ACTOPLUS MET®

(pioglitazone hydrochloride and metformin hydrochloride) tablets

ACTOPLUS MET® XR

(pioglitazone hydrochloride and metformin hydrochloride extended-release) tablets

WARNING: CONGESTIVE HEART FAILURE AND LACTIC ACIDOSIS

Congestive Heart Failure

- Thiazolidinediones, including pioglitazone, which is a component of ACTOPLUS MET and ACTOPLUS MET XR, cause or exacerbate congestive heart failure in some patients (see **WARNINGS, *Pioglitazone***). After initiation of ACTOPLUS MET or ACTOPLUS MET XR, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to the current standards of care. Furthermore, discontinuation or dose reduction of ACTOPLUS MET or ACTOPLUS MET XR must be considered.
- ACTOPLUS MET and ACTOPLUS MET XR are not recommended in patients with symptomatic heart failure. Initiation of ACTOPLUS MET or ACTOPLUS MET XR in patients with established NYHA Class III or IV heart failure is contraindicated (see **CONTRAINDICATIONS** and **WARNINGS, *Pioglitazone***).

Lactic Acidosis

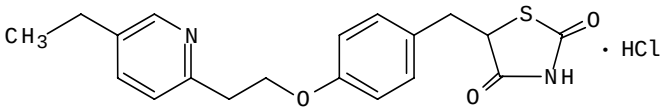
- Lactic acidosis is a rare, but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure.
- The onset is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.
- Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate.
- If acidosis is suspected, ACTOPLUS MET or ACTOPLUS MET XR should be discontinued and the patient hospitalized immediately (see **WARNINGS, *Metformin Hydrochloride***).

DESCRIPTION

ACTOPLUS MET® tablets are formulated with pioglitazone hydrochloride and immediate-release metformin hydrochloride. ACTOPLUS MET® XR tablets are formulated with pioglitazone hydrochloride and extended-release metformin hydrochloride. Both ACTOPLUS MET® and ACTOPLUS MET® XR contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: pioglitazone and metformin. ACTOPLUS MET® is available in 15 mg pioglitazone/500 mg metformin hydrochloride and 15 mg pioglitazone/850 mg metformin hydrochloride tablets. ACTOPLUS MET® XR is available in 15 mg pioglitazone/1000 mg extended-release metformin hydrochloride and 30 mg pioglitazone/1000 mg extended-release metformin hydrochloride tablets.

Pioglitazone 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.

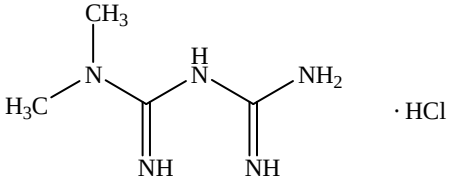
Pioglitazone (±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione monohydrochloride belongs to a different chemical class and has a different pharmacological action than the sulfonylureas, biguanides, or the α-glucosidase inhibitors. The molecule contains one asymmetric center, 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 $C_{19}H_{20}N_2O_3S$•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 $C_4H_{11}N_5$•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

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

ACTOPLUS MET XR is available as a tablet for once-a-day oral administration containing pioglitazone hydrochloride and metformin hydrochloride equivalent to 15 mg pioglitazone and 1000 mg metformin hydrochloride (ACTOPLUS MET XR 15 mg/1000 mg) or 30 mg pioglitazone and 1000 mg metformin hydrochloride (ACTOPLUS MET XR 30 mg/1000 mg). ACTOPLUS MET XR is formulated with the following excipients: candelilla wax, cellulose acetate, povidone, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, hypromellose, polyethylene glycols (PEG 400, PEG 8000), sodium lauryl sulfate, titanium dioxide, and triacetin. Tablets are imprinted with ink containing shellac, iron oxide red (15 mg/1000 mg strength only), FD&C Blue No. 2 Lake (30 mg/1000 mg strength only), propylene glycol, and ammonium hydroxide.

