exceed 45 mg once daily in monotherapy or in combination with sulfonylurea, metformin, or insulin.

Dose adjustment in patients with renal insufficiency is not recommended (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism).

Therapy with ACTOS should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT greater than 2.5 times the upper limit of normal) at start of therapy (see PRECAUTIONS, General, Hepatic Effects and CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency). Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with ACTOS and periodically thereafter (see PRECAUTIONS, General, Hepatic Effects).

There are no data on the use of ACTOS in patients under 18 years of age; therefore, use of ACTOS in pediatric patients is not recommended.

No data are available on the use of ACTOS in combination with another thiazolidinedione.

HOW SUPPLIED
ACTOS is available in 15 mg, 30 mg, and 45 mg tablets as follows:

15 mg Tablet: white to off-white, round, convex, non-scored tablet with "ACTOS" on one side, and "15" on the other, available in:
NDC 64764-151-04 Bottle of 30
NDC 64764-151-05 Bottle of 90
NDC 64764-151-06 Bottle of 500

30 mg Tablet: white to off-white, round, flat, non-scored tablet with "ACTOS" on one side, and "30" on the other, available in:
NDC 64764-301-14 Bottle of 30
NDC 64764-301-15 Bottle of 90
NDC 64764-301-16 Bottle of 500

45 mg Tablet: white to off-white, round, flat, non-scored tablet with "ACTOS" on one side, and "45" on the other, available in:
NDC 64764-451-24 Bottle of 30
NDC 64764-451-25 Bottle of 90
NDC 64764-451-26 Bottle of 500

STORAGE
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed, and protect from moisture and humidity.

Rx only

Manufactured by:
Takeda Chemical Industries, Ltd.
Osaka, Japan

Marketed by:
Takeda Pharmaceuticals America, Inc.
475 Half Day Road
Lincolnshire, IL 60069
and
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

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5012100-07 Revised: July 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-073/S023

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

APPLICATION #:	**21073/S023**	**APPLICATION TYPE:**	**NDA.....**
SPONSOR:	**Takeda**	**PROPRIETARY NAME:**	**Pioglitazone.....**
CATEGORY OF DRUG:	**Antidiabetic**	**USAN / Established Name:**	**ACTOS.....**
		ROUTE:	**ORAL.....**
MEDICAL REVIEWER:	**Robert I Misbin..**	**REVIEW DATE:**	**July 23, 2004.....**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
June 16, 2004	June 17, 2004		
July 20, 2004		Addition to label requested by FDA	

Phase 4 study of Actos vs Glyburide	**Overnight hospitalization for worsening congestive heart failure occurred in 9.9% of patients on Actos compared to 4.7% of patients on Glyburide.**

Recommendation: Wording added to the label about heart failure should be approved

The revised label will serve to restrict the use of ACTOS in patients with heart failure.

Signed: **Medical Reviewer: Robert I Misbin MD** **Date: July 23, 2004**

Medical Team Leader: _____ **Date: _____**

Table of Contents:

Executive Summary:

On October 10, 2003, Takeda informed DMEDP that their Data Monitoring Board had recommended to terminate the phase 4 trial of pioglitazone vs glyburide in patients with mild to moderate congestive heart failure (CHF). This recommendation was based on the finding of a greater incidence of hospitalization for CHF in the pioglitazone group vs the glyburide group. Takeda requested that specific labeling changes concerning this trial should be deferred until after Takeda and FDA had reviewed the trial results in detail.

Takeda submitted a study report on June 16, 2004:

Congestive Heart Failure:

There was a statistical difference (p=0.024) between PIO and Glyburide which is evident at about six weeks and continued thereafter. Progression of CHF was observed in 13.4% of patients on PIO compared to 8.2% on Glyburide. A breakdown of the components of the composite CHF endpoint is shown in the table below. Overnight hospitalization for worsening CHF accounts completely for the difference between PIO and GLY.

Incidence Rate for First Event by Treatment Group Based on CEC Determination

CHF Progression Event	Pioglitazone N=262 n (%)	Glyburide N=256 n (%)	P-Value (a)
Composite event	35 (13.4)	21 (8.2)	0.024
Death due to cardiovascular causes	5 (1.9)	6 (2.3)	
Overnight hospitalization for worsening CHF	26 (9.9)	12 (4.7)	
Emergency room visit for CHF	4 (1.5)	3 (1.2)	

Most of the difference between PIO and GLY occurred in-patients > 64 years old and in patients who had been taking insulin at baseline.

The two groups were well matched at baseline with respect to echocardiographic findings. At the final visit, there was a statistically significant increase in Cardiac Index in patients on PIO vs patients on GLY. There was no treatment difference in ejection fraction between the two groups. However, for patients with a first cardiac event, it appears that treatment with PIO vs GLY resulted in a small improvement in ejection fraction. These findings were interpreted by the Sponsor as evidence that PIO is not cardiotoxic.

Control of Hyperglycemia

The two groups were well matched at baseline with respect to glucose control. Mean FPG was 186 mg/dl in both groups. Mean HbA1c was 8.74% for PIO group and 8.95% for the GLY group. After a small initial rise in glucose levels reflecting washout from previous treatment, a fall in FPG is evident by four weeks in PIO patients. The fall continues to week 20 and is sustained to week 24. Beyond week 16, the greater reduction in FPG with PIO than with GLY is statistically significant. At week 24, the greater reduction in HbA1c with PIO than with GLY is statistically significant.

Takeda had submitted the following language to be added to the Warning Section as a change being effected (CBE).

In type 2 diabetes and congestive heart failure (systolic dysfunction)

TGRD proposed language based on data analyzed from an early terminated, Phase IV study, 01-00-TL-OPI-504; recommendation addresses

Consensus Statement developed jointly in 2003 by the American Heart Association and the American Diabetes Association,

DMEDP recommended that the label should include a description of the trial and its safety findings. In the current submission, Takeda proposes the following wording to precede the paragraph given above:

A 24-week post-marketing safety study was performed to compare ACTOS (n=262) to glyburide (n=256) in uncontrolled diabetic patients (mean HbA_{1C} 8.8% at baseline) with NYHA Class II and III heart failure and ejection fraction less than 40% (mean EF 30% at baseline). Over the course of the study, overnight hospitalization for congestive heart failure was reported in 9.9% of patients on ACTOS compared to 4.7% of patients on glyburide with a treatment difference observed from 6 weeks. This adverse event associated with ACTOS was more marked in patients using insulin at baseline and in patients over 64 years of age. No difference in cardiovascular mortality between the treatment groups was observed.

Recommendation: The revised label should be approved

Background:

Pioglitazone (PIO) was approved in July 1999. As a condition of approval, Takeda committed to perform a phase IV study to evaluate the potential of PIO to cause or exacerbate congestive heart failure (CHF). FDA requested this commitment because of the finding that PIO, like other thiazolidinediones (TZD), caused cardiomegaly in laboratory animals. Whether this was a chronic effect of long-standing fluid retention or a direct toxic effect on the heart was unknown. Pre-approval studies with PIO, troglitazone, and rosiglitazone had shown hemodilution and edema as evidence of fluid retention but little or no evidence of impaired myocardial function.

The trial was designed to be a comparison of PIO to the sulfonylurea (SFU), Glyburide (GLY), in patients with existing heart failure. While recognizing the potential of PIO to exacerbate heart failure, the trial was felt to be ethical because patients with heart failure have limited options for treating hyperglycemia. Metformin is contraindicated because of fear of lactic acidosis. SFU's are effective initially but wane over time. The glucose-lowering effect of TZD's like PIO is more durable. Therefore, the potential benefit of improved glycemic control with PIO was felt to offset the potential for congestive heart failure. The trial began (first patient dosed) on 09 June 2000.

On October 10, 2003, Takeda informed DMEDP of the Data Monitoring Board's recommendation to terminate the phase 4 trial of pioglitazone vs glyburide in patients with mild to moderate congestive heart failure. This recommendation was based on the finding of a greater incidence of hospitalization for CHF in the pioglitazone group vs the glyburide group. A greater withdrawal rate among the pioglitazone patients was also noted. During a telecon on October 28, 2003, DMEDP accepted Takeda's plan to terminate the study and submit a final study report in May of 2004.

