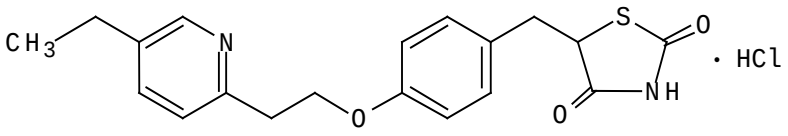
actos®

(Pioglitazone Hydrochloride Tablets)

actos® 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-] thiazolidinedione monohydrochloride belongs to a different chemical class and has a different pharmacological action than the sulfonylureas, metformin, or the α-glucosidase inhibitors. 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 enantiomers. The structural formula is as shown:



Pioglitazone hydrochloride is an odorless white crystalline powder that has a molecular formula of $C_{19}H_{20}N_2O_3S \cdot HCl$ 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.

CHEMICAL NAME

(±)-5-[p-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione hydrochloride

COMPOSITION

actos® 15 : Each tablet contains 15 mg of pioglitazone
actos® 30 : Each tablet contains 30 mg of pioglitazone

DESCRIPTION

actos® 15 : White to yellowish white tablet, quadrisect on one side and bisect on the other.
actos® 30 : White to yellowish white tablet.

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 hepatic glucose output. Unlike sulfonylureas, pioglitazone is not an insulin secretagogue. Pioglitazone is a potent agonist for peroxisome proliferator-activated receptor-gamma ($PPAR_\gamma$). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle and liver. Activation of $PPAR_\gamma$ nuclear receptors modulates the transcription of number of insulin responsive genes involved in the control of glucose and lipid metabolism.

In animal models of diabetes, pioglitazone reduces the hyperglycemia, hyperinsulinemia, and hypertriglyceridemia characteristic of insulin-resistant states such as type 2 diabetes. The metabolic changes produced by pioglitazone result in increased

responsiveness 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 approximately 30% to 50% of the peak total pioglitazone serum concentrations and 20% to 25% of the total areas under the serum concentration-time curve (AUC).

Maximum serum concentration (Cmax), AUC, and trough serum concentrations (Cmin) 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 $\pm$ 0.41 (mean $\pm$ SD) L/kg of body weight. Pioglitazone is extensively protein bound (>99%) in human serum, principally to serum albumin. 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 pioglitazone) 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 6β-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 Effect).

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 Cmax and AUC values were increased 20% to 60% in females. As monotherapy and in combination with sulfonylurea, metformin, or insulin, ***actos***® improved glycemic control in both males and females. In controlled clinical trials, hemoglobin 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 individualized 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 Interaction

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 Cmax 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 Cmax and 0.88 (0.80 - 0.96) for AUC. In view of high variability of nifedipine pharmacokinetics, the clinical significance of this finding is unknown.

Ketoconazole: Co-administration of ***actos***® for 7 days with ketoconazole 200 mg administration twice daily resulted in least square mean (90% CI) values for unchanged pioglitazone of 1.14 (1.06 - 1.23) for Cmax, 1.34 (1.26 - 1.41) for AUC and 1.87 (1.71 - 2.04) for Cmin.

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 unchanged pioglitazone of 0.69 (0.57 - 0.85) for Cmax, 0.76 (0.65 - 0.88) for AUC and 0.96 (0.87 - 1.05) for Cmin. For unchanged atorvastatin the least square mean (90% CI) values were 0.77 (0.66 - 0.90) for Cmax, 0.86 (0.78 - 0.94) for AUC and 0.92 (0.82 - 1.02) for Cmin.

Theophylline: Co-administration of ***actos***® for 7 days with theophylline 400 mg administered twice daily resulted in no change in the pharmacokinetics of either drug.

Cytochrome P450: See **PRECAUTIONS**

Gemfibrozil: Concomitant administration of gemfibrozil (oral 600 mg twice daily), an inhibitor of CYP2C8, with pioglitazone (oral 30 mg) in 10 healthy volunteers pre-treated for 2 days prior with gemfibrozil (oral 600 mg twice daily) resulted in pioglitazone exposure (AUC0-24) being 226% of the pioglitazone exposure in the absence of gemfibrozil.

