

NDA 21-073/S-028
NDA 21-842/S-002

ACTOPLUS MET™

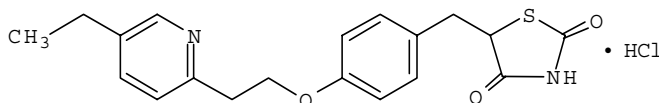
(pioglitazone hydrochloride and metformin hydrochloride) tablets

DESCRIPTION

ACTOPLUS MET™ (pioglitazone hydrochloride and metformin hydrochloride) tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: pioglitazone hydrochloride and metformin hydrochloride. The concomitant use of pioglitazone and metformin has been previously approved based on clinical trials in patients with type 2 diabetes inadequately controlled on metformin. Additional efficacy and safety information about pioglitazone and metformin monotherapies may be found in the prescribing information for each individual drug.

Pioglitazone hydrochloride is an oral antihyperglycemic agent that acts primarily by decreasing insulin resistance. Pioglitazone is used in the management of type 2 diabetes. Pharmacological studies indicate that pioglitazone improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Pioglitazone improves glycemic control while reducing circulating insulin levels.

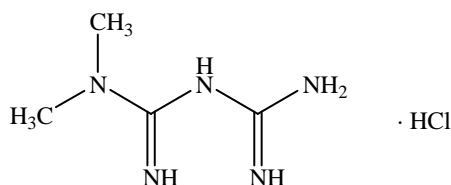
Pioglitazone [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-]thiazolidinedione monohydrochloride belongs to a different chemical class and has a different pharmacological action than the sulfonylureas, biguanides, or the α -glucosidase inhibitors. The molecule contains one asymmetric center, and the synthetic compound is a racemate. The two enantiomers of pioglitazone interconvert *in vivo*. The structural formula is as shown:



pioglitazone hydrochloride

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. 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.

Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin hydrochloride is a white crystalline powder with a molecular formula of $C_4H_{11}N_5 \cdot HCl$ and a molecular weight of 165.62. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula is as shown:



metformin hydrochloride

NDA 21-073/S-028
NDA 21-842/S-002

ACTOPLUS MET is available as a tablet for oral administration containing 15 mg pioglitazone hydrochloride (as the base) with 500 mg metformin hydrochloride (15 mg/500 mg) or 15 mg pioglitazone hydrochloride (as the base) with 850 mg metformin hydrochloride (15 mg/850 mg) formulated with the following excipients: povidone USP, microcrystalline cellulose NF, croscarmellose sodium NF, magnesium stearate NF, hypromellose 2910 USP, polyethylene glycol 8000 NF, titanium dioxide USP, and talc USP.

CLINICAL PHARMACOLOGY

Mechanism of Action

ACTOPLUS MET

ACTOPLUS MET combines two antihyperglycemic agents with different mechanisms of action to improve glycemic control in patients with type 2 diabetes: pioglitazone hydrochloride, a member of the thiazolidinedione class, and metformin hydrochloride, a member of the biguanide class. Thiazolidinediones are insulin-sensitizing agents that act primarily by enhancing peripheral glucose utilization, whereas biguanides act primarily by decreasing endogenous hepatic glucose production.

Pioglitazone hydrochloride

Pioglitazone depends on the presence of insulin for its mechanism of action. Pioglitazone 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 γ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPAR γ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism.

In animal models of diabetes, pioglitazone reduces the hyperglycemia, 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.

NDA 21-073/S-028
NDA 21-842/S-002

Metformin hydrochloride

Metformin hydrochloride improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances, see **PRECAUTIONS, General: Metformin hydrochloride**) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Pharmacokinetics and Drug Metabolism

Absorption and Bioavailability:

ACTOPLUS MET

In bioequivalence studies of ACTOPLUS MET 15 mg/500 mg and 15 mg/850 mg, the area under the curve (AUC) and maximum concentration (C_{max}) of both the pioglitazone and the metformin component following a single dose of the combination tablet were bioequivalent to ACTOS[®] 15 mg concomitantly administered with Glucophage[®] (500 mg or 850 mg respectively) tablets under fasted conditions in healthy subjects (**Table 1**).

Table 1. Mean (SD) Pharmacokinetic Parameters for ACTOPLUS MET[™]

| Regimen | N | AUC(0-inf) (ng·h/mL) | N | C_{max} (ng/mL) | N | T_{max} (h) | N | $T_{1/2}$ (h) |
|----------------------------------------------------------------|----|-------------------------|----|----------------------|----|------------------|----|------------------|
| pioglitazone HCl | | | | | | | | |
| 15 mg/500 mg ACTOPLUS MET [™] | 51 | 5984 (1599) | 63 | 585 (198) | 63 | 1.83 (0.93) | 51 | 8.69 (3.86) |
| 15 mg ACTOS [®] and 500 mg Glucophage [®] | 54 | 5810 (1472) | 63 | 608 (204) | 63 | 1.75 (0.90) | 54 | 7.90 (3.08) |
| 15 mg/850 mg ACTOPLUS MET [™] | 52 | 5671 (1585) | 60 | 569 (222) | 60 | 1.89 (0.80) | 52 | 7.19 (1.84) |
| 15 mg ACTOS [®] and 850 mg Glucophage [®] | 55 | 5957 (1680) | 61 | 603 (239) | 61 | 2.01 (1.54) | 55 | 7.16 (1.85) |
| metformin HCl | | | | | | | | |
| 15 mg/500 mg ACTOPLUS MET [™] | 59 | 7783 (2266) | 63 | 1203 (325) | 63 | 2.32 (0.88) | 59 | 8.57 (14.30) |
| 15 mg ACTOS [®] and 500 mg Glucophage [®] | 59 | 7599 (2385) | 63 | 1215 (329) | 63 | 2.53 (0.95) | 59 | 6.73 (5.87) |
| 15 mg/850 mg ACTOPLUS MET [™] | 47 | 11927 (3311) | 60 | 1827 (536) | 60 | 2.41 (0.91) | 47 | 17.56 (20.08) |
| 15 mg ACTOS [®] and 850 mg Glucophage [®] | 52 | 11569 (3494) | 61 | 1797 (525) | 61 | 2.26 (0.85) | 52 | 17.01 (18.09) |

NDA 21-073/S-028
NDA 21-842/S-002

Administration of ACTOPLUS MET 15 mg/850 mg with food resulted in no change in overall exposure of pioglitazone. With metformin there was no change in AUC; however mean peak serum concentration of metformin was decreased by 28% when administered with food. A delayed time to peak serum concentration was observed for both components (1.9 hours for pioglitazone and 0.8 hours for metformin) under fed conditions. These changes are not likely to be clinically significant.