Takeda requested that specific labeling changes concerning this trial should be deferred. However, DMEDP pointed out that the proposed label would be incorrect if not revised to reflect the recent finding. The current label stated:

Patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during clinical trials.

It was agreed that a substantive revision of the label would be delayed until after Takeda and FDA had reviewed the trial results in detail. In the meanwhile, the terms "these" and [redacted] would be added to the label as follows to correct the inaccuracy:

Patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during these clinical trials; [redacted] ACTOS is not recommended in these patients (see PRECAUTIONS, Cardiovascular

Study 504

Trial design

This was a double dummy-blinded comparison of Pioglitazone to Glyburide in patients with type 2 diabetes and congestive heart failure. Use of a TZD within 90 days or previous TZD failure were exclusion criteria. Major inclusion criteria were:

HbA1c at least 7%

Congestive heart failure (CHF) with left ventricular ejection fraction less than 40% at screening plus NYHA functional capacity class II or early class III.

Treatment with a SFU and/or insulin for at least 30 days prior to visit 1.

Greater than 99% of patients randomized had been taking antidiabetic mediations. Glyburide or glipizide were used by about 57% in both groups. Metformin combined with other antidiabetic medications had been used previously by 8.6% of the PIO group and 8.4% of the GLY group. The protocol stipulated that metformin had to have been discontinued at least 30 days before visit 1.

As shown in the following table, approximately one third of patients in both groups were taking insulin at baseline. 20% of patients randomized to PIO and 10% of patients to GLY started insulin during the course of the study.

Baseline and Concomitant Insulin Use

Event	Pioglitazone N=262 n (%)	Glyburide N=256 n (%)
Subjects using insulin at Baseline (a)	89 (34.0)	83 (32.4)
Subjects using insulin during the study (b)	142 (54.2)	109 (42.6)
Subjects with insulin added since Baseline	53 (20.2)	26 (10.2)

(a) Insulin therapy prior to start of study drug dosing; all Baseline insulin users continued insulin use during the study.
(b) Insulin therapy initiated with or after the start of study drug dosing.

Patients were randomly assigned to either 30 mg PIO (2 x 15 mg tablets plus two placebo capsules) or 10 mg glyburide (2 x 5 mg tablets plus 2 placebo tablets). If the patients FPG > 140 at any study visit, the doses were increased to 45 mg of Pioglitazone (3 x 15 mg) or 15 mg of glyburide (3x 5 mg) with appropriate placebos. Once patients were taking the maximum dose of study medications, insulin could be added (or dose increased for patients already taking insulin at baseline), at the investigator's discretion, because of persistent hyperglycemia.

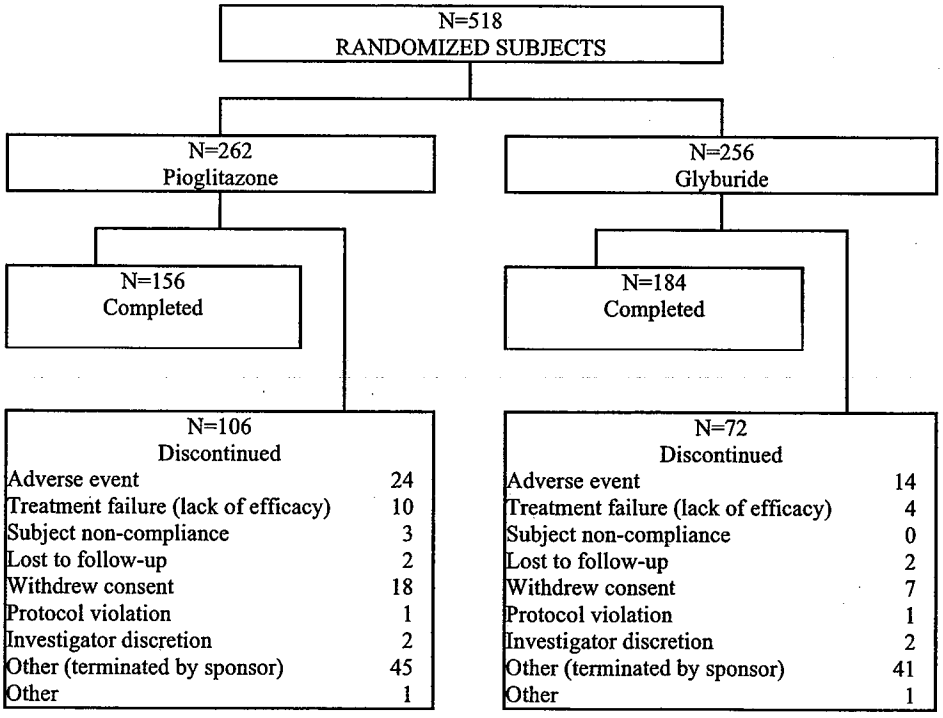
As shown in the following table, greater than 95% of patients were taking 30 - 45 mg of PIO or 10-15 mg of GLY at endpoint.

Summary of Maximum Dose and Last Dose of Study Drug

	Pioglitazone N=262 n(%)	Glyburide N=256 n(%)
Maximum dose		
Glyburide 5 mg or pioglitazone 15 mg	4 (1.5)	2 (0.8)
Glyburide 10 mg or pioglitazone 30 mg	68 (26.0)	90 (35.2)
Glyburide 15 mg or pioglitazone 45 mg	189 (72.1)	163 (63.7)
Glyburide 20 mg or pioglitazone 60 mg	1 (0.4)	1 (0.4)
Last dose		
Glyburide 5 mg or pioglitazone 15 mg	9 (3.4)	12 (4.7)
Glyburide 10 mg or pioglitazone 30 mg	70 (26.7)	89 (34.8)
Glyburide 15 mg or pioglitazone 45 mg	183 (69.8)	155 (60.5)

The disposition of patients is shown below:

Disposition of Subjects



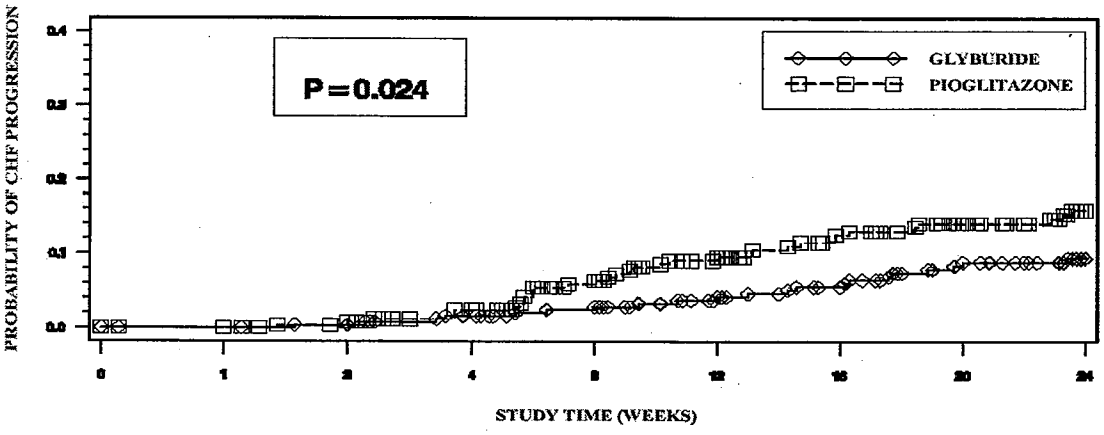
Of note is the greater number of PIO patients who withdrawal because of "lack of efficacy" or "withdrawal of consent". Of patients who did not use insulin at baseline, withdrawal because of lack of efficacy or withdrawal of consent were 24/173 (14%) for PIO and 7/173 (4%) for Glyburide. For patients with NYHA class III at baseline withdrawal because of lack of efficacy or withdrawal of consent was 6/49 (12%) for PIO and 2/46 (4%) for Glyburide.

Cardiac parameters were well matched at baseline. 81.3% had NYHA class III in both groups. Mean Ejection Fraction was about 29.5% and mean Functional Shortening was about 21.5%. Over 90% were taking an agent that acted on the renin-angiotension system. Greater than 80% were taking diuretics and about 50% in both groups were taking digitalis.