Rifampin: Concomitant administration of rifampin (oral 600 mg once daily), an inducer of CYP2C8 with pioglitazone (oral 30 mg) in 10 healthy volunteers pre-treated for 5 days prior with rifampin (oral 600 mg once daily) resulted in a decrease in the AUC of pioglitazone by 54%.

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 decreased in the 15 mg, 30 mg, and 45 mg ***actos***® dose groups compared to a mean increase 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**
Triglyceride (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 randomized 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

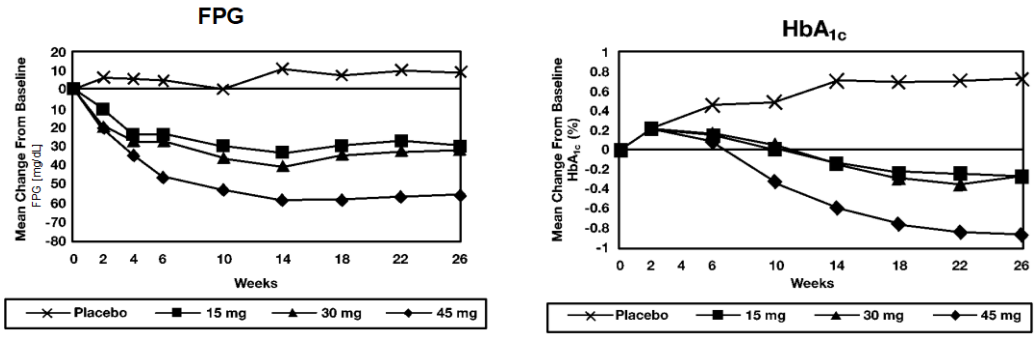


Table 2 shows HbA_{1c} and FPG values for the entire study population.

Table 2 :Glycemic Parameters in 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	N=79	N=79	N=85	N=76
HbA_{1c} (%)				
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*
	N=79	N=79	N=84	N=77
FPG (mg/dL)				
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 patients 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 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*® 30mg⁺ Once daily**	***actos*® 45mg⁺ 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/L)	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

* $p < 0.050$ 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, treatment 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≤ 0.05 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 antidiabetic 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.

INDICATIONS

actos® is indicated as oral monotherapy in type 2 diabetes mellitus patients, particularly overweight patients, inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance.

actos® is also indicated for oral combination treatment in type 2 diabetes mellitus patients with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with either metformin or sulphonylurea :

- In combination with metformin particularly in overweight patients
- In combination with a sulphonylurea only in patients who show intolerance to metformin or for whom metformin is contraindicated

DOSAGE AND ADMINISTRATION

actos® should be taken orally once daily with or without food

Dosage in Adults

actos® may be initiated at 15 mg or 30mg once daily. The dose may be increased to up to a maximum dose of 45 mg once daily. For patients not responding adequately to monotherapy, combination therapy should be considered.

In combination with metformin, the current metformin dose can be continued upon initiation of pioglitazone therapy. If patients report hypoglycaemia, the dose of metformin should be decreased.

In combination with sulphonylurea, the current sulphonylurea dose can be continued upon initiation of pioglitazone therapy. If patients report hypoglycaemia, the dose of sulphonylurea should be decreased.

The dose of ***actos***® should not exceed 45 mg once daily in monotherapy or in combination with metformin or sulphonylurea.

Elderly
No dosage adjustment is necessary for elderly patients

Patients with renal impairment
No dosage adjustment is necessary in patients with impaired renal function (creatinine clearance > 4ml/min). No information is available from dialysed patients therefore pioglitazone should not be used in such patients.

Patients with hepatic impairment
Pioglitazone should not be used in patients with hepatic impairment.

Children and adolescents
There are no data available on the use of pioglitazone in patients under 18 years of age, and therefore its use is not recommended in this age group.

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 If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Further more, discontinuation or dose reduction of ACTOS must be considered.
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 and ***actos***® is contraindicated in patients with cardiac failure or history of cardiac failure (NYHA stage I to IV) (see CONTRAINDICATIONS and 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 30mg ***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 HbA1c 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.

