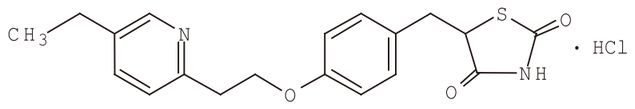
actos®

(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 $C_{19}H_{20}N_2O_3S.HCl$ 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

White to yellowish white tablet.

Code Area

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 and highly selective 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 increased 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. 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 vivo 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.

Interaction studies have shown that pioglitazone has no relevant effect on either the pharmacokinetics or pharmacodynamics of digoxin, warfarin, phenprocoumon and metformin. Concomitant administration of pioglitazone with gemfibrozil (an inhibitor of CYP 2C8) or with rifampicin (an inducer of CYP 2C8) is reported to increase or decrease, respectively, the plasma concentration of pioglitazone.

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 patients 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, haemoglobin 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.

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.

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.

A Dose Ranging Study (Study PNFP-001)

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 (Observed Values) Study PNFP-001

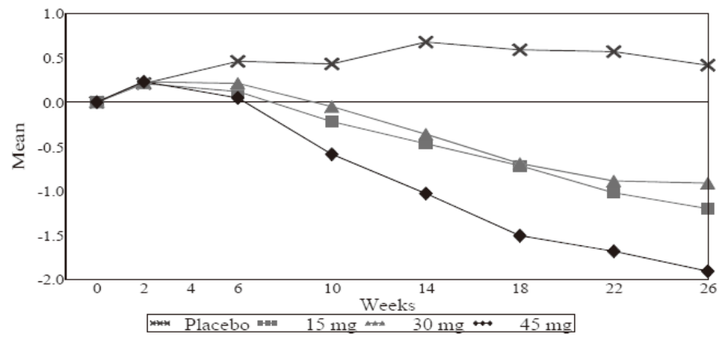


Table 1 shows HbA_{1c} and FPG values for the entire study population

Table 1 : Glycemic Parameters in 26-Week Placebo-Controlled Dose-Ranging Monotherapy Trial (Study PNFP-001).

	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≤ 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 2. 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 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
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

A Dose-Titration Study (Study PNFP-012)

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 3).

Table 3: Glycemic Parameters in a 24-week Placebo-Controlled Forced-Titration Study Monotherapy Trial (Study PNFP-012)

	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/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

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.

A 16-Week Monotherapy Study (study PNFP-026)

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 4).

Table 4: Glycemic parameters in a 16-week placebo-Controlled Monotherapy Trial (Study PNFP-026)

	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} > 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.

A 16-Week Add-on to Sulfonylurea Study (Study PNFP-010)

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.

A 24- Week Add-on to Sulfonylurea Study (Study PNFP-341)

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.

A 16-Week Add-on to Metformin Study (Study PNFP-027)

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.

A 24- Week Add-on to Metformin Study (Study PNFP-342)

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 in increments up to 45mg once daily.

In combination with metformin, the current metformin dose can be continued upon initiation of pioglitazone therapy.

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.

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.

SPECIAL WARNINGS AND SPECIAL PRECAUTION FOR USE

Fluid retention and cardiac failure

Pioglitazone can cause fluid retention, which may exacerbate or precipitate heart failure. When treating patients who have at least one risk factor for development of congestive heart failure (e.g. prior myocardial infarction or symptomatic coronary artery disease or the elderly), physicians should start with the lowest available dose and increase the dose gradually. Patients should be observed for signs and symptoms of heart failure, weight gain or oedema; particularly those with

reduced cardiac reserve. There have been post-marketing cases of cardiac failure reported when pioglitazone was used in combination with insulin or in patients with a history of cardiac failure. Patients should be observed for signs and symptoms of heart failure, weight gain and oedema when pioglitazone is used in combination with insulin. Since insulin and pioglitazone are both associated with fluid retention, concomitant administration may increase the risk of oedema. Post marketing cases of peripheral oedema and cardiac failure have also been reported in patients with concomitant use of pioglitazone and nonsteroidal anti-inflammatory drugs, including selective COX-2 inhibitors. Pioglitazone should be discontinued if any deterioration in cardiac status occurs.

A cardiovascular outcome study of pioglitazone has been performed in patients under 75 years with type 2 diabetes mellitus and pre-existing major macrovascular disease. Pioglitazone or placebo was added to existing antidiabetic and cardiovascular therapy for up to 3.5 years. This study showed an increase in reports of heart failure, however this did not lead to an increase in mortality in this study.