Pioglitazone hydrochloride

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.

Metformin hydrochloride

The absolute bioavailability of a 500 mg metformin tablet given under fasting conditions is approximately 50% - 60%. Studies using single oral doses of metformin tablets of 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration, a 25% lower AUC in plasma concentration versus time curve, and a 35 minute prolongation of time to peak plasma concentration following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution:

Pioglitazone hydrochloride

The mean apparent volume of distribution (V/F) of pioglitazone following single-dose administration is 0.63 ± 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.

Metformin hydrochloride

The apparent volume of distribution (V/F) of metformin following single oral doses of 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin, steady-state plasma concentrations of metformin are reached within 24 - 48 hours and are generally <1 $\mu\text{g/mL}$. During controlled clinical trials, maximum metformin plasma levels did not exceed 5 $\mu\text{g/mL}$, even at maximum doses.

Metabolism, Elimination and Excretion:

Pioglitazone hydrochloride

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.

NDA 21-073/S-028
NDA 21-842/S-002

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 **PRECAUTIONS, Drug Interactions, Pioglitazone hydrochloride**). Urinary 6 β -hydroxycortisol/cortisol ratios measured in patients treated with pioglitazone showed that pioglitazone is not a strong CYP3A4 enzyme inducer.

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.

Metformin hydrochloride

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Special Populations

Renal Insufficiency:

Pioglitazone hydrochloride

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.

Metformin hydrochloride

In patients with decreased renal function (based on creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance (see **CONTRAINDICATIONS** and **WARNINGS, Metformin hydrochloride**, also see GLUCOPHAGE[®] prescribing information, **CLINICAL PHARMACOLOGY, Pharmacokinetics**). Since metformin is contraindicated in patients with renal impairment, ACTOPLUS MET is also contraindicated in these patients.

NDA 21-073/S-028
NDA 21-842/S-002

Hepatic Insufficiency:

Pioglitazone hydrochloride

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.

Therapy with ACTOPLUS MET 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, General: Pioglitazone hydrochloride**).

Metformin hydrochloride

No pharmacokinetic studies of metformin have been conducted in subjects with hepatic insufficiency.

Elderly:

Pioglitazone hydrochloride

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.

Metformin hydrochloride

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (see GLUCOPHAGE[®] prescribing information, CLINICAL PHARMACOLOGY, Special Populations, Geriatrics).

ACTOPLUS MET treatment should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced (see **WARNINGS, Metformin hydrochloride** and **DOSAGE AND ADMINISTRATION**; also see GLUCOPHAGE[®] prescribing information).

Pediatrics:

Pioglitazone hydrochloride

Pharmacokinetic data in the pediatric population are not available.

Metformin hydrochloride

After administration of a single oral metformin 500 mg tablet with food, geometric mean metformin C_{max} and AUC differed less than 5% between pediatric type 2 diabetic patients (12 to 16 years of age) and gender- and weight-matched healthy adults (20 to 45 years of age), and all with normal renal function.

NDA 21-073/S-028
NDA 21-842/S-002

Gender:

Pioglitazone hydrochloride

As monotherapy and in combination with sulfonylurea, metformin, or insulin, pioglitazone improved glycemic control in both males and females. The mean C_{max} and AUC values were increased 20% to 60% in females. In controlled clinical trials, hemoglobin A1C (A1C) decreases from baseline were generally greater for females than for males (average mean difference in A1C 0.5%). Since therapy should be individualized for each patient to achieve glycemic control, no dose adjustment is recommended based on gender alone.

Metformin hydrochloride

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analyzed according to gender (males = 19, females = 16). Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of metformin was comparable in males and females.

Ethnicity:

Pioglitazone hydrochloride

Pharmacokinetic data among various ethnic groups are not available.

Metformin hydrochloride

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes, the antihyperglycemic effect was comparable in whites (n=249), blacks (n=51), and Hispanics (n=24).

Drug-Drug Interactions

Co-administration of a single dose of metformin (1000 mg) and pioglitazone after 7 days of pioglitazone (45 mg) did not alter the pharmacokinetics of the single dose of metformin. Specific pharmacokinetic drug interaction studies with ACTOPLUS MET have not been performed, although such studies have been conducted with the individual pioglitazone and metformin components.

Pioglitazone hydrochloride

The following drugs were studied in healthy volunteers with co-administration of pioglitazone 45 mg once daily. Results are listed below:

Oral Contraceptives: Co-administration of pioglitazone (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.

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

NDA 21-073/S-028
NDA 21-842/S-002

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

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

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

Cytochrome P450: See **PRECAUTIONS, Drug Interactions, Pioglitazone hydrochloride**

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 (AUC_{0-24}) being 226% of the pioglitazone exposure in the absence of gemfibrozil (see **PRECAUTIONS, Drug Interactions, Pioglitazone hydrochloride**).¹

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% (see **PRECAUTIONS, Drug Interactions, Pioglitazone hydrochloride**).²

In other drug-drug interaction studies, pioglitazone had no significant effect on the pharmacokinetics of fexofenadine, glipizide, digoxin, warfarin, ranitidine HCl or theophylline.