ACTOPLUS MET XR: SYSTEM COMPONENTS AND PERFORMANCE

ACTOPLUS MET XR consists of an extended-release metformin core coated tablet with an immediate-release pioglitazone layer. The metformin core tablet is an extended-release formulation using the patented single composition osmotic technology (SCOT™) for once-daily (q.d.) oral administration. The tablet is similar in appearance to other film-coated oral administered tablets but it consists of an osmotically active core formulation that is surrounded by a semipermeable membrane and coated with a pioglitazone drug layer. Two laser drilled exit ports exist in the membrane, one on either side of the tablet. The core formulation is composed primarily of drug with small concentrations of excipients. The semipermeable membrane is permeable to water but not to higher molecular weight components of biological fluids. Upon ingestion, the pioglitazone layer is dissolved, water is then taken up through the membrane, which in turn dissolves the metformin and excipients in the core formulation. The dissolved metformin and excipients exit through the laser drilled ports in the membrane. The rate of drug delivery is constant and dependent upon the maintenance of a constant osmotic gradient across the membrane. This situation exists so long as there is undissolved metformin present in the core tablet. Following the dissolution of the core materials, the rate of drug delivery slowly decreases until the osmotic gradient across the membrane falls to zero at which time delivery ceases. The membrane coating remains intact during the transit of the dosage form through the gastrointestinal tract and is excreted in the feces.

CLINICAL PHARMACOLOGY

Mechanism of Action

ACTOPLUS MET and ACTOPLUS MET XR

ACTOPLUS MET and ACTOPLUS MET XR combine two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: pioglitazone, 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

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

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

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 immediate-release metformin component following a single dose of the combination tablet were bioequivalent to pioglitazone (ACTOS®) 15 mg concomitantly administered with immediate-release metformin (Glucophage®) 500 mg or 850 mg tablets, respectively, 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								
15 mg/500 mg ACTOPLUS MET®	51	5984 (1599)	63	585 (198)	63	1.8 (0.9)	51	8.7 (3.9)
15 mg pioglitazone and 500 mg immediate-release metformin	54	5810 (1472)	63	608 (204)	63	1.7 (0.9)	54	7.9 (3.1)
15 mg/850 mg ACTOPLUS MET®	52	5671 (1585)	60	569 (222)	60	1.9 (0.8)	52	7.2 (1.8)
15 mg pioglitazone and 850 mg immediate-release metformin	55	5957 (1680)	61	603 (239)	61	2.0 (1.5)	55	7.2 (1.8)
metformin								
15 mg/500 mg ACTOPLUS MET®	59	7783 (2266)	63	1203 (325)	63	2.3 (0.9)	59	8.6 (14.3)
15 mg pioglitazone and 500 mg immediate-release metformin	59	7599 (2385)	63	1215 (329)	63	2.5 (0.9)	59	6.7 (5.9)
15 mg/850 mg ACTOPLUS MET®	47	11927 (3311)	60	1827 (536)	60	2.4 (0.9)	47	17.6 (20.1)
15 mg pioglitazone and 850 mg immediate-release metformin	52	11569 (3494)	61	1797 (525)	61	2.3 (0.8)	52	17.0 (18.1)

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.

ACTOPLUS MET XR

In bioequivalence studies of ACTOPLUS MET XR 15 mg/1000 mg and 30 mg/1000 mg, the area under the curve (AUC) and maximum concentration (C_{max}) of both the pioglitazone and the extended-release metformin components following a single dose of the combination tablet were bioequivalent to pioglitazone (ACTOS®)15 mg and 30 mg concomitantly administered with extended-release metformin hydrochloride (FORTAMET®) 1000 mg tablets under fed conditions in healthy subjects (**Table 2**).