Prospective Pioglitazone Clinical Trial In Macrovascular Events (PROactive)
In PROactive, 5238 patients with type 2 diabetes and a prior history of macrovascular disease were treated with ACTOS (n=2605), force-titrated up to 45 mg once daily, or placebo (n=2633) (see **ADVERSE REACTIONS**). The percentage of patients who had an event of serious heart failure was higher for patients treated with ACTOS (5.7%, n=149) than for patients treated with placebo (4.1%, n=108). The incidence of death subsequent to a report of serious heart failure was 1.5% (n=40) in patients treated with ACTOS and 1.4% (n=37) in placebo-treated patients. In patients treated with an insulincontaining regimen at baseline, the incidence of serious heart failure was 6.3% (n=54/864) with ACTOS and 5.2% (n=47/896) with placebo. For those patients treated with a sulfonylurea-containing regimen at baseline, the incidence of serious heart failure was 5.8% (n=94/1624) with ACTOS and 4.4% (n=71/1626) with placebo.

Bladder Cancer
Preclinical and clinical trial data suggest an increased risk of bladder cancer in pioglitazone users.

Tumors were observed in the urinary bladder of male rats in the two-year carcinogenicity study. In two 3-year trials in which ***actos***® was compared to placebo or glyburide, there were 16/3656 (0.44%) reports of bladder cancer in patients taking ***actos***® compared to 5/3679 (0.14%) in patients not taking ***actos***®. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were six (0.16%) cases on ***actos***® and two (0.05%) cases on placebo.

A five-year interim report of a large prospective observational cohort study conducted in the United States found a non-significant increase in the risk for bladder cancer in subjects ever exposed to ACTOS, compared to subjects never exposed to ACTOS (HR 1.2 [95% CI 0.9 – 1.5]). Compared to never exposure, a duration of ACTOS therapy longer than 12 months was associated with an increase in risk (HR 1.4 [95% CI 0.9 – 2.1]), which reached statistical significance after more than 24 months of ACTOS use (HR 1.4 [95% CI 1.03 – 2.0]). However, the final 10 year results of this study found no significant increase in the risk of bladder cancer in diabetic patients ever exposed to ***actos***®, compared to those never exposed to ***actos***® (HR= 1.06 [95% CI 0.89 -1.26]). Additionally, there was no increased risk of bladder cancer with increased cumulative dose or time since starting ***actos***® or duration of exposure. In this study analysis of the hazard ratios for other diabetes medications including (other TZDs, metformin, sulfonylureas and insulin ranged from 0.91 to 1.09; which also were not

statistically significant. There is no clear hypothesis for why the 5 year interim data and final 10 year data are different.

Another large retrospective 10-year cohort study conducted in four European countries found no increased risk of bladder cancer in diabetic patients ever exposed to pioglitazone, compared to those never exposed to pioglitazone (HR=0.99 [95% CI 0.75, 1.30]).
Additionally, no increase risk was observed with increased cumulative dose or duration of pioglitazone exposure.

There are insufficient data to determine whether pioglitazone is a tumor promoter for urinary bladder tumors. Consequently, do not use ***actos***® in patients with active bladder cancer and in patients with a prior history of bladder cancer. Patients should be advised to promptly seek the attention of their physician if macroscopic hematuria or other symptoms such as urinary urgency develop during treatment

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 hypoglycemic agents may be at risk for hypoglycemia and a reduction in the dose of the concomitant 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 cardiac failure or history of cardiac failure (NYHA stages I to IV)

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 DRUG REACTIONS). In postmarketing experience, reports of initiation or worsening of edema have been received. Since thiazolidinediones, including ***actos***®, can cause fluid retention, which can exacerbate or lead to congestive heart failure, ***actos***® should be used with caution in patients at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure.

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}	**Median** (25^{th} / 75^{th}	**Median** (25^{th} / 75^{th}	**Median** (25^{th} / 75^{th}

		percentile)	percentile)	percentile)	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 DRUG REACTIONS: Laboratory Abnormalities).