Analysis of Primary Variable

A Kaplan Meier estimate of a first event is shown below:

Kaplan-Meier Estimates of Probability of First Event Based on Determination by Clinical Endpoint Committee



There was a statistical difference (p=0.024) between PIO and Glyburide which is evident at about six weeks and continued thereafter. Progression of CHF was observed in 13.4% of patients on PIO compared to 8.2% on Glyburide. A breakdown of the components of the composite CHF endpoint is shown in the table below. Overnight hospitalization for worsening CHF accounts completely for the difference between PIO and GLY. Death due cardiovascular causes adjudicated by the CEC to be a first event occurred in 5 patients on PIO and 6 patients on GLY. Death due cardiovascular causes adjudicated by the CEC but not a first event occurred in 6 patients on PIO and 2 patients on GLY. Five of these six patients died between 6 and >110 days after last dose of PIO. Finally, three patients on PIO died of non-cardiovascular causes (respiratory failure following tracheobronchitis, renal neoplasm, septic shock)

Incidence Rate for First Event by Treatment Group Based on CEC Determination

CHF Progression Event	Pioglitazone N=262 n (%)	Glyburide N=256 n (%)	P-Value (a)
Composite event	35 (13.4)	21 (8.2)	0.024
Death due to cardiovascular causes	5 (1.9)	6 (2.3)	
Overnight hospitalization for worsening CHF	26 (9.9)	12 (4.7)	
Emergency room visit for CHF	4 (1.5)	3 (1.2)	

(a) P-value determined by log rank test.

As shown below, most of the difference between PIO and GLY occurred at non-US sites.

Incidence Rate of First Events by Treatment Group and Site Location (US versus Non-US Sites)

Event	Pioglitazone N=262 n (%)	Glyburide N=256 n (%)	P-Value (a)
US sites	**N=134**	**N=130**	
Composite event	13 (9.7)	9 (6.9)	0.241
Death due to cardiovascular causes	2 (1.5)	1 (0.8)	
Overnight hospitalization for worsening CHF	9 (6.7)	6 (4.6)	
Emergency room visit for CHF	2 (1.5)	2 (1.5)	
Non-US sites (b)	**N=128**	**N=126**	
Composite event	22 (17.2)	12 (9.5)	0.061
Death due to cardiovascular causes	3 (2.3)	5 (4.0)	
Overnight hospitalization for worsening CHF	17 (13.3)	6 (4.8)	
Emergency room visit for CHF	2 (1.6)	1 (0.8)	

(a) P-value determined by log rank test.
(b) Non-US sites include Argentina (N=249), Mexico (N=4), and Colombia (N=1).

As shown in the table below, most of the difference between PIO and GLY occurred in-patients > 64 years old.

Incidence Rate of First Events by Treatment Group and Age

Event	Pioglitazone N=262 n (%)	Glyburide N=256 n (%)	P-Value (a)
Age ≤64 years at Baseline	**N=133**	**N=144**	
Composite event	16 (12.0)	13 (9.0)	0.270
Death due to cardiovascular causes	2 (1.5)	3 (2.1)	
Overnight hospitalization for worsening CHF	10 (7.5)	8 (5.6)	
Emergency room visit for CHF	4 (3.0)	2 (1.4)	
Age >64 years at Baseline	**N=129**	**N=112**	
Composite event	19 (14.7)	8 (7.1)	0.037
Death due to cardiovascular causes	3 (2.3)	3 (2.7)	
Overnight hospitalization for worsening CHF	16 (12.4)	4 (3.6)	
Emergency room visit for CHF	0 (0)	1 (0.9)	

The next two tables show results according to use of insulin at baseline or during the trial. From the first table, it can be seen that the difference between PIO and GLY was most evident in patients who were using insulin at baseline. But use of insulin during the trial, as shown in the subsequent table, appeared to make little difference.

Incidence Rate of First Event by Treatment Group and Baseline Insulin Use

Event	Pioglitazone N=262 n (%)	Glyburide N=256 n (%)	P-Value (a)
With Insulin Use at Baseline	**N=89**	**N=83**	
Composite event	17 (19.1)	7 (8.4)	0.032
Death due to cardiovascular causes	1 (1.1)	3 (3.6)	
Overnight hospitalization for worsening CHF	14 (15.7)	3 (3.6)	
Emergency room visit for CHF	2 (2.2)	1 (1.2)	
Without Insulin Use at Baseline	**N=173**	**N=173**	
Composite event	18 (10.4)	14 (8.1)	0.285
Death due to cardiovascular causes	4 (2.3)	3 (1.7)	
Overnight hospitalization for worsening CHF	12 (6.9)	9 (5.2)	
Emergency room visit for CHF	2 (1.2)	2 (1.2)	

Incidence Rate of First Event by Treatment Group and Concomitant Insulin Use

Event	Pioglitazone N=262 n (%)	Glyburide N=256 n (%)	P-Value (a)
With Concomitant Insulin Use	**N=142**	**N=109**	
Composite event	24 (16.9)	12 (11.0)	0.172
Death due to cardiovascular causes	1 (0.7)	4 (3.7)	
Overnight hospitalization for worsening CHF	20 (14.1)	7 (6.4)	
Emergency room visit for CHF	3 (2.1)	1 (0.9)	
Without Concomitant Insulin Use	**N=120**	**N=147**	
Composite event	11 (9.2)	9 (6.1)	0.185
Death due to cardiovascular causes	4 (3.3)	2 (1.4)	
Overnight hospitalization for worsening CHF	6 (5.0)	5 (3.4)	
Emergency room visit for CHF	1 (0.8)	2 (1.4)	

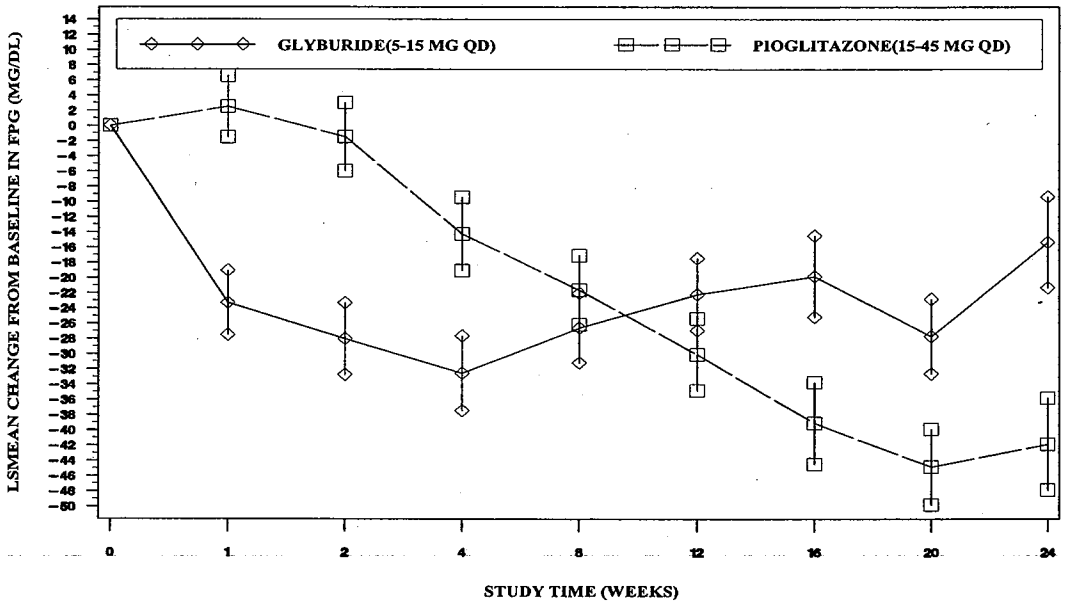
(a) P-value determined by log rank test.

Measures of Glucose Control

The two groups were well matched at baseline. Mean FPG was 186 mg/dl in both groups. Mean HbA1c was 8.74% for PIO group and 8.95% for the GLY group.