Metformin hydrochloride

See **PRECAUTIONS, Drug Interactions, Metformin hydrochloride**

Pharmacodynamics and Clinical Effects

Pioglitazone hydrochloride

Clinical studies demonstrate that pioglitazone improves insulin sensitivity in insulin-resistant patients. Pioglitazone 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 pioglitazone results in lower plasma glucose concentrations, lower plasma insulin levels, and lower A1C values. Based on results from an open-label extension study, the glucose-lowering effects of pioglitazone appear to persist for at least one year. In controlled clinical studies, pioglitazone in combination with metformin had an additive effect on glycemic control.

NDA 21-073/S-028
NDA 21-842/S-002

Patients with lipid abnormalities were included in placebo-controlled monotherapy clinical studies with pioglitazone. Overall, patients treated with pioglitazone had mean decreases in triglycerides, mean increases in HDL cholesterol, and no consistent mean changes in LDL cholesterol and total cholesterol compared to the placebo group. A similar pattern of results was seen in 16-week and 24-week combination therapy studies of pioglitazone with metformin.

Clinical Studies

There have been no clinical efficacy studies conducted with ACTOPLUS MET. However, the efficacy and safety of the separate components have been previously established and the co-administration of the separate components has been evaluated for efficacy and safety in two clinical studies. These clinical studies established an added benefit of pioglitazone in patients with inadequately controlled type 2 diabetes while on metformin therapy. Bioequivalence of ACTOPLUS MET with co-administered pioglitazone and metformin tablets was demonstrated for both ACTOPLUS MET strengths (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism).

Clinical Trials of Pioglitazone Add-on Therapy in Patients Not Adequately Controlled on Metformin

Two treatment-randomized, controlled clinical studies in patients with type 2 diabetes were conducted to evaluate the safety and efficacy of pioglitazone plus metformin. Both studies included patients receiving metformin, either alone or in combination with another antihyperglycemic agent, who had inadequate glycemic control. All other antihyperglycemic agents were discontinued prior to starting study treatment. In the first study, 328 patients received either 30 mg of pioglitazone or placebo once daily for 16 weeks in addition to their established metformin regimen. In the second study, 827 patients received either 30 mg or 45 mg of pioglitazone once daily for 24 weeks in addition to their established metformin regimen.

In the first study, the addition of pioglitazone 30 mg once daily to metformin treatment significantly reduced the mean A1C by 0.83% and the mean FPG by 37.7 mg/dL at Week 16 from that observed with metformin alone. In the second study, the mean reductions from Baseline at Week 24 in A1C 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, respectively. Based on these reductions in A1C and FPG (Table 2), the addition of pioglitazone to metformin resulted in significant improvements in glycemic control irrespective of the metformin dose.

NDA 21-073/S-028
NDA 21-842/S-002

Table 2. Glycemic Parameters in 16-Week and 24-Week Pioglitazone Hydrochloride + Metformin Hydrochloride Combination Studies

| Parameter | Placebo + metformin | Pioglitazone 30 mg + metformin |
|-----------------------------------------------|-----------------------------------|-----------------------------------|
| 16-Week Study | | |
| A1C (%) | N=153 | N=161 |
| Baseline mean | 9.77 | 9.92 |
| Mean change from Baseline at 16 Weeks | 0.19 | -0.64 ^{*,†} |
| Difference in change from placebo + metformin | | -0.83 |
| Responder rate (%) (a) | 21.6 | 54.0 |
| FPG (mg/dL) | N=157 | N=165 |
| Baseline mean | 259.9 | 254.4 |
| Mean change from Baseline at 16 Weeks | -5.2 | -42.8 ^{*,†} |
| Difference in change from placebo + metformin | | -37.7 |
| Responder rate (%) (b) | 23.6 | 59.4 |
| Parameter | Pioglitazone 30 mg + metformin | Pioglitazone 45 mg + metformin |
| 24-Week Study | | |
| A1C (%) | N=400 | N=398 |
| Baseline mean | 9.88 | 9.81 |
| Mean Change from Baseline at 24 Weeks | -0.80 [*] | -1.01 [*] |
| Responder rate (%) (a) | 55.8 | 63.3 |
| FPG (mg/dL) | N=398 | N=399 |
| Baseline mean | 232.5 | 232.1 |
| Mean Change from Baseline at 24 Weeks | -38.2 [*] | -50.7 ^{*,‡} |
| Responder rate (%) (b) | 52.3 | 63.7 |

* significant change from Baseline $p \leq 0.050$.

† significant difference from placebo plus metformin, $p \leq 0.050$.

‡ significant difference from 30 mg pioglitazone, $p \leq 0.050$.

(a) patients who achieved an A1C $\leq 6.1\%$ or $\geq 0.6\%$ decrease from Baseline.

(b) patients who achieved a decrease in FPG by ≥ 30 mg/dL.

INDICATIONS AND USAGE

ACTOPLUS MET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of pioglitazone and metformin or whose diabetes is not adequately controlled with metformin alone, or for those patients who have initially responded to pioglitazone alone and require additional glycemic control.

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

NDA 21-073/S-028

NDA 21-842/S-002

CONTRAINDICATIONS

ACTOPLUS MET (pioglitazone hydrochloride and metformin hydrochloride) is contraindicated in patients with:

1. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 1.5 mg/dL [males], ≥ 1.4 mg/dL [females], or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see **WARNINGS, *Metformin hydrochloride*** and **PRECAUTIONS, General: *Metformin hydrochloride***).
2. Known hypersensitivity to pioglitazone, metformin or any other component of ACTOPLUS MET.
3. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

ACTOPLUS MET should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function (see **PRECAUTIONS, General: *Metformin hydrochloride***).

WARNINGS

Metformin hydrochloride

Lactic Acidosis: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with ACTOPLUS MET (pioglitazone hydrochloride and metformin hydrochloride) tablets; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (> 5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels > 5 $\mu\text{g/mL}$ are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure (see PRECAUTIONS, General: *Metformin hydrochloride*).