Table 2. Mean (SD) Pharmacokinetic Parameters for ACTOPLUS MET® XR

Regimen	N	AUC(0-inf) (ng•h/mL)	N	C_{max} (ng/mL)	N	T_{max} (h)	N	$T_{1/2}$ (h)
pioglitazone								
15 mg/1000 mg ACTOPLUS MET® XR	59	5113 (1598)	60	487 (126)	60	3.0 (1.0)	60	5.8 (1.4)
15 mg pioglitazone and 1000 mg extended-release metformin	59	5979 (1726)	60	560 (130)	60	3.1 (1.1)	60	6.3 (2.0)
30 mg/1000 mg ACTOPLUS MET® XR	55	8242 (2587)	57	777 (250)	57	3.5 (1.4)	55	6.7 (3.8)
30 mg pioglitazone and 1000 mg extended-release metformin	55	9177 (2200)	57	866 (243)	57	3.1 (1.3)	55	7.6 (3.3)
metformin								
15 mg/1000 mg ACTOPLUS MET® XR	50	14454 (3579)	60	1551 (404)	60	7.2 (1.9)	50	11.7 (7.0)
15 mg pioglitazone and 1000 mg extended-release metformin	50	14787 (3313)	60	1590 (361)	60	6.9 (1.8)	50	11.0 (5.0)
30 mg/1000 mg ACTOPLUS MET® XR	54	12705 (3577)	58	1322 (335)	58	8.0 (2.0)	54	11.1 (5.0)
30 mg pioglitazone and 1000 mg extended-release metformin	54	12796 (3882)	58	1332 (414)	58	7.4 (2.0)	54	11.4 (5.5)

Administration of ACTOPLUS MET® XR 30 mg/1000 mg with food resulted in no change in total (AUC) exposure of pioglitazone; however, a decrease in C_{max} by approximately 18% was observed. With the extended-release metformin component there was an increase in C_{max} by approximately 98% and AUC exposure by approximately 85% when administered with food. These levels are comparable to exposures obtained with extended release metformin when administered with food. Time to peak serum concentration was prolonged by approximately 3 and 2 hours for pioglitazone and extended-release metformin respectively, under fed conditions.

Pioglitazone
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 immediate-release metformin tablet given under fasting conditions is approximately 50% - 60%. Studies using single oral doses of immediate-release 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 immediate-release 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 immediate-release metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

The appearance of metformin in plasma from an extended-release metformin tablet is slower and more prolonged compared to immediate-release metformin (see FORTAMET prescribing information). In a multiple-dose crossover study, 23 patients with type 2 diabetes mellitus were administered either extended-release metformin hydrochloride 2000 mg once a day (after dinner) or immediate-release (IR) metformin hydrochloride 1000 mg twice a day (after breakfast and after dinner). After 4 weeks of treatment, steady-state pharmacokinetic parameters, area under the concentration-time curve (AUC), time to peak plasma concentration (T_{max}), and maximum concentration (C_{max}) were evaluated. Results are presented in **Table 3**.

Table 3. Extended-Release Metformin vs. Immediate-Release Metformin Steady-State Pharmacokinetic Parameters at 4 Weeks

Pharmacokinetic Parameters (mean ± SD)	Extended-Release Metformin 2000 mg (administered daily with dinner)	Immediate-Release Metformin 2000 mg (administered as 1000 mg twice daily)
$AUC_{0\text{-}24\ hrs}$ (ng • hr/mL)	26,811 ± 7055	27,371 ± 5,781
T_{max} (hr)	6 (3-10)	3 (1-8)
C_{max} (ng/mL)	2849 ± 797	1820 ± 370

In four single-dose studies and one multiple-dose study, the bioavailability of extended-release metformin 2000 mg given once daily, in the evening, under fed conditions [as measured by the area under the plasma concentration versus time curve (AUC)] was similar to the same total daily dose administered as immediate-release metformin 1000 mg given twice daily. The geometric mean ratios (extended-release metformin/immediate-release metformin) of $AUC_{0\text{-}24hr}$, $AUC_{0\text{-}72hr}$, and $AUC_{0\text{-}inf.}$ for these five studies ranged from 0.96 to 1.08.

In a single-dose, four-period replicate crossover design study, comparing two 500 mg extended-release metformin tablets to one 1000 mg extended-release metformin tablet administered in the evening with food to 29 healthy male subjects, two 500 mg extended-release metformin tablets were found to be equivalent to one 1000 mg extended-release metformin tablet.

In a study carried out with extended-release metformin, there was a dose-associated increase in metformin exposure over 24 hours following oral administration of 1000, 1500, 2000, and 2500 mg.

In three studies with extended-release metformin using different treatment regimens (2000 mg after dinner, 1000 mg after breakfast and after dinner, and 2500 mg after dinner), the

pharmacokinetics of metformin as measured by AUC appeared linear following multiple-dose administration.

The extent of absorption (as measured by AUC) of extended-release metformin increased by approximately 60% when given with food. When extended-release metformin was administered with food, C_{max} was increased by approximately 30% and T_{max} was more prolonged compared with the fasting state (6.1 versus 4.0 hours).