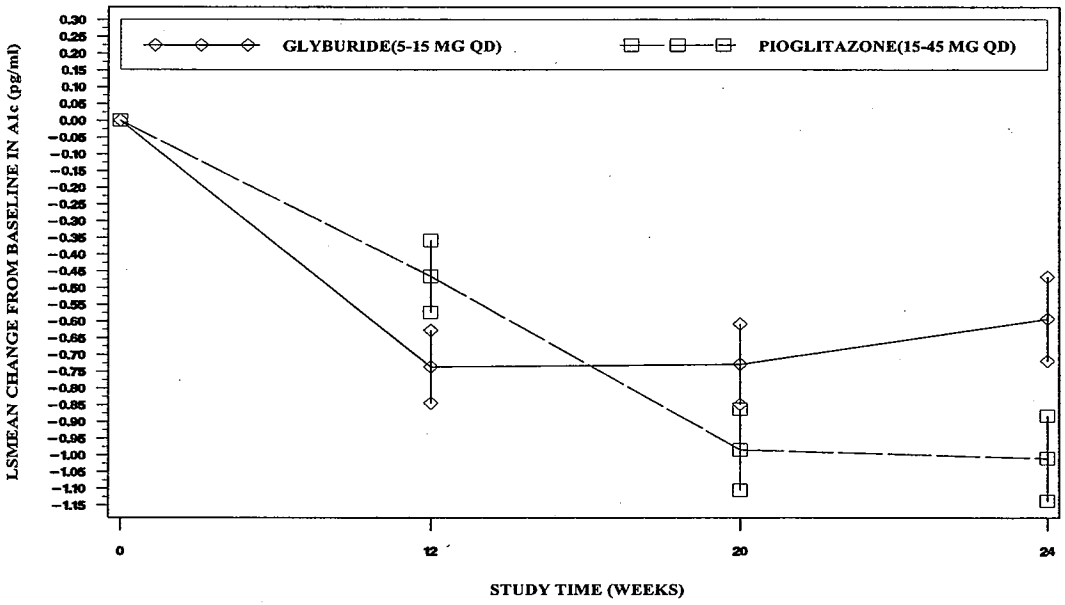
The following figure shows the LS means for changes in FPG. The fall in FPG occurred after 1 week of GLY and is maximum at four weeks. After an initial rise reflecting washout from previous treatment, a fall in FPG is evident by four weeks in PIO patients. The fall continues to week 20 and is sustained to week 24. Beyond week 16, the greater reduction in FPG with PIO than with GLY is statistically significant.

LS Mean Change From Baseline in FPG (SE) by Study Visit (Intent To Treat)



The following figure shows the LS means for changes in HbA1c. At week 24, the greater reduction in HbA1c with PIO than with GLY is statistically significant.

LS Mean Change From Baseline in A1c (SE) by Study Visit (Intent To Treat)



Other findings:

Edema:

As shown in the table below, 11.8% of patients on PIO reported edema as an adverse event compared to 7% of patients on GLY.

	Pioglitazone N=262 n (%)	Glyburide N=256 n (%)
With Selected Adverse Event of Edema (a)	31 (.11.8)	18 (7.0)
Edema lower limb	25 (9.5)	13 (5.1)
Edema NOS	5 (1.9)	1 (0.4)
Edema peripheral	3 (1.1)	0 (0)
Peripheral swelling	1 (0.4)	2 (0.8)
Fluid retention	2 (0.8)	2 (0.8)

Blood pressure

Statistically significant treatment group differences in reductions in systolic and diastolic blood pressure were observed. Mean systolic blood pressure at baseline was 124 for PIO and 123 for GLY. Mean change at endpoint was –0.8 for PIO and +2.3 for Glyburide. Mean diastolic blood pressure at baseline was 74.3 for PIO and 73.5 for GLY. Mean change at endpoint was –2.7 for PIO and +0.4 for Glyburide.

Echocardiographic findings:

As shown in the following tables, the two groups were well matched at baseline with respect to echocardiographic findings. At the final visit, there was a statistically significant increase in Cardiac Index in patients on PIO vs GLY. There was no treatment difference in ejection fraction between the two groups. However, for patients with a first cardiac event, it appears that treatment with PIO vs GLY resulted in a small improvement in ejection fraction. These findings were interpreted by the Sponsor as evidence that PIO is not cardiotoxic.

Mean Change From Baseline to Final Visit for Echocardiogram Parameters

Change from Baseline to Final Visit	Pioglitazone N=262		Glyburide N=256		P-value (a)
	N	Mean (SD)	N	Mean (SD)	
Left ventricular mass (g)					
Baseline	196	200.616 (56.9986)	204	206.229 (57.4517)	
Change from Baseline to Final Visit	114	-4.147 (47.0794)	142	-6.902 (37.5219)	0.959
Cardiac index (L/min/m^2)					
Baseline	198	1.830 (0.6020)	196	1.771 (0.5001)	
Change from Baseline to Final Visit	117	0.142 (0.7854)	133	-0.029 (0.5525)	0.012
Fractional shortening (%)					
Baseline	226	21.949 (6.9976)	223	21.043 (6.5142)	
Change from Baseline to Final Visit	146	0.135 (6.7881)	164	1.161 (6.4179)	0.280
Left ventricular ejection fraction (%)					
Baseline	203	29.727 (10.2699)	206	29.371 (10.0213)	
Change from Baseline to Final Visit	121	3.645 (10.1955)	141	2.470 (9.8580)	0.413

Mean Change From Baseline in Ejection Fraction by Occurrence of First Event (Subjects With a First Event versus Subjects Without a First Event) and Treatment Group

Ejection Fraction (%)	Pioglitazone		Glyburide		P-Value
Subject with an event					
Baseline	31	25.05 (10.79)	19	27.72 (7.17)	0.971
Change from Baseline (a)	13	1.39 (7.44)	9	-2.63 (7.56)	0.045
Subjects without an event					
Baseline	172	30.57 (9.97)	187	29.54 (10.27)	0.661
Change from Baseline (a)	108	3.92 (10.47)	132	2.82 (9.92)	0.346

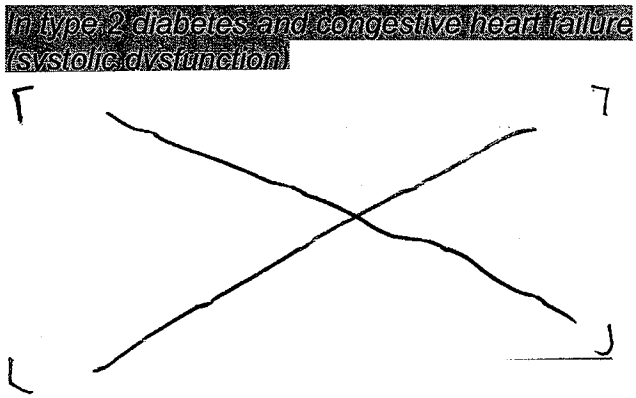
(a) At Final Visit.

Hematological measures:

Statistically significant treatment group differences in reductions in hematocrit, hemoglobin, RBC, and WBC were seen at week 16 and beyond. A decrease in hematocrit of greater than 0.8% from baseline was seen in 11.5% of patients on PIO and 7% on GLY.

Action Proposed by the Sponsor:

Takeda had submitted the following language to be added to the Warning Section as a change being effected (CBE).



TGRD proposed language based on data analyzed from an early terminated, Phase IV study, 01-00-TL-OPI-504; recommendation addresses

Following the recommendation of DMEDP, Takeda has revised the label to include the following description of the trial and the safety finding:

A 24-week post-marketing safety study was performed to compare ACTOS (n=262) to glyburide (n=256) in uncontrolled diabetic patients (mean HbA_{1C} 8.8% at baseline) with NYHA Class II and III heart failure and ejection fraction less than 40% (mean EF 30% at baseline). Over the course of the study, overnight hospitalization for congestive heart failure was reported in 9.9% of patients on ACTOS compared to 4.7% of patients on glyburide with a treatment difference observed from 6 weeks. This adverse event associated with ACTOS was more marked in patients using insulin at baseline and in patients over 64 years of age. No difference in cardiovascular mortality between the treatment groups was observed.