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur (see PRECAUTIONS, General: *Metformin hydrochloride*). Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and, if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of

therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling (see PRECAUTIONS, General: *Metformin hydrochloride*).

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery (see CONTRAINDICATIONS and PRECAUTIONS, General: *Metformin hydrochloride*).

Pioglitazone hydrochloride

Cardiac Failure and Other Cardiac Effects: Pioglitazone, like other thiazolidinediones, can cause fluid retention when used alone or in combination with other antihyperglycemic agents, including insulin. Fluid retention may lead to or exacerbate heart failure. Patients should be observed for signs and symptoms of heart failure (see **Information for Patients**). ACTOS should be discontinued if any deterioration in cardiac status occurs. Patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during pre-approval clinical trials; ACTOS is not recommended in these patients (see **PRECAUTIONS, General: *Pioglitazone hydrochloride*, Cardiovascular**).

In one 16-week U.S. double-blind, placebo-controlled clinical trial involving 566 patients with type 2 diabetes, pioglitazone 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 pioglitazone plus insulin (1.1%) and two of the 188 patients receiving 30 mg pioglitazone 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 pioglitazone was co-administered 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 A1C 8.8% at baseline) with NYHA Class II and III heart failure and ejection fraction less than 40% (mean EF 30% at baseline). Over the course of the study, overnight hospitalization for congestive heart failure was reported in 9.9% of patients on ACTOS compared to 4.7% of patients on glyburide with a treatment difference observed from 6 weeks. This adverse event associated with ACTOS was more marked in patients using insulin at baseline and in patients over 64 years of age. No difference in cardiovascular mortality between the treatment groups was observed.

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

PRECAUTIONS

General: Pioglitazone hydrochloride

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

Hypoglycemia: Patients receiving pioglitazone 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 pioglitazone 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 pioglitazone in combination with insulin. Patients with NYHA Class III and IV cardiac status were not studied in pre-approval pioglitazone clinical trials. Pioglitazone is not indicated in patients with NYHA Class III or IV cardiac status.

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

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

Weight Gain: Dose related weight gain was observed with pioglitazone alone and in combination with other hypoglycemic agents (**Table 3**). The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Table 3. Weight Changes (kg) from Baseline during Double-Blind Clinical Trials with Pioglitazone

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

Note: Trial durations of 16 to 26 weeks

Ovulation: Therapy with pioglitazone, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. Thus, adequate contraception in premenopausal women should be recommended while taking ACTOPLUS MET. This possible effect has not been investigated in clinical studies so the frequency of this occurrence is not known.

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

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

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

In postmarketing experience with pioglitazone, 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 on pioglitazone, it is recommended that patients treated with ACTOPLUS MET undergo periodic monitoring of liver enzymes.

Serum ALT (alanine aminotransferase) levels should be evaluated prior to the initiation of therapy with ACTOPLUS MET 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 ACTOPLUS MET should be guided by clinical judgment pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

Therapy with ACTOPLUS MET 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 ACTOPLUS MET should be evaluated to determine the cause of the liver enzyme elevation. Initiation or continuation of therapy with ACTOPLUS MET 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, ACTOPLUS MET 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 of the American Diabetes Association. 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 (see **ADVERSE REACTIONS**).

General: *Metformin hydrochloride*

Monitoring of renal function: Metformin is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive ACTOPLUS MET. In patients with advanced age, ACTOPLUS MET should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, particularly those ≥ 80 years of age, renal function should be monitored regularly and, generally, ACTOPLUS MET should not be titrated to the maximum dose of the metformin component (see **WARNINGS, *Metformin hydrochloride*** and **DOSAGE AND ADMINISTRATION**).

Before initiation of therapy with ACTOPLUS MET and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and ACTOPLUS MET discontinued if evidence of renal impairment is present.

Use of concomitant medications that may affect renal function or metformin disposition:

Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see **PRECAUTIONS, Drug Interactions, Metformin hydrochloride**), should be used with caution.

Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials): Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see **CONTRAINDICATIONS**). Therefore, in patients in whom any such study is planned, ACTOPLUS MET should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstated only after renal function has been re-evaluated and found to be normal.

Hypoxic states: Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients receiving ACTOPLUS MET therapy, the drug should be promptly discontinued.

Surgical procedures: Use of ACTOPLUS MET should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol intake: Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving ACTOPLUS MET.

Impaired hepatic function: Since impaired hepatic function has been associated with some cases of lactic acidosis, ACTOPLUS MET should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B₁₂ levels: In controlled clinical trials of metformin at 29 weeks' duration, a decrease to subnormal levels of previously normal serum vitamin B₁₂ levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B₁₂ absorption from the B₁₂-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B₁₂ supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on ACTOPLUS MET and any apparent abnormalities should be appropriately investigated and managed (see **PRECAUTIONS, General: Metformin hydrochloride** and **Laboratory Tests**). Certain individuals (those with inadequate vitamin B₁₂ or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B₁₂ levels. In these patients, routine serum vitamin B₁₂ measurements at two- to three-year intervals may be useful.

Change in clinical status of patients with previously controlled type 2 diabetes: A patient with type 2 diabetes previously well-controlled on ACTOPLUS MET who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate and metformin levels. If acidosis of either form occurs, ACTOPLUS MET must be stopped immediately and other appropriate corrective measures initiated (see **WARNINGS, *Metformin hydrochloride***).

Hypoglycemia: Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with hypoglycemic agents (such as sulfonylureas or insulin) or ethanol. Elderly, debilitated or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs.

Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold ACTOPLUS MET and temporarily administer insulin. ACTOPLUS MET may be reinstated after the acute episode is resolved.

Laboratory Tests

FPG and A1C measurements should be performed periodically to monitor glycemic control and therapeutic response to ACTOPLUS MET.