Elderly
Combination use with insulin should be considered with caution in the elderly because of increased risk of serious heart failure.
In light of age- related risks (especially bladder cancer, fractures and heart failure), the balance of benefits and risks should be considered carefully both before and during treatment in the elderly.

Bladder Cancer
Cases of bladder cancer were reported more frequently in a meta-analysis of controlled clinical trials with pioglitazone (19 cases from 12506 patients, 0.15%) than in control groups (7 cases from 10212 patients, 0.07%) HR=2.64 (95% CI 1.11-6.31, P=0.029). After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 7 cases (0.06%) on pioglitazone and 2 cases (0.02%) in control groups. Available epidemiological data also suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone, although not all studies identified a statistically significant increased risk.
Risk factors for bladder cancer should be assessed before initiating pioglitazone treatment (risks include age, smoking history, exposure to some occupational or chemotherapy agents e.g. cyclophosphamide or prior radiation treatment in the pelvic region). Any macroscopic haematuria should be investigated before starting pioglitazone therapy.
Patients should be advised to promptly seek the attention of their physician if macroscopic haematuria or other symptoms such as dysuria or urinary urgency develop during treatment.

Monitoring of liver function
There have been rare reports of hepatocellular dysfunction during post-marketing experience (see section 4.8). It is recommended, therefore, that patients treated with pioglitazone undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy with pioglitazone in all patients. Therapy with pioglitazone should not be initiated in patients with increased baseline liver enzyme levels (ALT > 2.5 X upper limit of normal) or with any other evidence of liver disease.
Following initiation of therapy with pioglitazone, it is recommended that liver enzymes be monitored periodically based on clinical judgement. If ALT levels are increased to 3 X upper limit of normal during pioglitazone therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain > 3 X the upper limit of normal, therapy should be discontinued. If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with pioglitazone should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, the medicinal product should be discontinued.

Weight gain
In clinical trials with pioglitazone there was evidence of dose related weight gain, which may be due to fat accumulation and in some cases associated with fluid retention. In some cases weight increase may be a symptom of cardiac failure, therefore weight should be closely monitored. Part of the treatment of diabetes is dietary control. Patients should be advised to adhere strictly to a calorie-controlled diet.

Haematology
There was a small reduction in mean haemoglobin (4% relative reduction) and haematocrit (4.1% relative reduction) during therapy with pioglitazone, consistent with haemodilution. Similar changes were seen in metformin (haemoglobin 3-4% and haematocrit 3.6–4.1% relative reductions) and to a lesser extent sulphonylurea and insulin (haemoglobin 1–2% and haematocrit 1–3.2% relative reductions) treated patients in comparative controlled trials with pioglitazone.

Hypoglycaemia
As a consequence of increased insulin sensitivity, patients receiving pioglitazone in dual or triple oral therapy with a sulphonylurea or in dual therapy with insulin may be at risk for dose-related hypoglycaemia, and a reduction in the dose of the sulphonylurea or insulin may be necessary.

Eye disorders
Post-marketing reports of new-onset or worsening diabetic macular oedema with decreased visual acuity have been reported with thiazolidinediones, including pioglitazone. Many of these patients reported concurrent peripheral oedema. It is unclear whether or not there is a direct association between pioglitazone and macular oedema but prescribers should be alert to the possibility of macular oedema if patients report disturbances in visual acuity; an appropriate ophthalmological referral should be considered.

Others
Pioglitazone exerts its anti-hyperglycemic affect only in the presence of insulin and should therefore not be used in patients with type I diabetes or for the treatment of diabetic ketoacidosis.
An increased incidence in bone fractures in women was seen in a pooled analysis of adverse reactions of bone fracture from randomised, controlled, double blind clinical trials in over 8100 pioglitazone and 7400 comparator treated patients, on treatment for up to 3.5 years.

Fractures were observed in 2.6% of women taking pioglitazone compared to 1.7% of women treated with a comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.3%) versus comparator (1.5%).

The fracture incidence calculated was 1.9 fractures per 100 patient years in women treated with pioglitazone and 1.1 fractures per 100 patient years in women treated with a comparator. The observed excess risk of fractures for women in this dataset on pioglitazone is therefore 0.8 fractures per 100 patient years of use.

In the 3.5 year cardiovascular risk PROactive study, 44/870 (5.1%; 1.0 fractures per 100 patient years) of pioglitazone-treated female patients experienced fractures compared to 23/905 (2.5%; 0.5 fractures per 100 patient years) of female patients treated with comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus comparator (2.1%).

