HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ACTOPLUS MET safely and effectively. See full prescribing information for ACTOPLUS MET.

ACTOPLUS MET (pioglitazone and metformin hydrochloride) tablets for oral use
Initial U.S. Approval: 2005

WARNING: CONGESTIVE HEART FAILURE AND LACTIC ACIDOSIS
See full prescribing information for complete boxed warning
Congestive Heart Failure
- **Thiazolidinediones, including pioglitazone, which is a component of ACTOPLUS MET, cause or exacerbate congestive heart failure in some patients. (5.1)**
- **After initiation of ACTOPLUS MET, and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., excessive, rapid weight gain, dyspnea, and/or edema). If heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of ACTOPLUS MET must be considered. (5.1)**
- **ACTOPLUS MET is not recommended in patients with symptomatic heart failure.**
- **Initiation of ACTOPLUS MET in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated. (4, 5.1)**

Lactic Acidosis
- **Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure. (5.2)**
- **Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate. (5.2)**
- **If acidosis is suspected, discontinue ACTOPLUS MET and hospitalize the patient immediately. (5.2)**

----------RECENT MAJOR CHANGES----------

Dosage and Administration	
Recommendations for All Patients (2.1)	02/2012
Concomitant Use with an Insulin Secretagogue or Insulin (2.2)	02/2012
Coadministration with Strong CYP2C8 Inhibitors (2.3)	02/2012
Warnings and Precautions	
Hepatic Effects (5.4)	02/2012
Urinary Bladder Tumors (5.6)	07/2011

----------INDICATIONS AND USAGE----------

ACTOPLUS MET is a thiazolidinedione and biguanide combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both pioglitazone and metformin is appropriate. (1, 14)

Important Limitation of Use:
- Not for treatment of type 1 diabetes or diabetic ketoacidosis. (1.2)

----------DOSAGE AND ADMINISTRATION----------
- Individualize the starting dose of ACTOPLUS MET based on the patient's current regimen. (2)
- May adjust the dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of pioglitazone 45 mg and metformin 2550 mg. (2)
- Maximum recommended dose of pioglitazone is 15 mg once daily in patients taking strong CYP2C8 inhibitors (e.g., gemfibrozil). (2.3, 7.1)
- ACTOPLUS MET should be given in divided daily doses with meals to reduce the gastrointestinal (GI) side effects due to metformin. (2)
- Dose increases should be accompanied by careful monitoring for adverse events related to fluid retention. (2)
- Obtain liver tests before starting ACTOPLUS MET. If abnormal, use caution when treating with ACTOPLUS MET, investigate the probable cause, treat (if possible), and follow appropriately. Monitoring liver tests while on ACTOPLUS MET is not recommended in patients without liver disease. (5.4)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 15 mg pioglitazone/500 mg metformin HCl and 15 mg pioglitazone/850 mg metformin HCl (3)

----------CONTRAINDICATIONS----------
- Do not initiate ACTOPLUS MET in patients with established NYHA Class III or IV heart failure. (4)
- Do not use in patients with a history of a serious hypersensitivity reaction to ACTOPLUS MET or its ingredients. (4)
- Renal impairment.
- Metabolic acidosis, including diabetic ketoacidosis. (4, 5.2)

----------WARNINGS AND PRECAUTIONS----------
- Congestive heart failure: Fluid retention may occur and can exacerbate or lead to congestive heart failure. Combination use with insulin and use in congestive heart failure NYHA Class I and II may increase risk. Monitor patients for signs and symptoms. (5.1)
- Edema: Dose-related edema may occur. (5.3)
- Lactic acidosis: Warn against excessive alcohol intake. ACTOPLUS MET is not recommended in hepatic impairment and is contraindicated in renal impairment. Ensure normal renal function before initiating and at least annually thereafter. (5.2)
- Temporarily discontinue in patients undergoing radiologic studies with intravascular iodinated contrast materials or any surgical procedures necessitating restricted intake of food and fluids. (5.12)
- Hepatic effects: Postmarketing reports of hepatic failure, sometimes fatal. Causality cannot be excluded. If liver injury is detected, promptly interrupt ACTOPLUS MET and assess patient for probable cause, then treat cause if possible, to resolution or stabilization. Do not restart ACTOPLUS MET if liver injury is confirmed and no alternate etiology can be found. (5.4)
- Fractures: Increased incidence in female patients. Apply current standards of care for assessing and maintaining bone health. (5.5)
- Bladder cancer: Preclinical and clinical trial data, and results from an observational study suggest an increased risk of bladder cancer in pioglitazone users. The observational data further suggest that the risk increases with duration of use. Do not use in patients with active bladder cancer. Use caution when using in patients with a prior history of bladder cancer. (5.6)
- Hypoglycemia: When used with insulin or an insulin secretagogue, a lower dose of the insulin or insulin secretagogue may be needed to reduce the risk of hypoglycemia. (5.7)
- Macular edema: Postmarketing reports. Recommend regular eye exams in all patients with diabetes according to current standards of care with prompt evaluation for acute visual changes. (5.8)
- Vitamin B_{12} deficiency: Metformin may lower vitamin B_{12} levels. Monitor hematologic parameters annually. (5.14)
- Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ACTOPLUS MET or any other antidiabetic drug. (5.15)