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

Metformin hydrochloride
Distribution studies with extended-release metformin have not been conducted; however, the apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin 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 immediate-release metformin, steady-state plasma concentrations of metformin are reached within 24 - 48 hours and are generally <1 µg/mL. During controlled clinical trials of immediate-release metformin, maximum metformin plasma levels did not exceed 5 µg/mL, even at maximum doses.

Metabolism, Elimination and Excretion:
Pioglitazone
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 **PRECAUTIONS, Drug Interactions,** *Pioglitazone*). Urinary 6ß-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.

Metabolism studies with extended-release metformin tablets have not been conducted.

In healthy nondiabetic adults (N=18) receiving extended-release metformin 2500 mg daily, the percent of the metformin dose excreted in urine over 24 hours was 40.9% and the renal clearance was 542 ± 310 mL/min. After repeated administration of extended-release metformin, there is little or no accumulation of metformin in plasma, with most of the drug being eliminated via renal excretion over a 24-hour dosing interval.

Special Populations
Renal Insufficiency:
Pioglitazone
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 and ACTOPLUS MET XR are also contraindicated in these patients.

Hepatic Insufficiency:
Pioglitazone

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 or ACTOPLUS MET XR 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***).

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

Elderly:
Pioglitazone
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 immediate-release metformin in healthy elderly subjects suggest that total plasma clearance of metformin 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 or ACTOPLUS MET XR 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
Pharmacokinetic data in the pediatric population are not available. Use in pediatric patients is not recommended for the treatment of diabetes due to lack of long-term safety data. Risks including fractures and other adverse effects associated with pioglitazone, one of the components of ACTOPLUS MET and ACTOPLUS MET XR, have not been determined in this population (see **WARNINGS** and **PRECAUTIONS**).

Metformin hydrochloride
After administration of a single oral immediate-release 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.

Pharmacokinetic data for extended-release metformin tablets in the pediatric population are not available.

Gender:

Pioglitazone

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, decreases from baseline in HbA1c were generally greater for females than for males (average mean difference in HbA1c 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 immediate-release metformin was comparable in males and females.

Five studies indicated that with extended-release metformin treatment, the pharmacokinetic results for males and females were comparable.

Ethnicity:

Pioglitazone

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 immediate-release 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 immediate-release 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 or ACTOPLUS MET XR have not been performed, although such studies have been conducted with the individual pioglitazone and metformin components.

Pioglitazone

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.

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*

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*).[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*).[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
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 HbA1c 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.

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 or ACTOPLUS MET XR. 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 immediate-release metformin tablets and ACTOPLUS MET XR with co-administered pioglitazone and extended-release metformin tablets was demonstrated for both tablet strengths of ACTOPLUS MET and ACTOPLUS MET XR, respectively (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 HbA1c by 0.8% and the mean fasting plasma glucose (FPG) by 38 mg/dL at Week 16 compared to that observed with metformin alone. In this 16 week study, patients randomized to either pioglitazone or placebo treatment received a median metformin daily dose of 1500 mg with doses ranging from 500 mg to 3400 mg. In the second study, the mean reductions from Baseline at Week 24 in HbA1c were 0.8% and 1.0% for the 30 mg and 45 mg doses, respectively. Mean reductions from Baseline in FPG were 38 mg/dL and 51 mg/dL, respectively. In this 24 week study, patients randomized to either pioglitazone 30 mg or pioglitazone 45 mg treatment received a median metformin daily dose of 1700 mg with doses ranging from 500 mg to 3000 mg. Based on these reductions in HbA1c and FPG (**Table 4**), the addition of pioglitazone to metformin resulted in significant improvements in glycemic control irrespective of the metformin dose.