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

Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with metformin therapy, if this is suspected, Vitamin B₁₂ deficiency should be excluded.

Information for Patients

Patients should be instructed regarding the importance of adhering to dietary instructions, a regular exercise program, and regular testing of blood glucose and A1C. 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.

The risks of lactic acidosis, its symptoms and conditions that predispose to its development, as noted in the **WARNINGS, *Metformin hydrochloride*** and **PRECAUTIONS, General: *Metformin hydrochloride*** sections, should be explained to patients. Patients should be advised to discontinue ACTOPLUS MET immediately and to promptly notify their health care professional if unexplained hyperventilation, myalgia, malaise, unusual somnolence or other nonspecific symptoms occur. Gastrointestinal symptoms are common during initiation of metformin treatment and may occur during initiation of ACTOPLUS MET therapy; however, patients should consult with their physician if they develop unexplained symptoms.

Although gastrointestinal symptoms that occur after stabilization are unlikely to be drug related, such an occurrence of symptoms should be evaluated to determine if it may be due to lactic acidosis or other serious disease.

Patients should be counseled against excessive alcohol intake, either acute or chronic, while receiving ACTOPLUS MET.

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 ACTOPLUS MET 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 informed about the importance of regular testing of renal function and hematologic parameters when receiving treatment with ACTOPLUS MET.

Therapy with a thiazolidinedione, which is the active pioglitazone component of the ACTOPLUS MET tablet, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking ACTOPLUS MET. 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.

Combination antihyperglycemic therapy may cause hypoglycemia. When initiating ACTOPLUS MET, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients.

Patients should be told to take ACTOPLUS MET as prescribed and instructed that any change in dosing should only be done if directed by their physician.

Drug Interactions

Pioglitazone hydrochloride

In vivo drug-drug interaction studies have suggested that pioglitazone may be a weak inducer of CYP450 isoform 3A4 substrate.

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, Pioglitazone hydrochloride**).

Metformin hydrochloride

Furosemide: A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration.

Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine: A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic Drugs: Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of ACTOPLUS MET and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Other: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving ACTOPLUS MET, the patient should be closely observed to maintain adequate glycemic control.

In healthy volunteers, the pharmacokinetics of metformin and propranolol and metformin and ibuprofen were not affected when co-administered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol and probenecid.

Carcinogenesis, Mutagenesis, Impairment of Fertility

ACTOPLUS MET

No animal studies have been conducted with ACTOPLUS MET. The following data are based on findings in studies performed with pioglitazone or metformin individually.

Pioglitazone hydrochloride

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 pioglitazone 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).

Metformin hydrochloride

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately four times a human daily dose of 2000 mg of the metformin component of ACTOPLUS MET based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose of the metformin component of ACTOPLUS MET based on body surface area comparisons.

Animal Toxicology

Pioglitazone hydrochloride

Heart enlargement has been observed in mice (100 mg/kg), rats (4 mg/kg and above) and dogs (3 mg/kg) treated orally with the pioglitazone HCl component of ACTOPLUS MET (approximately 11, 1, and 2 times the maximum recommended human oral dose for mice, rats, and dogs, respectively, based on mg/m²). 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/m²). 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/m²), 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/m²).

Pregnancy: Pregnancy Category C

ACTOPLUS MET

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies, as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible. ACTOPLUS MET should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

There are no adequate and well-controlled studies in pregnant women with ACTOPLUS MET or its individual components. No animal studies have been conducted with the combined products in ACTOPLUS MET. The following data are based on findings in studies performed with pioglitazone or metformin individually.

Pioglitazone hydrochloride

Pioglitazone was not teratogenic in rats at oral doses up to 80 mg/kg or in rabbits given up to 160 mg/kg during organogenesis (approximately 17 and 40 times the maximum recommended human oral dose based on mg/m², respectively). Delayed parturition and embryotoxicity (as evidenced by increased postimplantation losses, delayed development and reduced fetal weights) were observed in rats at oral doses of 40 mg/kg/day and above (approximately 10 times the maximum recommended human oral dose based on mg/m²). No functional or behavioral toxicity was observed in offspring of rats. In rabbits, embryotoxicity was observed at an oral dose of 160 mg/kg (approximately 40 times the maximum recommended human oral dose based on mg/m²). Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats at oral doses of 10 mg/kg and above during late gestation and lactation periods (approximately 2 times the maximum recommended human oral dose based on mg/m²).

Metformin hydrochloride

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about two and six times a human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Nursing Mothers

No studies have been conducted with the combined components of ACTOPLUS MET. In studies performed with the individual components, both pioglitazone and metformin are secreted in the milk of lactating rats. It is not known whether pioglitazone and/or metformin is secreted in human milk.

Because many drugs are excreted in human milk, ACTOPLUS MET should not be administered to a breastfeeding woman. If ACTOPLUS MET is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use

Safety and effectiveness of ACTOPLUS MET in pediatric patients have not been established.

Elderly Use

Pioglitazone hydrochloride

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

Metformin hydrochloride

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. Metformin is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, ACTOPLUS MET should only be used in patients with normal renal function (see **CONTRAINDICATIONS, WARNINGS, Metformin hydrochloride** and **CLINICAL PHARMACOLOGY, Special Populations**). Because aging is associated with reduced renal function, ACTOPLUS MET should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of ACTOPLUS MET (see **WARNINGS, Metformin hydrochloride** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

The most common adverse events reported in at least 5% of patients in the controlled 16-week clinical trial between placebo plus metformin and pioglitazone 30 mg plus metformin were upper respiratory tract infection (15.6% and 15.5%), diarrhea (6.3% and 4.8%), combined edema/peripheral edema (2.5% and 6.0%) and headache (1.9% and 6.0%), respectively.