Some epidemiological studies have suggested a similarly increased risk of fracture in both men and women.

The risk of fractures should be considered in the long term care of patients treated with pioglitazone.

As a consequence of enhancing insulin action, pioglitazone treatment in patients with polycystic ovarian syndrome may result in resumption of ovulation. These patients may be at risk of pregnancy. Patients should be aware of the risk of pregnancy and if a patient wishes to become pregnant or if pregnancy occurs, the treatment should be discontinued.

Pioglitazone should be used with caution during concomitant administration of cytochrome P450 2C8 inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin). Glycaemic control should be monitored closely. Pioglitazone dose adjustment within the recommended posology or changes in diabetic treatment should be considered.

Actos tablets contain lactose monohydrate and therefore should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

Effects on ability to drive and use machines
Actos has no or negligible influence on the ability to drive and use machines. However patients who experience visual disturbance should be cautious when driving or using machines.

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.
- Diabetic ketoacidosis
- Current bladder cancer or a history of bladder cancer
- Uninvestigated macroscopic haematuria

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Interaction studies have shown that pioglitazone has no relevant effect on either the pharmacokinetics or pharmacodynamics of digoxin, warfarin, phenprocoumon and metformin. Co-administration of pioglitazone with sulphonylureas does not appear to affect the pharmacokinetics of the sulphonylurea. Studies in man suggest no induction of the main inducible cytochrome P450, 1A, 2C8/9 and 3A4. *In vitro* studies have shown no inhibition of any subtype of cytochrome P450. Interactions with substances metabolised by these enzymes, e.g. oral contraceptives, cyclosporin, calcium channel blockers, and HMGCoA reductase inhibitors are not to be expected.
Co-administration of pioglitazone with gemfibrozil (an inhibitor of cytochrome P450 2C8) is reported to result in a 3-fold increase in AUC of pioglitazone. Since there is a potential for an increase in dose-related adverse events, a decrease in the dose of pioglitazone may be needed when gemfibrozil is concomitantly administered. Close monitoring of glycaemic control should be considered (see section 4.4). Co-administration of pioglitazone with rifampicin (an inducer of cytochrome P450 2C8) is reported to result in a 54% decrease in AUC of pioglitazone. The pioglitazone dose may need to be increased when rifampicin is concomitantly administered. Close monitoring of glycaemic control should be considered.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy
There are no adequate human data to determine the safety of pioglitazone during pregnancy. Foetal growth restriction was apparent in animal studies with pioglitazone. This was attributable to the action of pioglitazone in diminishing the maternal hyperinsulinaemia and increased insulin resistance that occurs during pregnancy thereby reducing the availability of metabolic substrates for foetal growth. The relevance of such a mechanism in humans is unclear and pioglitazone should not be used in pregnancy.

Breast-feeding
Pioglitazone has been shown to be present in the milk of lactating rats. It is not known whether pioglitazone is secreted in human milk. Therefore, pioglitazone should not be administered to breast-feeding women

Fertility
In animal fertility studies there was no effect on copulation, impregnation or fertility index.

ADVERSE DRUG REACTIONS

Tabulated list of adverse reactions Adverse reactions reported in excess (> 0.5%) of placebo and as more than an isolated case in patients receiving pioglitazone in double-blind studies are listed below as MedDRA preferred term by system organ class and absolute frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each system organ class, adverse reactions are presented in order of decreasing incidence followed by decreasing seriousness.

Adverse reaction	**Frequency of adverse reactions of pioglitazone by treatment regimen**		
	Mono-therapy	**Combination**	
		with metformin	**with sulphonylurea**
Infections and infestations			
upper respiratory tract infection	common	common	common
sinusitis	uncommon	uncommon	uncommon
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
bladder cancer	uncommon	uncommon	uncommon
Blood and lymphatic system disorders			
anaemia		common	
Immune System Disorders			
hypersensitivity and allergic reactions[1]	Not known	Not known	Not known
Metabolism and nutrition disorders			
hypo-glycaemia			Uncommon
appetite increased			Uncommon
Nervous system disorders			
hypo-aesthesia	common	common	common
headache		common	uncommon
dizziness			common
insomnia	uncommon	uncommon	uncommon
Eye disorders			
visual disturbance[2]	common	common	uncommon
macular oedema[3]	not known	not known	not known
Ear and labyrinth disorders			
vertigo			uncommon
Gastrointestinal disorders			
flatulence		uncommon	common
Skin and subcutaneous tissue disorders			
sweating			uncommon
Musculoskeletal and connective tissue disorders			
fracture bone[4]	common	common	common
arthralgia		common	
Renal and urinary disorders			
haematuria		common	
glycosuria			uncommon
proteinuria			uncommon
Reproductive system and breast disorders			
erectile dysfunction		common	
General disorders and administration site conditions			
fatigue			uncommon
Investigations			
weight increased[5]	common	common	common
blood creatine phospho-kinase increased			
increased lactic dehydro-genase			uncommon
alanine aminotransferase increased[6]	not known	not known	not known