Table 4. Glycemic Parameters in 16-Week and 24-Week Pioglitazone + Metformin Hydrochloride Combination Studies

Parameter	**Placebo + Metformin**	**Pioglitazone 30 mg + metformin**
16-Week Study		
HbA1c (%)	**N=153**	**N=161**
Baseline mean	9.8	9.9
Mean change from Baseline at 16 Weeks	0.2	-0.6*, †
Difference in change from placebo + metformin		-0.8
Responder rate (%) (a)	**22**	**54**
Fasting Plasma Glucose (FPG) (mg/dL)	**N=157**	**N=165**
Baseline mean	260	254
Mean change from Baseline at 16 Weeks	-5	-43*, †
Difference in change from placebo + metformin		-38
Responder rate (%) (b)	**24**	**59**
Parameter	**Pioglitazone 30 mg + metformin**	**Pioglitazone 45 mg + metformin**
24-Week Study		
HbA1c (%)	**N=400**	**N=398**
Baseline mean	9.9	9.8
Mean Change from Baseline at 24 Weeks	-0.8*	-1.0*
Responder rate (%) (a)	**56**	**63**
Fasting Plasma Glucose (FPG) (mg/dL)	**N=398**	**N=399**
Baseline mean	233	232
Mean Change from Baseline at 24 Weeks	-38*	-51* , ‡
Responder rate (%) (b)	**52**	**64**

* 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 HbA1c ≤ 6.1% or ≥ 0.6% decrease from Baseline.
(b) patients who achieved a decrease in FPG by ≥ 30 mg/dL.

INDICATIONS AND USAGE

ACTOPLUS MET and ACTOPLUS MET XR are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with pioglitazone and metformin or who have inadequate glycemic control on pioglitazone alone or metformin alone.

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. Prior to initiation or escalation of oral antidiabetic therapy in patients with type 2 diabetes mellitus, secondary causes of poor glycemic control, e.g., infection, should be investigated and treated.

CONTRAINDICATIONS

Initiation of ACTOPLUS MET and ACTOPLUS MET XR in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated (see **BOXED WARNING**).

In addition, ACTOPLUS MET and ACTOPLUS MET XR are 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 or ACTOPLUS MET XR.
3. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

ACTOPLUS MET or ACTOPLUS MET XR 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) or ACTOPLUS MET XR (pioglitazone hydrochloride and metformin hydrochloride extended-release) 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 µg/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
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. If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of pioglitazone must be considered. Patients with NYHA Class III and IV cardiac status were not studied during pre-approval clinical trials and pioglitazone is not recommended in these patients (see **BOXED WARNING** and **CONTRAINDICATIONS**).

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 pioglitazone (n=262) to glyburide (n=256) in uncontrolled diabetic patients (mean HbA1c 8.8% at baseline) with NYHA

Class II and III heart failure and ejection fraction less than 40% (mean EF 30% at baseline). Over the course of the study, overnight hospitalization for congestive heart failure was reported in 9.9% of patients on pioglitazone compared to 4.7% of patients on glyburide with a treatment difference observed from 6 weeks. This adverse event associated with pioglitazone 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.

Pioglitazone 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 congestive heart failure exacerbation.

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

PRECAUTIONS
Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ACTOPLUS MET, ACTOPLUS MET XR, or any other anti-diabetic drug.

General: *Pioglitazone*
Pioglitazone exerts its antihyperglycemic effect only in the presence of insulin. Therefore, ACTOPLUS MET and ACTOPLUS MET XR 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 (see **WARNINGS**, ***Pioglitazone***). 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. Since thiazolidinediones, including pioglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, ACTOPLUS MET or ACTOPLUS MET XR should be used with caution in patients at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure (see **BOXED WARNING**, **WARNINGS**, ***Pioglitazone***, and **PRECAUTIONS**, **Information for Patients**).

Weight Gain: Dose related weight gain was observed with pioglitazone alone and in combination with other hypoglycemic agents (**Table 5**). The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Table 5. Weight Changes (kg) from Baseline during Double-Blind Clinical Trials with Pioglitazone

		Control Group (Placebo)	**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 or ACTOPLUS MET XR. 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 or ACTOPLUS MET XR 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 ≥ 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 or ACTOPLUS MET XR undergo periodic monitoring of liver enzymes.

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

Therapy with ACTOPLUS MET or ACTOPLUS MET XR 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 or ACTOPLUS MET XR should be evaluated to determine the cause of the liver enzyme elevation. Initiation or continuation of therapy with ACTOPLUS MET or ACTOPLUS MET XR 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 or ACTOPLUS MET XR therapy should be discontinued.

Macular Edema: Macular edema has been reported in postmarketing 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**).