Hepatic Effects: In pre-approval clinical studies worldwide, over 4,500 subjects were treated with ***actos***®. In US clinical studies, over 4,700 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 US, a total of 4 of 1,526 (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.

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 transaminase) 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 judgement 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.

Macular Edema: Macular edema has been reported in post-marketing experience in diabetic patients who were taking pioglitazone or another thiazolidinedione. Some patients presented with blurred vision or decreased visual acuity, but some patients appear to have been diagnosed on routine ophthalmologic examination. Some patients had peripheral edema at the time macular edema was diagnosed. Some patients had improvement in their macular edema after discontinuation of their thiazolidinedione. It is unknown whether or not there is a causal relationship between pioglitazone and macular edema. Patients with diabetes should have regular eye exams by an ophthalmologist, per the standards of care. Additionally, any diabetic who reports any kind of visual symptom should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings.

Fractures: In a randomized trial (PROactive) in patients with type 2 diabetes (mean duration of diabetes 9.5 years), an increased incidence of bone fracture was noted in female patients taking pioglitazone. During a mean follow-up of 34.5 months, the incidence of bone fracture in females was 5.1% (44/870) for pioglitazone versus 2.5% (23/905) for placebo. This difference was noted after the first year of treatment and remained during the course of the study. The majority of fractures observed in female patients were nonvertebral fractures including lower limb and distal upper limb. No increase in fracture rates was observed in men treated with pioglitazone 1.7% (30/1735) versus placebo 2.1% (37/1728). The risk of fracture should be considered in the care of patients, especially female patients, treated with pioglitazone and attention should be given to assessing and maintaining bone health according to current standards of care.
Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ACTOS.

Urinary Bladder Tumors: Risk factors for bladder cancer should be assessed before initiating pioglitazone treatment. Some of the risk factors include but is not limited to the following: current or past history of smoking, family history of bladder cancer, exposure to chemicals in the workplace or to certain cancer treatments such as cyclophosphamide and radiation therapy to abdomen or pelvis.

Bladder cancer occurs more commonly in elderly patients and in men compared to women.
Caution should be exercised when pioglitazone is to be prescribed for this group of patients.

All patients prescribed pioglitazone should be counselled to seek medical attention if they experience blood in urine, urinary urgency, pain on urination, or back or abdominal pain, as these may be signs and symptoms of bladder cancer.

Physicians are advised to review the treatment of patients on pioglitazone after three to six months (and regularly thereafter) to ensure that only patients with a favourable benefit-risk profile continue treatment with pioglitazone. Existing patients on pioglitazone should be reviewed to ensure that the benefit-risk profile remains favourable for continued use of pioglitazone.

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 DRUG 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 in 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 premenopausal women should be recommended. This possible effect has not been investigated in clinical studies so the frequency of this occurrence is not known.

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.

CONTRAINDICATIONS

actos® is contraindicated in patients with the following conditions:

- known hypersensitivity to pioglitazone or to any of the excipients of the tablet
- cardiac failure or history of cardiac failure (NYHA stages I to IV)
- hepatic impairment.
- active or history of bladder cancer
- uninvestigated macroscopic haematuria

actos® is also contraindicated for use in combination with insulin

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.

An enzyme inhibitor of CYP2C8 (such as gemfibrozil) may significantly increase the AUC of pioglitazone and an enzyme inducer of CYP2C8 (such as rifampin) may significantly decrease

the AUC of pioglitazone. Therefore, if an inhibitor or inducer of CYP2C8 is started or stopped during treatment with pioglitazone, changes in diabetes treatment may be needed based on clinical response (see **CLINICAL PHARMACOLOGY, 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 except 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.

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. In two 3-year studies in which pioglitazone was compared to placebo or glyburide, there were 16/3656 (0.44%) reports of bladder cancer in patients taking pioglitazone compared to 5/3679 (0.14%) in patients not taking pioglitazone. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were six (0.16%) cases on pioglitazone and two (0.05%) on placebo.

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, respectively, 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).