Description of selected adverse reactions
[1] Postmarketing reports of hypersensitivity reactions in patients treated with pioglitazone have been reported. These reactions include anaphylaxis, angioedema, and urticaria.
[2] Visual disturbance has been reported mainly early in treatment and is related to changes in blood glucose due to temporary alteration in the turgidity and refractive index of the lens as seen with other hypoglycaemic treatments.
[3] Oedema was reported in 6–9% of patients treated with pioglitazone over one year in controlled clinical trials. The oedema rates for comparator groups (sulphonylurea, metformin) were 2–5%. The reports of oedema were generally mild to moderate and usually did not require discontinuation of treatment.
[4] A pooled analysis was conducted of adverse reactions of bone fractures from randomised, comparator controlled, double blind clinical trials in over 8100 patients in the pioglitazone-treated groups and 7400 in the comparator-treated groups of up to 3.5 years duration. A higher rate of fractures was observed in women taking pioglitazone (2.6%) versus comparator (1.7%). No increase in fracture rates was observed in men treated with pioglitazone (1.3%) versus comparator (1.5%).
In the 3.5 year PROactive study, 44/870 (5.1%) of pioglitazone-treated female patients experienced fractures compared to 23/905 (2.5%) of female patients treated with comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus comparator (2.1%).
[5] In active comparator controlled trials mean weight increase with pioglitazone given as monotherapy was 2–3 kg over one year. This is similar to that seen in a sulphonylurea active comparator group. In combination trials pioglitazone added to metformin resulted in mean weight increase over one year of 1.5 kg and added to a sulphonylurea of 2.8 kg. In comparator groups addition of sulphonylurea to metformin resulted in a mean weight gain of 1.3 kg and addition of metformin to a sulphonylurea a mean weight loss of 1.0 kg.
[6] In clinical trials with pioglitazone the incidence of elevations of ALT greater than three times the upper limit of normal was equal to placebo but less than that seen in metformin or sulphonylurea comparator groups. Mean levels of liver enzymes decreased with treatment with pioglitazone. Rare cases of elevated liver enzymes and hepatocellular dysfunction have occurred in post-marketing experience. Although in very rare cases fatal outcome has been reported, causal relationship has not been established.

STORAGE

Store below 30°C

Shelf-Life

Refer to outer carton

PACKAGING
actos® 15 & ***actos***® 30
30 tablets (3 x 10's) in a box.

Manufacturer
Bora Pharmaceutical Laboratories Inc. No.1, Kedong 3rd Rd., Hsinchu Science Park, Zhunan Township, Miaoli County, Taiwan, R.O.C.

Product Registration Holder:
DKSH MALAYSIA SDN. BHD.
B-11-01, The Ascent, Paradigm,
No.1, Jalan SS7/26A, Kelana Jaya,
47301 Petaling Jaya, Selangor, Malaysia

Date of Revision
Apr. 2025

LA-3249-01

Mechanical Artwork Identification Panel

General Information

Market:	*MY*
Component Type:	*PI*
Product Name:	*Actos 15mg and 30mg*
Material Number:	*LA-3249-01*
Printing Version No.:	*R01*
Smallest Body Text Size:	*6.5PT*
Dimension:	*420x594mm*

Version Control

3 Version No.

Mechanical AW History

Date:	Version record and revision description:
02.01.25	V1 - Artwork Build
22.01.25	V2 - Artwork Change
03.06.25	V3 - Artwork Change
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Colours

1. K
2. Color Name
3. Color Name
4. Color Name
5. Color Name
6. Color Name
7. Color Name
8. Color Name
9. Color Name
10. Color Name

File Name: PI_LA-3249-01R01_Actos_15mg and 30mg_30Tablets_MY_V3
Account Manager: Nic. Jiang
Job Coordinator: Paul. Wang
Operator: Zechen. Yang