The incidence and type of adverse events reported in at least 5% of patients in any combined treatment group from the 24-week study comparing pioglitazone 30 mg plus metformin and pioglitazone 45 mg plus metformin are shown in Table 4; the rate of adverse events resulting in study discontinuation between the two treatment groups was 7.8% and 7.7%, respectively.

Table 4. Adverse Events That Occurred in $\geq 5\%$ of Patients in Any Treatment Group During the 24-Week Study

| Adverse Event Preferred Term | Pioglitazone 30 mg + metformin N=411 n (%) | Pioglitazone 45 mg + metformin N=416 n (%) |
|-----------------------------------|--------------------------------------------------|--------------------------------------------------|
| Upper Respiratory Tract Infection | 51 (12.4) | 56 (13.5) |
| Diarrhea | 24 (5.8) | 20 (4.8) |
| Nausea | 24 (5.8) | 15 (3.6) |
| Headache | 19 (4.6) | 22 (5.3) |
| Urinary Tract Infection | 24 (5.8) | 22 (5.3) |
| Sinusitis | 18 (4.4) | 21 (5.0) |
| Dizziness | 22 (5.4) | 20 (4.8) |
| Edema Lower Limb | 12 (2.9) | 47 (11.3) |
| Weight Increased | 12 (2.9) | 28 (6.7) |

Most clinical adverse events were similar between groups treated with pioglitazone in combination with metformin and those treated with pioglitazone monotherapy. Other adverse events reported in at least 5% of patients in controlled clinical trials between placebo and pioglitazone monotherapy included myalgia (2.7% and 5.4%), tooth disorder (2.3% and 5.3%), diabetes mellitus aggravated (8.1% and 5.1%) and pharyngitis (0.8% and 5.1%), respectively.

In U.S. double-blind studies, anemia was reported in $\leq 2\%$ of patients treated with pioglitazone plus metformin (see **PRECAUTIONS, General: Pioglitazone hydrochloride**).

In monotherapy studies, edema was reported for 4.8% (with doses from 7.5 mg to 45 mg) of patients treated with pioglitazone versus 1.2% of placebo-treated patients. Most of these events were considered mild or moderate in intensity (see **PRECAUTIONS, General: Pioglitazone hydrochloride**).

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

Laboratory Abnormalities

Hematologic: Pioglitazone may cause decreases in hemoglobin and hematocrit. The fall in hemoglobin and hematocrit with pioglitazone appears to be dose related. Across all clinical studies, mean hemoglobin values declined by 2% to 4% in patients treated with pioglitazone. 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 pioglitazone therapy and have rarely been associated with any significant hematologic clinical effects (see **PRECAUTIONS, General: Pioglitazone hydrochloride**).

In controlled clinical trials of metformin at 29 weeks' duration, a decrease to subnormal levels of previously normal serum vitamin B₁₂ levels, without clinical manifestations, was observed in approximately 7% of patients.

Such decrease, possibly due to interference with B₁₂ absorption from the B₁₂-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B₁₂ supplementation (see **PRECAUTIONS, General: Metformin hydrochloride**).

Serum Transaminase Levels: During all clinical studies in the U.S., 14 of 4780 (0.30%) patients treated with pioglitazone 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 pioglitazone, 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 pioglitazone 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, General: Pioglitazone hydrochloride**).

CPK Levels: During required laboratory testing in clinical trials with pioglitazone, 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 pioglitazone, 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 pioglitazone therapy is unknown.

OVERDOSAGE

Pioglitazone hydrochloride

During controlled clinical trials, one case of overdose with pioglitazone 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 overdose, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

Metformin hydrochloride

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases (see **WARNINGS, Metformin hydrochloride**). Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated metformin from patients in whom metformin overdose is suspected.

DOSAGE AND ADMINISTRATION

General

The use of antihyperglycemic therapy in the management of type 2 diabetes should be individualized on the basis of effectiveness and tolerability while not exceeding the maximum recommended daily dose of pioglitazone 45 mg and metformin 2550 mg.

Dosage Recommendations

Selecting the starting dose of ACTOPLUS MET should be based on the patient's current regimen of pioglitazone and/or metformin. ACTOPLUS MET should be given in divided daily doses with meals to reduce the gastrointestinal side effects associated with metformin.

Starting dose for patients inadequately controlled on metformin monotherapy

Based on the usual starting dose of pioglitazone (15-30 mg daily), ACTOPLUS MET may be initiated at either the 15 mg/500 mg or 15 mg/850 mg tablet strength once or twice daily, and gradually titrated after assessing adequacy of therapeutic response.

Starting dose for patients who initially responded to pioglitazone monotherapy and require additional glycemic control

Based on the usual starting doses of metformin (500 mg twice daily or 850 mg daily), ACTOPLUS MET may be initiated at either the 15 mg/500 mg twice daily or 15 mg/850 mg tablet strength once daily, and gradually titrated after assessing adequacy of therapeutic response.

Starting dose for patients switching from combination therapy of pioglitazone plus metformin as separate tablets

ACTOPLUS MET may be initiated with either the 15 mg/500 mg or 15 mg/850 mg tablet strengths based on the dose of pioglitazone and metformin already being taken.

No studies have been performed specifically examining the safety and efficacy of ACTOPLUS MET in patients previously treated with other oral hypoglycemic agents and switched to ACTOPLUS MET. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur.

Sufficient time should be given to assess adequacy of therapeutic response. Ideally, the response to therapy should be evaluated using A1C, which is a better indicator of long-term glycemic control than FPG alone. A1C reflects glycemia over the past two to three months. In clinical use, it is recommended that patients be treated with ACTOPLUS MET for a period of time adequate to evaluate change in A1C (8-12 weeks) unless glycemic control as measured by FPG deteriorates.

Special Patient Populations

ACTOPLUS MET is not recommended for use in pregnancy or for use in pediatric patients.