Also, the first paragraph of WARNINGS:

"Patients with New York Heart Association (NYHA) class III and IV cardiac status were not studied during these clinical trials "

has been changed to

Patients with New York Heart Association (NYHA) class III and IV cardiac status were not studied during pre-approval clinical trials

Recommendation: The revisions to the label should be approved

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Misbin
7/23/04 03:50:18 PM
MEDICAL OFFICER

David Orloff
7/23/04 04:30:11 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

APPLICATION #:	**21073**	**APPLICATION TYPE:**	**NDA.....**
SPONSOR:	**Takeda**	**PROPRIETARY NAME:**	**Pioglitazone.....**
CATEGORY OF DRUG:	**Antidiabetic**	**USAN / Established Name:**	**ACTOS.....**
		ROUTE:	**ORAL.....**
MEDICAL REVIEWER:	**Robert I Misbin..**	**REVIEW DATE:**	**June 30 2004.....**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
June 16, 2004	June 17, 2004		

Phase 4 study of Actos vs Glyburide	**Overnight hospitalization for worsening congestive heart failure occurred in 9.9% of patients on Actos compared to 4.7% of patients on Glyburide.**

Recommendation: Wording should be added to the ACTOS label about congestive heart failure

Signed: **Medical Reviewer: Robert I Misbin MD** **Date: June 30, 2004**

Medical Team Leader: _____ **Date:** _____

Table of Contents:

Executive Summary:

On October 10, 2003, Takeda informed DMEDP of their Data Monitoring Board's recommendation to terminate the phase 4 trial of pioglitazone vs glyburide in patients with mild to moderate congestive heart failure (CHF). This recommendation was based on the finding of a greater incidence of hospitalization for CHF in the pioglitazone group vs the glyburide group. Takeda requested that specific labeling changes concerning this trial should be deferred until after Takeda and FDA had reviewed the trial results in detail.

Takeda submitted a study report on June 16, 2004:

Congestive Heart Failure:

There was a statistical difference (p=0.024) between PIO and Glyburide which is evident at about six weeks and continued thereafter. Progression of CHF was observed in 13.4% of patients on PIO compared to 8.2% on Glyburide. A breakdown of the components of the composite CHF endpoint is shown in the table below. Overnight hospitalization for worsening CHF accounts completely for the difference between PIO and GLY.

Incidence Rate for First Event by Treatment Group Based on CEC Determination

CHF Progression Event	Pioglitazone N=262 n (%)	Glyburide N=256 n (%)	P-Value (a)
Composite event	35 (13.4)	21 (8.2)	0.024
Death due to cardiovascular causes	5 (1.9)	6 (2.3)	
Overnight hospitalization for worsening CHF	26 (9.9)	12 (4.7)	
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Most of the difference between PIO and GLY occurred in-patients > 64 years old and in patients who had been taking insulin at baseline.

The two groups were well matched at baseline with respect to echocardiographic findings. At the final visit, there was a statistically significant increase in Cardiac Index in patients on PIO vs patients on GLY. There was no treatment difference in ejection fraction between the two groups. However, for patients with a first cardiac event, it appears that treatment with PIO vs GLY resulted in a small improvement in ejection fraction. These findings were interpreted by the Sponsor as evidence that PIO is not cardiotoxic.

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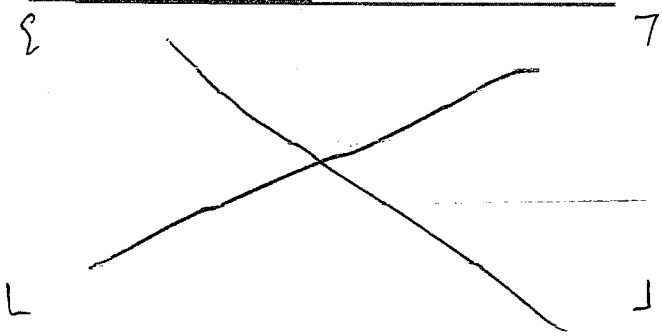

TGRD proposed language based on data analyzed from an early terminated, Phase IV study, 01-00-TL-OPI-504; recommendation addresses

Recommendation:

Consensus Statement developed jointly in 2003 by the American Heart Association and the American Diabetes Association.

A 24-week post-marketing safety study was performed to compare Actos (n=262) to Glyburide (n=256) in

Over the course of the study, overnight hospitalization for congestive heart failure had been reported in 9.9% of patients on Actos compared to 4.7% of patients on Glyburide.

Background:

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The trial was designed to be a comparison of PIO to the sulfonylurea (SFU), Glyburide (GLY), in patients with existing heart failure. While recognizing the potential of PIO to exacerbate heart failure, the trial was felt to be ethical because patients with heart failure have limited options for treating hyperglycemia. Metformin is contraindicated because of fear of lactic acidosis. SFU's are effective initially but wane over time. The glucose-lowering effect of TZD's like PIO is more durable. Therefore, the potential benefit of improved glycemic control with PIO was felt to offset the potential for congestive heart failure. The trial began (first patient dosed) on 09 June 2000.

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Takeda requested that specific labeling changes concerning this trial should be deferred. However, DMEDP pointed out that the proposed label would be incorrect if not revised to reflect the recent finding. The current label stated:

Patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during clinical trials.

It was agreed that a substantive revision of the label would be delayed until after Takeda and FDA had reviewed the trial results in detail. In the meanwhile, the terms "these" and [redacted] would be added to the label as follows to correct the inaccuracy:

Patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during these clinical trials; [redacted] ACTOS is not recommended in these patients (see PRECAUTIONS, Cardiovascular

Study 504

Trial design

This was a double dummy-blinded comparison of Pioglitazone to Glyburide in patients with type 2 diabetes and congestive heart failure. Use of a TZD within 90 days or previous TZD failure were exclusion criteria. Major inclusion criteria were:

HbA1c at least 7%

Congestive heart failure (CHF) with left ventricular ejection fraction less than 40% at screening plus NYHA functional capacity class II or early class III.

Treatment with a SFU and/or insulin for at least 30 days prior to visit 1.

Greater than 99% of patients randomized had been taking antidiabetic mediations. Glyburide or glipizide were used by about 57% in both groups. Metformin combined with other antidiabetic medications had been used previously by 8.6% of the PIO group and 8.4% of the GLY group. The protocol stipulated that metformin had to have been discontinued at least 30 days before visit 1.

As shown in the following table, approximately one third of patients in both groups were taking insulin at baseline. 20% of patients randomized to PIO and 10% of patients to GLY started insulin during the course of the study.

Baseline and Concomitant Insulin Use

Event	Pioglitazone N=262 n (%)	Glyburide N=256 n (%)
Subjects using insulin at Baseline (a)	89 (34.0)	83 (32.4)
Subjects using insulin during the study (b)	142 (54.2)	109 (42.6)
Subjects with insulin added since Baseline	53 (20.2)	26 (10.2)

(a) Insulin therapy prior to start of study drug dosing; all Baseline insulin users continued insulin use during the study.
(b) Insulin therapy initiated with or after the start of study drug dosing.

Patients were randomly assigned to either 30 mg PIO (2 x 15 mg tablets plus two placebo capsules) or 10 mg glyburide (2 x 5 mg tablets plus 2 placebo tablets). If the patients FPG > 140 at any study visit, the doses were increased to 45 mg of Pioglitazone (3 x 15 mg) or 15 mg of glyburide (3x 5 mg) with appropriate placebos. Once patients were taking the maximum dose of study medications, insulin could be added (or dose increased for patients already taking insulin at baseline), at the investigator's discretion, because of persistent hyperglycemia.

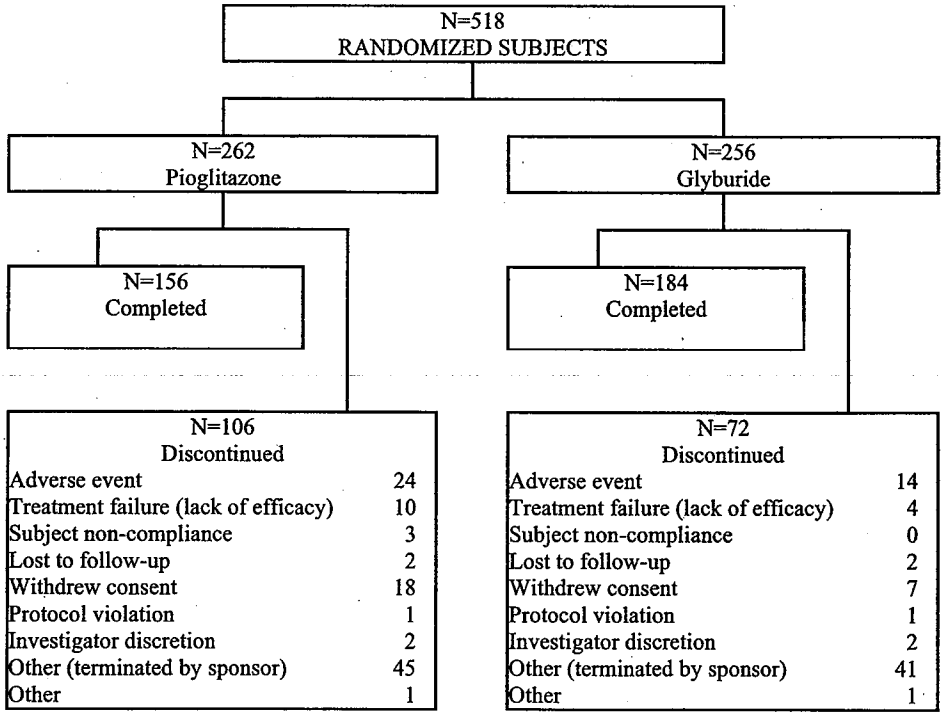
As shown in the following table, greater than 95% of patients were taking 30 - 45 mg of PIO or 10-15 mg of GLY at endpoint.