----------ADVERSE REACTIONS----------

Most common adverse reactions (>5%) with ACTOPLUS MET or pioglitazone and metformin coadministration include upper respiratory tract infection, edema, diarrhea, headache, and weight gain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-877-825-3327 and the ACTOPLUS MET website at: www.actoplusmet.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Strong CYP2C8 inhibitors (e.g., gemfibrozil) increase pioglitazone concentrations. Limit ACTOPLUS MET dose to 15 mg/850 mg daily. (2.3, 7.1)
- CYP2C8 inducers (e.g., rifampin) may decrease pioglitazone concentrations. (7.2)
- Cationic drugs: May reduce metformin elimination. Use with caution in patients who are taking cationic medications eliminated by renal tubular secretion. (7.4)

----------USE IN SPECIFIC POPULATIONS----------
- Nursing mothers: Discontinue drug or nursing, taking into consideration the importance of the drug to the mother. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 09/2012

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FULL PRESCRIBING INFORMATION

WARNING: CONGESTIVE HEART FAILURE AND LACTIC ACIDOSIS

Congestive Heart Failure

- **Thiazolidinediones, including pioglitazone, which is a component of ACTOPLUS MET, cause or exacerbate congestive heart failure in some patients *[see Warnings and Precautions (5.1)]*.**
- **After initiation of ACTOPLUS MET, and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., excessive, rapid weight gain, dyspnea, and/or edema). If heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of ACTOPLUS MET must be considered *[see Warnings and Precautions (5.1)]*.**
- **ACTOPLUS MET is not recommended in patients with symptomatic heart failure.**
- **Initiation of ACTOPLUS MET in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated *[see Contraindications (4) and Warnings and Precautions (5.1)]*.**

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 impairment, renal impairment, and acute congestive heart failure *[see Warnings and Precautions (5.2)]*.**
- **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 *[see Warnings and Precautions (5.2)]*.**
- **If acidosis is suspected, ACTOPLUS MET should be discontinued and the patient hospitalized immediately *[see Warnings and Precautions (5.2)].***

1 INDICATIONS AND USAGE

ACTOPLUS MET is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both pioglitazone and metformin is appropriate *[see Clinical Studies (14)]*.

1.2 Important Limitations of Use

Pioglitazone exerts its antihyperglycemic effect only in the presence of endogenous insulin. ACTOPLUS MET should not be used to treat type 1 diabetes or diabetic ketoacidosis, as it would not be effective in these settings.

Use caution in patients with liver disease *[see Warnings and Precautions (5.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommendations for All Patients

ACTOPLUS MET should be taken with meals to reduce the gastrointestinal side effects associated with metformin.

If therapy with a combination tablet containing pioglitazone and metformin is considered appropriate the recommended starting dose is:

- 15 mg/500 mg twice daily or 15 mg/850 mg once daily and gradually titrated, as needed, after assessing adequacy of therapeutic response and tolerability,
- for patients with New York Heart Association (NYHA) Class I or Class II congestive heart failure: 15 mg/500 mg or 15 mg/850 mg once daily and gradually titrated, as needed, after assessing adequacy of therapeutic response and tolerability,
- for patients inadequately controlled on metformin monotherapy: 15 mg/500 mg twice daily or 15 mg/850 mg once or twice daily (depending on the dose of metformin already being taken) and gradually titrated, as needed, after assessing adequacy of therapeutic response and tolerability,
- for patients inadequately controlled on pioglitazone monotherapy: 15 mg/500 mg twice daily or 15 mg/850 mg once daily and gradually titrated, as needed, after assessing adequacy of therapeutic response and tolerability.
- for patients who are changing from combination therapy of pioglitazone plus metformin as separate tablets: ACTOPLUS MET should be taken at doses that are as close as possible to the dose of pioglitazone and metformin already being taken.