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

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 or ACTOPLUS MET XR. In patients with advanced age, ACTOPLUS MET or ACTOPLUS MET XR 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 or ACTOPLUS MET XR 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 or ACTOPLUS MET XR 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 or ACTOPLUS MET XR 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 or ACTOPLUS MET XR should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted 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 or ACTOPLUS MET XR therapy, the drug should be promptly discontinued.

Surgical procedures: Use of ACTOPLUS MET or ACTOPLUS MET XR 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 or ACTOPLUS MET XR.

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

Vitamin B_{12} levels: In controlled clinical trials of metformin at 29 weeks' duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on ACTOPLUS MET or ACTOPLUS MET XR and any apparent abnormalities should be appropriately investigated and managed (see **PRECAUTIONS, General:** ***Metformin hydrochloride*** and **Laboratory Tests**). Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12}

levels. In these patients, routine serum vitamin B_{12} 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 or ACTOPLUS MET XR 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 and ACTOPLUS MET XR 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 insufficient, 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 or ACTOPLUS MET XR and temporarily administer insulin. ACTOPLUS MET or ACTOPLUS MET XR may be reinstituted after the acute episode is resolved.

Laboratory Tests
FPG and HbA1c measurements should be performed periodically to monitor glycemic control and therapeutic response to ACTOPLUS MET or ACTOPLUS MET XR.

Liver enzyme monitoring is recommended prior to initiation of therapy with ACTOPLUS MET or ACTOPLUS MET XR in all patients and periodically thereafter per the clinical judgment of the health care professional (see **PRECAUTIONS, General:** ***Pioglitazone*** 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 B_{12} 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 HbA1c. 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 or ACTOPLUS MET XR 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 or ACTOPLUS MET XR 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 or ACTOPLUS MET XR.

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 or ACTOPLUS MET XR 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 or ACTOPLUS MET XR.

Therapy with a thiazolidinedione, which is the active pioglitazone component of the ACTOPLUS MET and ACTOPLUS MET XR tablets, 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 or ACTOPLUS MET XR. 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 or ACTOPLUS MET XR, 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 or ACTOPLUS MET XR as prescribed and instructed that any change in dosing should only be done if directed by their physician. Patients should be informed that if they miss a dose, to take the next dose as prescribed unless directed otherwise by their physician. Patients should be informed that ACTOPLUS MET XR must be swallowed whole and not chewed, cut, or crushed, and that the inactive ingredients may occasionally be eliminated in the feces as a soft mass that may resemble the original tablet.

Drug Interactions

Pioglitazone

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*).

Metformin hydrochloride (Clinical Evaluation of Drug Interactions Conducted with Immediate-Release Metformin)

Glyburide: In a single-dose interaction study in type 2 diabetes patients, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain.

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 or

ACTOPLUS MET XR 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 or ACTOPLUS MET XR, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving ACTOPLUS MET or ACTOPLUS MET XR, the patient should be observed closely for hypoglycemia.

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 and ACTOPLUS MET XR

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

Pioglitazone

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 and ACTOPLUS MET XR 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 and ACTOPLUS MET XR based on body surface area comparisons.

Animal Toxicology

Pioglitazone

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

Pregnancy: Pregnancy Category C

ACTOPLUS MET and ACTOPLUS MET XR

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 and ACTOPLUS MET XR 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 ACTOPLUS MET XR or their individual components. No animal studies have been conducted with the combined products in ACTOPLUS MET or ACTOPLUS MET XR. The following data are based on findings in studies performed with pioglitazone or metformin individually.

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

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 or ACTOPLUS MET XR. 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 and ACTOPLUS MET XR should not be administered to a breastfeeding woman. If ACTOPLUS MET or ACTOPLUS MET XR 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 or ACTOPLUS MET XR in pediatric patients have not been established. Use in pediatric patients is not recommended for the treatment of diabetes due to lack of long-term safety data. Risks including fractures and other adverse effects associated with pioglitazone, one of the components of ACTOPLUS MET and ACTOPLUS MET XR, have not been determined in this population (see **WARNINGS** and **PRECAUTIONS**).

Elderly Use
Pioglitazone

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 immediate-release 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.