Summary of Maximum Dose and Last Dose of Study Drug

	Pioglitazone N=262 n(%)	Glyburide N=256 n(%)
Maximum dose		
Glyburide 5 mg or pioglitazone 15 mg	4 (1.5)	2 (0.8)
Glyburide 10 mg or pioglitazone 30 mg	68 (26.0)	90 (35.2)
Glyburide 15 mg or pioglitazone 45 mg	189 (72.1)	163 (63.7)
Glyburide 20 mg or pioglitazone 60 mg	1 (0.4)	1 (0.4)
Last dose		
Glyburide 5 mg or pioglitazone 15 mg	9 (3.4)	12 (4.7)
Glyburide 10 mg or pioglitazone 30 mg	70 (26.7)	89 (34.8)
Glyburide 15 mg or pioglitazone 45 mg	183 (69.8)	155 (60.5)

The disposition of patients is shown below:

Disposition of Subjects



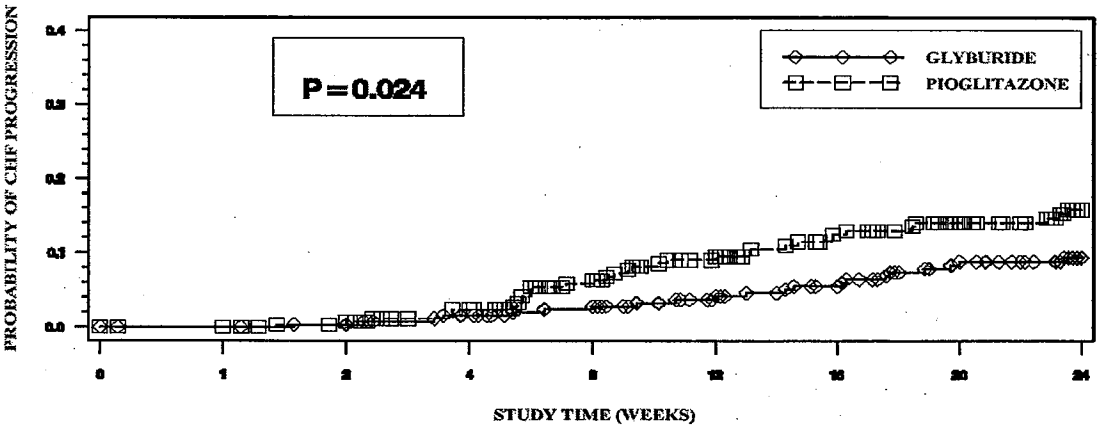
Of note is the greater number of PIO patients who withdrawal because of "lack of efficacy" or "withdrawal of consent". Of patients who did not use insulin at baseline, withdrawal because of lack of efficacy or withdrawal of consent were 24/173 (14%) for PIO and 7/173 (4%) for Glyburide. For patients with NYHA class III at baseline withdrawal because of lack of efficacy or withdrawal of consent was 6/49 (12%) for PIO and 2/46 (4%) for Glyburide.

Cardiac parameters were well matched at baseline. 81.3% had NYHA class III in both groups. Mean Ejection Fraction was about 29.5% and mean Functional Shortening was about 21.5%. Over 90% were taking an agent that acted on the renin-angiotension system. Greater than 80% were taking diuretics and about 50% in both groups were taking digitalis.

Analysis of Primary Variable

A Kaplan Meier estimate of a first event is shown below:

Kaplan-Meier Estimates of Probability of First Event Based on Determination by Clinical Endpoint Committee



There was a statistical difference (p=0.024) between PIO and Glyburide which is evident at about six weeks and continued thereafter. Progression of CHF was observed in 13.4% of patients on PIO compared to 8.2% on Glyburide. A breakdown of the components of the composite CHF endpoint is shown in the table below. Overnight hospitalization for worsening CHF accounts completely for the difference between PIO and GLY. Death due cardiovascular causes adjudicated by the CEC to be a first event occurred in 5 patients on PIO and 6 patients on GLY. Death due cardiovascular causes adjudicated by the CEC but not a first event occurred in 6 patients on PIO and 2 patients on GLY. Five of these six patients died between 6 and >110 days after last dose of PIO. Finally, three patients on PIO died of non-cardiovascular causes (respiratory failure following tracheobronchitis, renal neoplasm, septic shock)

Incidence Rate for First Event by Treatment Group Based on CEC Determination

CHF Progression Event	Pioglitazone N=262 n (%)	Glyburide N=256 n (%)	P-Value (a)
Composite event	35 (13.4)	21 (8.2)	0.024
Death due to cardiovascular causes	5 (1.9)	6 (2.3)	
Overnight hospitalization for worsening CHF	26 (9.9)	12 (4.7)	
Emergency room visit for CHF	4 (1.5)	3 (1.2)	

(a) P-value determined by log rank test.

As shown below, most of the difference between PIO and GLY occurred at non-US sites.

Incidence Rate of First Events by Treatment Group and Site Location (US versus Non-US Sites)

Event	Pioglitazone N=262 n (%)	Glyburide N=256 n (%)	P-Value (a)
US sites	**N=134**	**N=130**	
Composite event	13 (9.7)	9 (6.9)	0.241
Death due to cardiovascular causes	2 (1.5)	1 (0.8)	
Overnight hospitalization for worsening CHF	9 (6.7)	6 (4.6)	
Emergency room visit for CHF	2 (1.5)	2 (1.5)	
Non-US sites (b)	**N=128**	**N=126**	
Composite event	22 (17.2)	12 (9.5)	0.061
Death due to cardiovascular causes	3 (2.3)	5 (4.0)	
Overnight hospitalization for worsening CHF	17 (13.3)	6 (4.8)	
Emergency room visit for CHF	2 (1.6)	1 (0.8)	

(a) P-value determined by log rank test.
(b) Non-US sites include Argentina (N=249), Mexico (N=4), and Colombia (N=1).

As shown in the table below, most of the difference between PIO and GLY occurred in-patients > 64 years old.

Incidence Rate of First Events by Treatment Group and Age

Event	Pioglitazone N=262 n (%)	Glyburide N=256 n (%)	P-Value (a)
Age ≤64 years at Baseline	**N=133**	**N=144**	
Composite event	16 (12.0)	13 (9.0)	0.270
Death due to cardiovascular causes	2 (1.5)	3 (2.1)	
Overnight hospitalization for worsening CHF	10 (7.5)	8 (5.6)	
Emergency room visit for CHF	4 (3.0)	2 (1.4)	
Age >64 years at Baseline	**N=129**	**N=112**	
Composite event	19 (14.7)	8 (7.1)	0.037
Death due to cardiovascular causes	3 (2.3)	3 (2.7)	
Overnight hospitalization for worsening CHF	16 (12.4)	4 (3.6)	
Emergency room visit for CHF	0 (0)	1 (0.9)	

The next two tables show results according to use of insulin at baseline or during the trial. From the first table, it can be seen that the difference between PIO and GLY was most evident in patients who were using insulin at baseline. But use of insulin during the trial, as shown in the subsequent table, appeared to make little difference.