The initial and maintenance dosing of ACTOPLUS MET should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dosage adjustment should be based on a careful assessment of renal function. Generally, elderly, debilitated, and malnourished patients should not be titrated to the maximum dose of ACTOPLUS MET. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly (see **WARNINGS, Metformin hydrochloride** and **PRECAUTIONS, General: Metformin hydrochloride**).

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

Maximum Recommended Dose

ACTOPLUS MET tablets are available as a 15 mg pioglitazone plus 500 mg metformin or a 15 mg pioglitazone plus 850 mg metformin formulation for oral administration. The maximum recommended dose for pioglitazone is 45 mg daily. The maximum recommended daily dose for metformin is 2550 mg in adults.

HOW SUPPLIED

ACTOPLUS MET is available in 15 mg pioglitazone hydrochloride (as the base)/500 mg metformin hydrochloride and 15 mg pioglitazone hydrochloride (as the base)/850 mg metformin hydrochloride tablets as follows:

15 mg/500 mg tablet: white to off-white, oblong, film-coated tablet with “4833M” on one side, and “15/500” on the other, available in:

| | |
|----------------|------------------|
| Bottles of 60 | NDC 64764-155-60 |
| Bottles of 180 | NDC 64764-155-18 |

15 mg/850 mg tablet: white to off-white, oblong, film-coated tablet with “4833M” on one side, and “15/850” on the other, available in:

| | |
|----------------|------------------|
| Bottles of 60 | NDC 64764-158-60 |
| Bottles of 180 | NDC 64764-158-18 |

STORAGE

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

REFERENCES

1. Deng, LJ, et al. Effect of gemfibrozil on the pharmacokinetics of pioglitazone. *Eur J Clin Pharmacol* 2005; 61: 831-836, Table 1.
2. Jaakkola, T, et al. Effect of rifampicin on the pharmacokinetics of pioglitazone. *Clin Pharmacol Brit Jour* 2006; 61:1 70-78.

Rx only

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ACTOS®

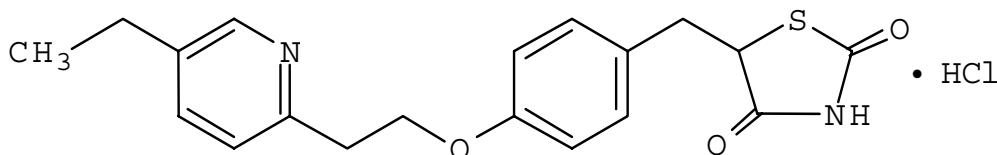
(pioglitazone hydrochloride) Tablets

DESCRIPTION

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

Pioglitazone [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-]

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.

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

CLINICAL PHARMACOLOGY

Mechanism of Action

ACTOS is a thiazolidinedione antidiabetic agent that depends on the presence of insulin for its mechanism of action. ACTOS decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased 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 γ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPAR γ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism.

In animal models of diabetes, pioglitazone reduces the hyperglycemia, 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 area under the serum concentration-time curve (AUC).

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

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

Distribution: The mean apparent volume of distribution (V_d/F) of pioglitazone following single-dose administration is 0.63 ± 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 Effects).

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

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

Gender : The mean C_{max} and AUC values were increased 20% to 60% in females. As monotherapy and in combination with sulfonylurea, metformin, or insulin, ACTOS 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 Interactions

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

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

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

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

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

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

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

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

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

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

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

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

Theophylline: Co-administration of ACTOS for 7 days with theophylline 400 mg 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 (see **PRECAUTIONS**).¹

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% (see **PRECAUTIONS**).²

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

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

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

Clinical Studies

Monotherapy

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

In a 26-week, dose-ranging study, 408 patients with type 2 diabetes were 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 (**Figure 1, Table 2**).

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

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

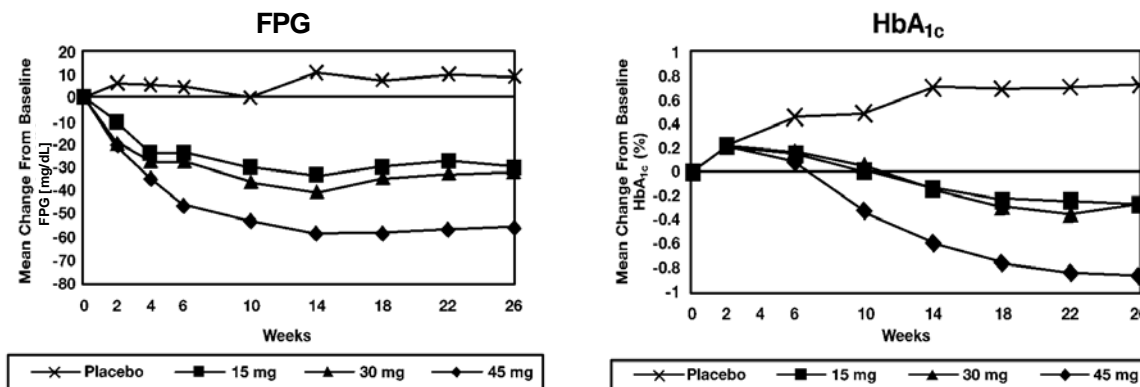


Table 2 shows HbA_{1c} and FPG values for the entire study population.

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

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

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

* p ≤ 0.050 vs. placebo

The study population included patients not previously treated with antidiabetic medication (naïve; 31%) and patients who were receiving antidiabetic medication at the time of study enrollment (previously treated; 69%). The data for the naïve and previously-treated patient subsets are shown in Table 3. All patients entered an 8 week washout/run-in period prior to double-blind treatment. This run-in period was associated with little change in HbA_{1c} and FPG values from screening to baseline for the naïve patients; however, for the previously-treated group, washout from previous antidiabetic medication resulted in deterioration of glycemic control and increases in HbA_{1c} and FPG.

Although most patients in the previously-treated group had a decrease from baseline in HbA_{1c} and FPG with ACTOS, in many cases the values did not return to screening levels by the end of the study. The study design did not permit the evaluation of patients who switched directly to ACTOS from another antidiabetic agent.