Of the 389 patients who received extended-release metformin in controlled Phase III clinical studies, 26.5% [103/389] were 65 years and older. No overall differences in effectiveness or safety were observed between these patients and younger 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 and ACTOPLUS MET XR 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 and ACTOPLUS MET XR 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 or ACTOPLUS MET XR (see **WARNINGS,** ***Metformin hydrochloride*** and **DOSAGE AND ADMINISTRATION**).

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

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 6; the rate of adverse events resulting in study discontinuation between the two treatment groups was 7.8% and 7.7%, respectively.

Table 6. Adverse Events That Occurred in ≥ 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 ≤ 2% of patients treated with pioglitazone plus metformin (see **PRECAUTIONS, General: *Pioglitazone***).

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***).

Prospective Pioglitazone Clinical Trial In Macrovascular Events (PROactive)
In PROactive, 5238 patients with type 2 diabetes and a prior history of macrovascular disease were treated with ACTOS (n=2605), force-titrated up to 45 mg daily, or placebo (n=2633), in addition to standard of care. Almost all subjects (95%) were receiving cardiovascular medications (beta blockers, ACE inhibitors, ARBs, calcium channel blockers, nitrates, diuretics, aspirin, statins, fibrates). Patients had a mean age of 61.8 years, mean duration of diabetes 9.5 years, and mean HbA1c of 8.1%. Average duration of follow-up was 34.5 months. The primary objective of this trial was to examine the effect of ACTOS on mortality and macrovascular morbidity in patients with type 2 diabetes mellitus who were at high risk for macrovascular events. The primary efficacy variable was the time to the first occurrence of any event in the cardiovascular composite endpoint (see Table 7 below). Although there was no statistically significant difference between ACTOS and placebo for the 3-year incidence of a first event within this composite, there was no increase in mortality or in total macrovascular events with ACTOS.

Table 7.

Number of First and Total Events for Each Component within the Cardiovascular Composite Endpoint		
	Placebo	**ACTOS**

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

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

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***).

In controlled clinical trials of metformin at 29 weeks' duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} 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 alanine aminotransferase (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, aspartate aminotransferase (AST), ALT, alkaline phosphatase, and γ-glutamyl transferase (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***).

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

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 overdosage, 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 overdosage is suspected.

DOSAGE AND ADMINISTRATION

General

The use of ACTOPLUS MET or ACTOPLUS MET XR in the management of type 2 diabetes should be individualized on the basis of effectiveness and tolerability.

- The starting doses of ACTOPLUS MET or ACTOPLUS MET XR should be based on the patient's current regimen of pioglitazone and/or metformin and the starting doses of these two drugs. The usual starting dose of pioglitazone is 15 to 30 mg daily. The usual starting dose of metformin is 850 to 1000 mg daily.
- To reduce the gastrointestinal side effects associated with metformin, ACTOPLUS MET and ACTOPLUS MET XR should be administered with a meal.
- After initiation of ACTOPLUS MET or ACTOPLUS MET XR or with dose increase, patients should be carefully monitored for adverse events related to fluid retention (see **BOXED WARNING** and **WARNINGS, *Pioglitazone***).
- The dosage of ACTOPLUS MET or ACTOPLUS MET XR should be gradually titrated, as needed, based on the adequacy of the therapeutic response.
- The total daily doses of ACTOPLUS MET or ACTOPLUS MET XR should not exceed the maximum recommended total daily doses of pioglitazone (45 mg) or metformin (2550 mg for immediate-release metformin and 2000 mg for extended-release metformin.)

No studies have been performed specifically examining the safety and efficacy of ACTOPLUS MET or ACTOPLUS MET XR in patients previously treated with other oral hypoglycemic agents and switched to ACTOPLUS MET or ACTOPLUS MET XR. 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 HbA1c, which is a better indicator of long-term glycemic control than FPG alone. HbA1c reflects glycemia over the past two to three months. In clinical use, it is recommended that patients be treated with ACTOPLUS MET or ACTOPLUS MET XR for a period of time adequate to evaluate change in HbA1c (8-12 weeks) unless glycemic control as measured by FPG deteriorates.

Dosage Recommendations
The dosage recommendations for ACTOPLUS MET and ACTOPLUS MET XR are summarized in Table 8.