Incidence Rate of First Event by Treatment Group and Baseline Insulin Use

Event	Pioglitazone N=262 n (%)	Glyburide N=256 n (%)	P-Value (a)
With Insulin Use at Baseline	**N=89**	**N=83**	
Composite event	17 (19.1)	7 (8.4)	0.032
Death due to cardiovascular causes	1 (1.1)	3 (3.6)	
Overnight hospitalization for worsening CHF	14 (15.7)	3 (3.6)	
Emergency room visit for CHF	2 (2.2)	1 (1.2)	
Without Insulin Use at Baseline	**N=173**	**N=173**	
Composite event	18 (10.4)	14 (8.1)	0.285
Death due to cardiovascular causes	4 (2.3)	3 (1.7)	
Overnight hospitalization for worsening CHF	12 (6.9)	9 (5.2)	
Emergency room visit for CHF	2 (1.2)	2 (1.2)	

Incidence Rate of First Event by Treatment Group and Concomitant Insulin Use

Event	Pioglitazone N=262 n (%)	Glyburide N=256 n (%)	P-Value (a)
With Concomitant Insulin Use	**N=142**	**N=109**	
Composite event	24 (16.9)	12 (11.0)	0.172
Death due to cardiovascular causes	1 (0.7)	4 (3.7)	
Overnight hospitalization for worsening CHF	20 (14.1)	7 (6.4)	
Emergency room visit for CHF	3 (2.1)	1 (0.9)	
Without Concomitant Insulin Use	**N=120**	**N=147**	
Composite event	11 (9.2)	9 (6.1)	0.185
Death due to cardiovascular causes	4 (3.3)	2 (1.4)	
Overnight hospitalization for worsening CHF	6 (5.0)	5 (3.4)	
Emergency room visit for CHF	1 (0.8)	2 (1.4)	

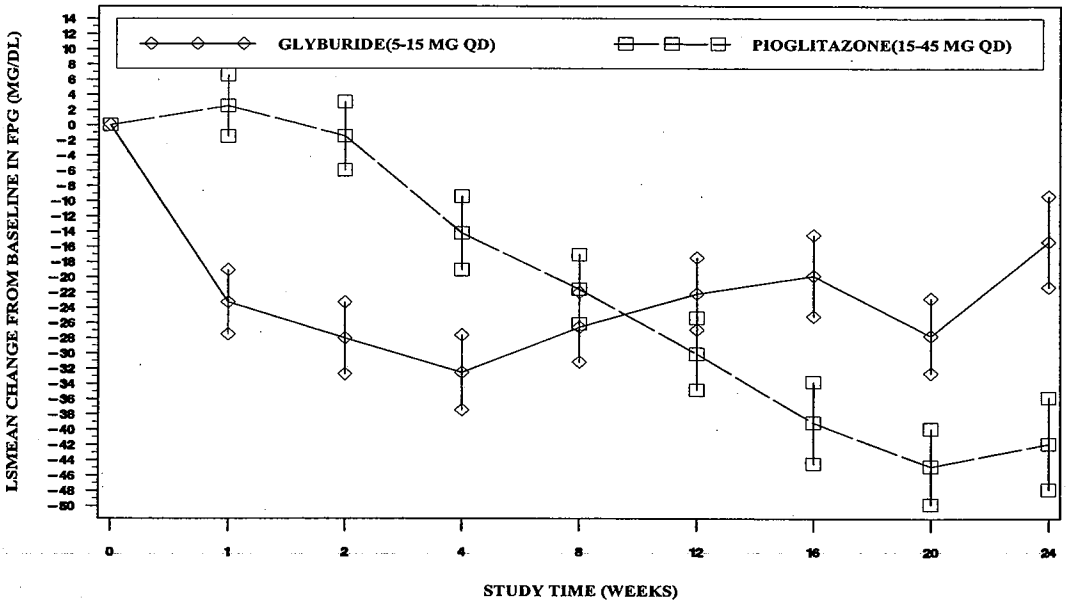
(a) P-value determined by log rank test.

Measures of Glucose Control

The two groups were well matched at baseline. Mean FPG was 186 mg/dl in both groups. Mean HbA1c was 8.74% for PIO group and 8.95% for the GLY group.

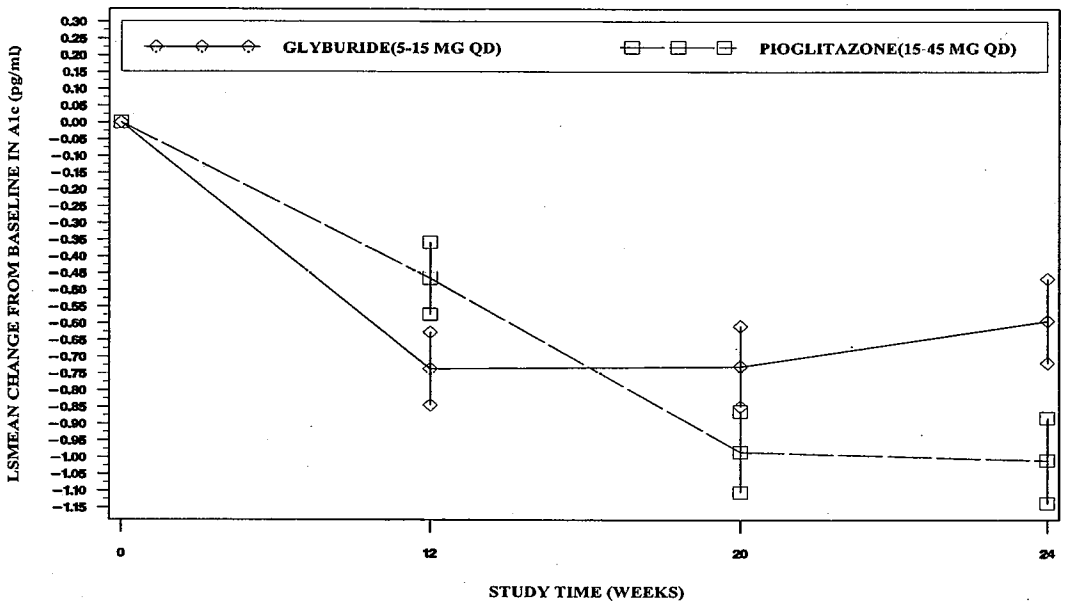
The following figure shows the LS means for changes in FPG. The fall in FPG occurred after 1 week of GLY and is maximum at four weeks. After an initial rise reflecting washout from previous treatment, a fall in FPG is evident by four weeks in PIO patients. The fall continues to week 20 and is sustained to week 24. Beyond week 16, the greater reduction in FPG with PIO than with GLY is statistically significant.

LS Mean Change From Baseline in FPG (SE) by Study Visit (Intent To Treat)



The following figure shows the LS means for changes in HbA1c. At week 24, the greater reduction in HbA1c with PIO than with GLY is statistically significant.

LS Mean Change From Baseline in A1c (SE) by Study Visit (Intent To Treat)



Other findings:

Edema:

As shown in the table below, 11.8% of patients on PIO reported edema as an adverse event compared to 7% of patients on GLY.

	Pioglitazone N=262 n (%)	**Glyburide N=256 n (%)**
With Selected Adverse Event of Edema (a)	31 (.11.8)	18 (7.0)
Edema lower limb	25 (9.5)	13 (5.1)
Edema NOS	5 (1.9)	1 (0.4)
Edema peripheral	3 (1.1)	0 (0)
Peripheral swelling	1 (0.4)	2 (0.8)
Fluid retention	2 (0.8)	2 (0.8)

Blood pressure

Statistically significant treatment group differences in reductions in systolic and diastolic blood pressure were observed. Mean systolic blood pressure at baseline was 124 for PIO and 123 for GLY. Mean change at endpoint was –0.8 for PIO and +2.3 for Glyburide. Mean diastolic blood pressure at baseline was 74.3 for PIO and 73.5 for GLY. Mean change at endpoint was –2.7 for PIO and +0.4 for Glyburide.

Echocardiographic findings:

As shown in the following tables, the two groups were well matched at baseline with respect to echocardiographic findings. At the final visit, there was a statistically significant increase in Cardiac Index in patients on PIO vs GLY. There was no treatment difference in ejection fraction between the two groups. However, for patients with a first cardiac event, it appears that treatment with PIO vs GLY resulted in a small improvement in ejection fraction. These findings were interpreted by the Sponsor as evidence that PIO is not cardiotoxic.