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

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

* Adjusted for baseline and pooled center

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

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

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

⁺ Final dose in forced titration

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

* p ≤ 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 (**Table 5**).

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

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

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

* $p \leq 0.050$ vs. placebo

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

Combination Therapy

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

ACTOS Plus Sulfonylurea Studies

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

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

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

ACTOS Plus Metformin Studies

Two clinical studies were conducted with ACTOS in combination with metformin. Both studies included patients with type 2 diabetes on metformin, either alone or in combination with another 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.

ACTOS Plus Insulin Studies

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

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

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

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS

Cardiac Failure and Other Cardiac Effects

ACTOS, like other thiazolidinediones, can cause fluid retention when used alone or in combination with other antidiabetic agents, including insulin. Fluid retention may lead to or exacerbate heart failure. Patients should be observed for signs and symptoms of heart failure (see **Information for Patients**). ACTOS should be discontinued if any deterioration in cardiac status occurs. Patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during pre-approval clinical trials; ACTOS is not recommended in these patients (see **PRECAUTIONS, Cardiovascular**).

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

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

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

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

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

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

PRECAUTIONS

General

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

Hypoglycemia: Patients receiving ACTOS in combination with insulin or oral 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 NYHA Class III or IV cardiac status.

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

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

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

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

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

Note: Trial durations of 16 to 26 weeks

NDA 21-073/S-028

NDA 21-842/S-002

Page 2

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

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

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

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

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

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

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

Therapy with ACTOS should not be initiated if the patient exhibits clinical evidence of active liver disease or the ALT levels exceed 2.5 times the upper limit of normal. Patients with mildly elevated liver enzymes (ALT levels at 1 to 2.5 times the upper limit of normal) at baseline or any time during therapy with ACTOS should be evaluated to determine the cause of the liver enzyme elevation. Initiation or continuation of therapy with ACTOS in patients with mildly elevated liver enzymes should proceed with caution and include appropriate clinical follow-up which may include more frequent liver enzyme monitoring.

NDA 21-073/S-028

NDA 21-842/S-002

Page 3

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 of the American Diabetes Association. 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 (see **ADVERSE REACTIONS**).

Laboratory Tests

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

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

Information for Patients

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

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

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

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

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

Therapy with ACTOS, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking ACTOS. Thus, adequate contraception in

NDA 21-073/S-028

NDA 21-842/S-002

Page 4

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

Drug Interactions

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

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/m²). 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/m²). 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/m²). 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/m²).

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/m²). 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/m²). Heart enlargement was seen in a 13-week study in monkeys at oral doses of 8.9 mg/kg and above

NDA 21-073/S-028
NDA 21-842/S-002
Page 5

(approximately 4 times the maximum recommended human oral dose based on mg/m²), 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/m²).

Pregnancy

Pregnancy Category C. Pioglitazone was not teratogenic in rats at oral doses up to 80 mg/kg or in rabbits given up to 160 mg/kg during organogenesis (approximately 17 and 40 times the maximum recommended human oral dose based on mg/m², respectively). Delayed parturition and embryotoxicity (as evidenced by increased postimplantation losses, delayed development and reduced fetal weights) were observed in rats at oral doses of 40 mg/kg/day and above (approximately 10 times the maximum recommended human oral dose based on mg/m²). No functional or behavioral toxicity was observed in offspring of rats. In rabbits, embryotoxicity was observed at an oral dose of 160 mg/kg (approximately 40 times the maximum recommended human oral dose based on mg/m²). Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats at oral doses of 10 mg/kg and above during late gestation and lactation periods (approximately 2 times the maximum recommended human oral dose based on mg/m²).

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

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

Nursing Mothers

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

Pediatric Use

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

Elderly Use

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

ADVERSE REACTIONS

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

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

NDA 21-073/S-028
NDA 21-842/S-002
Page 6

Table 7

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

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

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

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

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

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

In U.S. double-blind studies, anemia was reported in \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% (with doses from 7.5 mg to 45 mg) 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**).

NDA 21-073/S-028

NDA 21-842/S-002

Page 7

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, General**, Hepatic Effects).

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

OVERDOSAGE

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

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

DOSAGE AND ADMINISTRATION

ACTOS should be taken once daily without regard to meals.

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

NDA 21-073/S-028

NDA 21-842/S-002

Page 8

Monotherapy

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

Combination Therapy

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

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

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

Maximum Recommended Dose

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

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

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

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

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

HOW SUPPLIED

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

NDA 21-073/S-028

NDA 21-842/S-002

Page 9

15 mg Tablet: white to off-white, round, convex, non-scored tablet with "ACTOS" on one side, and "15" on the other, available in:

NDC 64764-151-04 Bottles of 30

NDC 64764-151-05 Bottles of 90

NDC 64764-151-06 Bottles of 500

30 mg Tablet: white to off-white, round, flat, non-scored tablet with "ACTOS" on one side, and "30" on the other, available in:

NDC 64764-301-14 Bottles of 30

NDC 64764-301-15 Bottles of 90

NDC 64764-301-16 Bottles of 500

45 mg Tablet: white to off-white, round, flat, non-scored tablet with "ACTOS" on one side, and "45" on the other, available in:

NDC 64764-451-24 Bottles of 30

NDC 64764-451-25 Bottles of 90

NDC 64764-451-26 Bottles of 500

STORAGE

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

REFERENCES

3. Deng, LJ, et al. Effect of gemfibrozil on the pharmacokinetics of pioglitazone. *Eur J Clin Pharmacol* 2005; 61: 831-836, Table 1.
4. Jaakkola, T, et al. Effect of rifampicin on the pharmacokinetics of pioglitazone. *Clin Pharmacol Brit Jour* 2006; 61:1 70-78.

Rx only

Manufactured by:

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Osaka, Japan

Marketed by:

Takeda Pharmaceuticals America, Inc.

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