Table 8. ACTOPLUS MET and ACTOPLUS MET XR Dosage Recommendations

	ACTOPLUS MET	**ACTOPLUS MET XR**
	Pioglitazone/immediate-release metformin hydrochloride	Pioglitazone/extended-release metformin hydrochloride
Tablet strengths	15 mg/500 mg 15 mg/850 mg	15 mg/1000 mg 30 mg/1000 mg
Starting Dose	15 mg/500 mg or 15 mg/850 mg tablets once or twice daily with food	15 mg/1000 mg or 30 mg/1000 mg tablets once daily with evening meal
Maximum Recommended Daily Dose	45 mg/2550 mg administered in divided doses with food	45 mg/2000 mg administered once daily with evening meal

ACTOPLUS MET
The usual **starting dose of ACTOPLUS MET** is 15 mg/500 mg or 15 mg/850 mg tablet strength of pioglitazone/immediate-release metformin administered once or twice daily with food to reduce the gastrointestinal side effects associated with metformin.

The **maximal total daily dose of ACTOPLUS MET** is 45 mg/2550 mg of pioglitazone/immediate-release metformin. This maximal dosage should be administered in divided doses with meals.

ACTOPLUS MET XR
The usual **starting dose of ACTOPLUS MET XR** is 15 mg/1000 mg or 30 mg/1000 mg tablet strength of pioglitazone/extended-release metformin administered once daily with the evening meal.

The **maximal total daily dose of ACTOPLUS MET XR** is 45 mg/2000 mg of pioglitazone/extended-release metformin administered once daily with the evening meal.

Patients should be informed that ACTOPLUS MET XR must be swallowed whole and not chewed, cut, or crushed, and that the inactive ingredients may occasionally be eliminated in the feces as a soft mass that may resemble the original tablet.

Special Patient Populations

Pregnancy: ACTOPLUS MET and ACTOPLUS MET XR are not recommended for use during pregnancy, or in breastfeeding women.

Geriatric: The initial and maintenance dosing of ACTOPLUS MET or ACTOPLUS MET XR 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 or ACTOPLUS MET XR. 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***).

Renal Impairment: Metformin is substantially excreted by the kidney. ACTOPLUS MET and ACTOPLUS MET XR should only be used in patients with normal renal function (see **CONTRAINDICATIONS**, **WARNINGS, *Metformin hydrochloride*, PRECAUTIONS** and **CLINICAL PHARMACOLOGY, Special Populations**). Any dosage adjustment in ACTOPLUS MET or ACTOPLUS MET XR should be based on a careful assessment of renal function.

Hepatic Impairment: Therapy with ACTOPLUS MET or ACTOPLUS MET XR 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*** and **CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency**). Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with ACTOPLUS MET or ACTOPLUS MET XR and periodically thereafter (see **PRECAUTIONS, General: *Pioglitazone*** and **PRECAUTIONS, Laboratory Tests**).

Pediatric: Use in pediatric patients is not recommended for the treatment of diabetes due to lack of long-term safety data. Risks including fractures and other adverse effects associated with pioglitazone, one of the components of ACTOPLUS MET and ACTOPLUS MET XR, have not been determined in this population (see **WARNINGS** and **PRECAUTIONS**).

HOW SUPPLIED
ACTOPLUS MET is available in 15 mg pioglitazone /500 mg metformin hydrochloride and 15 mg pioglitazone/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

ACTOPLUS MET XR is available in 15 mg pioglitazone/1000 mg metformin hydrochloride extended-release and 30 mg pioglitazone/1000 mg metformin hydrochloride extended-release tablets as follows:

15 mg/1000 mg tablet: round, white to off-white, film-coated tablet imprinted with “4833X” and “15/1000” in red on one side, available in:
Bottles of 30 NDC 64764-510-30
Bottles of 60 NDC 64764-510-60
Bottles of 90 NDC 64764-510-90

30 mg/1000 mg tablet: round, white to off-white, film-coated tablet imprinted with “4833X” and “30/1000” in light blue on one side, available in:
Bottles of 30 NDC 64764-310-30
Bottles of 60 NDC 64764-310-60
Bottles of 90 NDC 64764-310-90

STORAGE
ACTOPLUS MET
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.

ACTOPLUS MET XR

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Avoid excessive heat and humidity. Dispense in a tightly closed, light-resistant container.

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