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

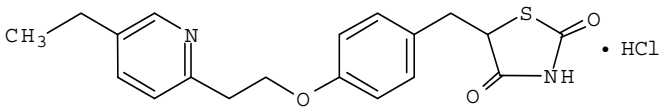
- Lactic acidosis is a rare, but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure.
- The onset is often subtle, accompanied 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.

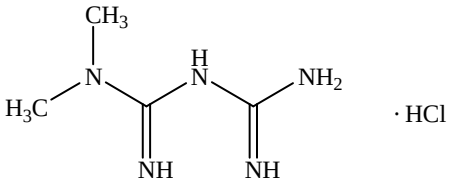
Pioglitazone (±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione monohydrochloride belongs to a different chemical class and has a different pharmacological action than the sulfonylureas, biguanides, or the α-glucosidase inhibitors. The molecule contains one asymmetric center, 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

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