ACTOPLUS MET may be titrated up to a maximum daily dose of 45 mg of pioglitazone and 2550 mg of metformin.

Metformin doses above 2000 mg may be better tolerated given three times a day.

After initiation of ACTOPLUS MET or with dose increase, monitor patients carefully for adverse reactions related to fluid retention such as weight gain, edema, and signs and symptoms of congestive heart failure *[see Boxed Warning and Warnings and Precautions (5.1)]*. Liver tests (serum alanine and aspartate aminotransferases, alkaline phosphatase, and total bilirubin) should be obtained prior to initiating ACTOPLUS MET. Routine periodic monitoring of liver tests during treatment with ACTOPLUS MET is not recommended in patients without liver disease. Patients who have liver test abnormalities prior to initiation of ACTOPLUS MET or who are found to have abnormal liver tests while taking ACTOPLUS MET should be managed as described under Warnings and Precautions *[see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)]*.

2.2 Concomitant Use with an Insulin Secretagogue or Insulin

If hypoglycemia occurs in a patient coadministered ACTOPLUS MET and an insulin secretagogue (e.g., sulfonylurea), the dose of the insulin secretagogue should be reduced.

If hypoglycemia occurs in a patient coadministered ACTOPLUS MET and insulin, the dose of insulin should be decreased by 10% to 25%. Further adjustments to the insulin dose should be individualized based on glycemic response.

2.3 Coadministration with Strong CYP2C8 Inhibitors

Coadministration of pioglitazone (one of the ingredients in ACTOPLUS MET) and gemfibrozil, a strong CYP2C8 inhibitor, increases pioglitazone exposure approximately 3-fold. Therefore, the maximum recommended dose of ACTOPLUS MET is 15 mg/850 mg daily when used in combination with gemfibrozil or other strong CYP2C8 inhibitors *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

- 15-mg/500-mg tablets: White to off-white, oblong, film-coated tablets debossed with "4833M" on one side and "15/500" on the other
- 15-mg/850-mg tablets: White to off-white, oblong, film-coated tablets debossed with "4833M" on one side and "15/850" on the other

4 CONTRAINDICATIONS

Do not initiate in patients with NYHA Class III or IV heart failure *[see Boxed Warning]*. In addition, ACTOPLUS MET is contraindicated in patients with:

- Renal impairment (e.g., 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 and Precautions (5.2, 5.10)]*.
- Known hypersensitivity to pioglitazone, metformin, or any other component of ACTOPLUS MET.
- Metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.

5 WARNINGS AND PRECAUTIONS

5.1 Congestive Heart Failure

Pioglitazone

Pioglitazone, like other thiazolidinediones, can cause dose-related fluid retention when used alone or in combination with other antidiabetic medications and is most common when pioglitazone is used in combination with insulin. Fluid retention may lead to or exacerbate congestive heart failure. Patients treated with ACTOPLUS MET should be observed for signs and symptoms of congestive heart failure. If congestive heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of ACTOPLUS MET must be considered *[see Boxed Warning*, *Contraindications (4), and Adverse Reactions (6.1)]*.

5.2 Lactic Acidosis

Metformin hydrochloride

Lactic Acidosis

Lactic acidosis is a serious, metabolic complication that can occur due to metformin accumulation during treatment with ACTOPLUS MET and, 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 concentrations (>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 mcg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is 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 impairment, 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, particularly when accompanied by 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. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. ACTOPLUS MET treatment should not be initiated in any patient unless measurement of creatinine clearance demonstrates that renal function is not reduced. 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 impairment. Patients should be cautioned against excessive alcohol intake when taking metformin, because alcohol potentiates the effects of metformin on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure necessitating restricted intake of food or fluids *[see Warnings and Precautions (5.10, 5.11, 5.12, 5.13)]*. Use of topiramate, a carbonic anhydrase inhibitor, in epilepsy and migraine prophylaxis may frequently cause dose-dependent metabolic acidosis and may exacerbate the risk of metformin-induced lactic acidosis *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

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. Patients should be educated to promptly report these symptoms should they occur. If present, ACTOPLUS MET should be withdrawn until lactic acidosis is ruled out. Serum electrolytes, ketones, blood glucose, blood pH, lactate levels, and 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 recur. 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 Warnings and Precautions (5.10)]*.