Mean Change From Baseline to Final Visit for Echocardiogram Parameters

Change from Baseline to Final Visit	Pioglitazone N=262		Glyburide N=256		P-value (a)
	N	Mean (SD)	N	Mean (SD)	
Left ventricular mass (g)					
Baseline	196	200.616 (56.9986)	204	206.229 (57.4517)	
Change from Baseline to Final Visit	114	-4.147 (47.0794)	142	-6.902 (37.5219)	0.959
Cardiac index (L/min/m^2)					
Baseline	198	1.830 (0.6020)	196	1.771 (0.5001)	
Change from Baseline to Final Visit	117	0.142 (0.7854)	133	-0.029 (0.5525)	0.012
Fractional shortening (%)					
Baseline	226	21.949 (6.9976)	223	21.043 (6.5142)	
Change from Baseline to Final Visit	146	0.135 (6.7881)	164	1.161 (6.4179)	0.280
Left ventricular ejection fraction (%)					
Baseline	203	29.727 (10.2699)	206	29.371 (10.0213)	
Change from Baseline to Final Visit	121	3.645 (10.1955)	141	2.470 (9.8580)	0.413

Mean Change From Baseline in Ejection Fraction by Occurrence of First Event (Subjects With a First Event versus Subjects Without a First Event) and Treatment Group

Ejection Fraction (%)	Pioglitazone		Glyburide		P-Value
Subject with an event					
Baseline	31	25.05 (10.79)	19	27.72 (7.17)	0.971
Change from Baseline (a)	13	1.39 (7.44)	9	-2.63 (7.56)	0.045
Subjects without an event					
Baseline	172	30.57 (9.97)	187	29.54 (10.27)	0.661
Change from Baseline (a)	108	3.92 (10.47)	132	2.82 (9.92)	0.346

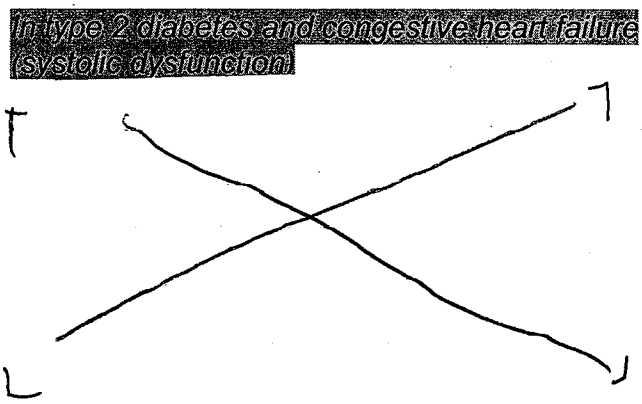
(a) At Final Visit.

Hematological measures:

Statistically significant treatment group differences in reductions in hematocrit, hemoglobin, RBC, and WBC were seen at week 16 and beyond. A decrease in hematocrit of greater than 0.8% from baseline was seen in 11.5% of patients on PIO and 7% on GLY.

Action Proposed by the Sponsor:

Takeda has submitted the following language to be added to the Warning Section as a change being effected (CBE).



TGRD proposed language based on data analyzed from an early terminated, Phase IV study, 01-00-TL-OPI-504; recommendation addresses

Comment and recommendation:

. Consensus Statement developed jointly in 2003 by the American Heart Association and the American Diabetes Association

The paragraph is

Takeda's proposed text should be preceded by this description of the trial and its major finding:

A 24-week post-marketing safety study was performed to compare Actos (n=262) to Glyburide (n=256) in

s. Over the course of the study, overnight hospitalization for congestive heart failure had been reported in 9.9% of patients on Actos compared to 4.7% of patients on Glyburide

Also, in the first paragraph of WARNINGS:

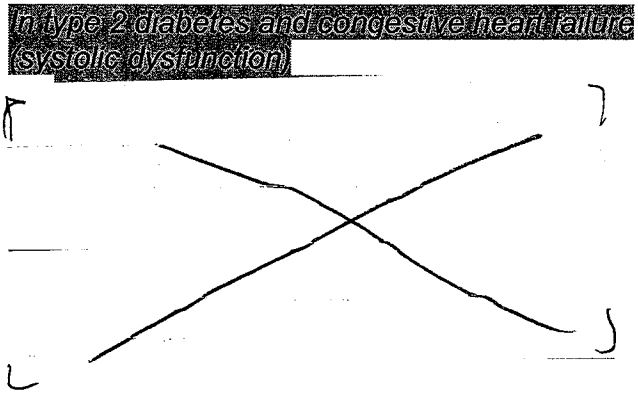
"Patients with New York Heart Association (NYHA) class III and IV cardiac status were not studied during these clinical trials "

should be changed to

"Patients with New York Heart Association (NYHA) class III and IV cardiac status were not studied during pre-approval clinical trials "

For Communication to the Sponsor:

The following language may to be added to the Warning Section as a CBE.



TGRD proposed language based on data analyzed from an early terminated, Phase IV study, 01-00-TL-OPI-504; recommendation addresses

2003 by the American Heart Association and the American Diabetes Association.

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"Patients with New York Heart Association (NYHA) class III and IV cardiac status were not studied during these clinical trials "

should be changed to

"Patients with New York Heart Association (NYHA) class III and IV cardiac status were not studied during pre-approval clinical trials "

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/s/

Robert Misbin
6/30/04 10:17:24 AM
MEDICAL OFFICER

David Orloff
7/1/04 05:45:06 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-073/S023

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-073/S-023

PRIOR APPROVAL SUPPLEMENT

Takeda Global Research & Development Center, Inc.
Attention: Mary Jo Pritza, MPH, PharmD
Manager, Regulatory Affairs
475 Half Day Road, Suite 500
Lincolnshire, IL 60069

Dear Ms. Pritza:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actos (pioglitazone HCl) Tablets, 15 mg, 30 mg, and 45 mg.

You were notified in our letter dated July 14, 2004, that your supplemental application was not accepted for filing due to non-payment of fees. This is to notify you that your amended supplement dated July 20, 2004, does not require payment of a user fee. This supplemental application provides for language that will strengthen restrictions to the **WARNINGS** section of the package insert.

Unless we notify you within 60 days of the above date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 19, 2004, in accordance with 21 CFR 314.101(a).

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please call me at 301-827-6422.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jena Weber
7/23/04 11:05:24 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-073/S-023

PRIOR APPROVAL SUPPLEMENT

Takeda Global Research & Development Center, Inc.
Attention: Mary Jo Pritza, MPH, PharmD
Manager, Regulatory Affairs
475 Half Day Road
Lincolnshire, IL 60069

Dear Ms. Pritza:

Please refer to your supplemental new drug application dated June 16, 2004, for Actos (pioglitazone HCl) Tablets, and to our letter dated July 13, 2004, informing you that this supplement contained clinical data which required review.

We have not received the appropriate user fee for this application. An application is considered incomplete and cannot be accepted for filing until all fees owed have been paid. Therefore, this application is not accepted for filing. We will not begin a review of this application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15251-6909

Checks sent by a courier should be addressed to:

Food and Drug Administration (360909)
Mellon Client Service Center, Room 670
500 Ross Street
Pittsburgh, PA 15262-0001

NOTE: This address is for courier delivery only. Make sure the FDA Post Office Box Number (P.O. Box 360909) and user fee identification number are on the enclosed check.

Please cite the application number listed above at the top of the first page of any communications concerning this application.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please call me at 301-827-6422.

Sincerely,

{See appended electronic signature page}

Jena M. Weber
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Jena Weber
7/14/04 02:42:17 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-073/S-023

CBE-30/CBE-0 SUPPLEMENT

Takeda Global Research & Development Center, Inc.
Attention: Mary Jo Pritza, MPH, PharmD
Manager, Regulatory Affairs
475 Half Day Road
Lincolnshire, IL 60069

Dear Ms. Pritza:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Actos (pioglitazone HCl) Tablets, 15 mg, 30 mg and 45 mg.
NDA Number:	21-073
Supplement number:	S-023
Date of supplement:	June 16, 2004
Date of receipt:	June 17, 2004

This supplemental application, submitted as "Supplement - Changes Being Effected in 30 days," provides for new language to the **WARNINGS** section of the package insert.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 16, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be **April 17, 2005.**

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/ Courier/Overnight Mail:
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Document Room 8B45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please call me at 301-827-6422.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Jena Weber
6/22/04 09:56:07 AM