Use in Pregnancy

Pregnancy Category C.
actos® should not be used during pregnancy unless the perceived benefit outweigh the potential risks to the mother and fetus.
No adequate human data have been generated to demonstrate the safety of pioglitazone, alone or in combination with metformin or glimepiride, during pregnancy.

In animal reproductive studies, no adverse development effects were observed in pregnant rats and rabbits that received pioglitazone at doses up to approximately 5 (rat) and 35 (rabbit) times the 45mg maximum clinical dose based on body surface area (mg/m^2). Delayed parturition and embryotoxicity (as evidenced by increased postimplantation losses, delayed development and reduced fetal weights) were observed in rats at oral doses of greater than or equal to 9 times the 45mg clinical dose, by body surface area. No functional or behavioral toxicity was observed in offspring of rats. In rabbits, embryotoxicity was observed at an oral dose of approximately 69 times the 45mg clinical dose, by body surface area. Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats at oral doses of greater than or equal to 2 times the 45mg clinical dose by body surface area.

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 recommended that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Use in 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 breast-feeding woman, or breastfeeding should be discontinued if the use of pioglitazone is considered essential.

Use in Children:
Safety and effectiveness of ***actos***® in pediatric patients have not been established.

Use in elderly:
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 DRUG REACTIONS

Over 8500 patients with type 2 diabetes have been treated with ACTOS in randomized, double-blind, controlled clinical trials. This includes 2605 high-risk patients with type 2 diabetes treated with ACTOS from the PROactive clinical trial. Over 6000 patients have been treated for 6 months or longer, and over 4500 patients for one year or longer. Over 3000 patients have received ACTOS for at least 2 years.
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 *actos*®-Treated Patients

(% 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 $\leq$ 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 compared to 2.1% of patients on sulfonylureas alone. In combination therapy studies with metformin, edema was reported in 6.0% of patients on combination therapy compared to 2.5% of patients on metformin alone. In combination therapy studies with insulin, edema was reported 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).

Prospective Pioglitazone Clinical Trial In Macrovascular Events (PROactive)

In PROactive, 5238 patients with type 2 diabetes and a prior history of macrovascular disease were treated with ACTOS (n=2605), force-titrated up to 45 mg daily or placebo (n=2633) in addition to standard of care. Almost all subjects (95%) were receiving cardiovascular medications (beta blockers, ACE inhibitors, ARBs, calcium channel blockers, nitrates, diuretics, aspirin, statins, fibrates). Patients had a mean age of 61.8 years, mean duration of diabetes 9.5 years, and mean HbA1c 8.1%. Average duration of follow-up was 34.5 months. The primary objective of this trial was to examine the effect of ACTOS on mortality and macrovascular morbidity in patients with type 2 diabetes mellitus who were at high risk for macrovascular events. The primary efficacy variable was the time to the first occurrence of any event in the cardiovascular composite endpoint (see table 8 below). Although there was no statistically significant difference between ACTOS and placebo for the 3-year incidence of a first event within this composite, there was no increase in mortality or in total macrovascular events with ACTOS.

Table 8

Number of First and Total Events for Each Component within the Cardiovascular Composite Endpoint				
	Placebo N=2633		**ACTOS N=2605**	
Cardiovascular Events	First Events (N)	Total Events (N)	First Events (N)	Total Events (N)
Any event	572	900	514	803
All-cause mortality	122	186	110	177
Non-fatal MI	118	157	105	131
Stroke	96	119	76	92
ACS	63	78	42	65
Cardiac intervention	101	240	101	195
Major leg amputation	15	28	9	28
Leg revascularization	57	92	71	115

Postmarketing reports of new onset or worsening diabetic macular edema with decreased visual acuity have also been received (see **PRECAUTIONS, General,** Macular Edema).

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***®, and 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.

STORAGE

Refer to outer carton

EXPIRATION DATE

Refer to outer carton

PACKAGING

actos® 15 & *actos*® 30

30 tablets (3 x 10's) in a box.

10 tablets (1 X 10's) in a box.

Product Registrant

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Date of revision

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