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 (4) and Warnings and Precautions (5.10)]*.

5.3 Edema

In controlled clinical trials with pioglitazone, edema was reported more frequently in patients treated with pioglitazone than in placebo-treated patients and is dose related *[see Adverse Reactions (6.1)]*. In postmarketing experience, reports of new onset or worsening of edema have been received.

ACTOPLUS MET should be used with caution in patients with edema. Because thiazolidinediones, including pioglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, ACTOPLUS MET should be used with caution in patients at risk for congestive heart failure. Patients treated with ACTOPLUS MET should be monitored for signs and symptoms of congestive heart failure *[see Boxed Warning*, *Warnings and Precautions (5.1)*, *and Patient Counseling Information (17.1)]*.

5.4 Hepatic Effects

There have been postmarketing reports of fatal and nonfatal hepatic failure in patients taking pioglitazone, although the reports contain insufficient information necessary to establish the probable cause. There has been no evidence of drug-induced hepatotoxicity in the pioglitazone controlled clinical trial database to date *[see Adverse Reactions (6.1)]*.

Patients with type 2 diabetes may have fatty liver disease or cardiac disease with episodic congestive heart failure, both of which may cause liver test abnormalities, and they may also have other forms of liver disease, many of which can be treated or managed. Therefore, obtaining a liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) and assessing the patient is recommended before initiating ACTOPLUS MET therapy.

In patients with abnormal liver tests, ACTOPLUS MET should be initiated with caution.

Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have abnormal liver tests (ALT greater than three times the upper limit of the reference range), ACTOPLUS MET treatment should be interrupted and investigation done to establish the probable cause. ACTOPLUS MET should not be restarted in these patients without another explanation for the liver test abnormalities.

Patients who have serum ALT greater than three times the reference range with serum total bilirubin greater than two times the reference range without alternative etiologies are at risk for severe drug-induced liver injury, and should not be restarted on ACTOPLUS MET. For patients with lesser elevations of serum ALT or bilirubin and with an alternate probable cause, treatment with ACTOPLUS MET can be used with caution.

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

5.5 Fractures

In PROactive (the Prospective Pioglitazone Clinical Trial in Macrovascular Events), 5238 patients with type 2 diabetes and a history of macrovascular disease were randomized to pioglitazone (N=2605), force-titrated up to 45 mg daily or placebo (N=2633) in addition to standard of care. 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

persisted 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 the incidence of fracture was observed in men treated with pioglitazone (1.7%) versus placebo (2.1%). The risk of fracture should be considered in the care of patients, especially female patients, treated with ACTOPLUS MET and attention should be given to assessing and maintaining bone health according to current standards of care.

5.6 Urinary Bladder Tumors

Tumors were observed in the urinary bladder of male rats in the two-year carcinogenicity study *[see Nonclinical Toxicology (13.1)]*. In two 3-year trials 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%) cases on placebo.

A five-year interim report of an ongoing 10-year observational cohort study found a nonsignificant increase in the risk for bladder cancer in subjects ever exposed to pioglitazone, compared to subjects never exposed to pioglitazone (HR 1.2 [95% CI 0.9 – 1.5]). Compared to never exposure, a duration of pioglitazone therapy longer than 12 months was associated with an increase in risk (HR 1.4 [95% CI 0.9 – 2.1]), which reached statistical significance after more than 24 months of pioglitazone use (HR 1.4 [95% CI 1.03 – 2.0]). Interim results from this study suggested that taking pioglitazone longer than 12 months increased the relative risk of developing bladder cancer in any given year by 40%, which equates to an absolute increase of three cases in 10,000 (from approximately seven in 10,000 [without pioglitazone] to approximately 10 in 10,000 [with pioglitazone]).

There are insufficient data to determine whether pioglitazone is a tumor promoter for urinary bladder tumors. Consequently, ACTOPLUS MET should not be used in patients with active bladder cancer and the benefits of glycemic control versus unknown risks for cancer recurrence with ACTOPLUS MET should be considered in patients with a prior history of bladder cancer.

5.7 Hypoglycemia

Patients receiving ACTOPLUS MET in combination with insulin or other antidiabetic medications (particularly insulin secretagogues such as sulfonylureas) may be at risk for hypoglycemia. A reduction in the dose of the concomitant antidiabetic medication may be necessary to reduce the risk of hypoglycemia [*see Dosage and Administration (2.2)*].

Hypoglycemia can also occur when caloric intake is deficient or when strenuous exercise is not compensated by caloric supplement. 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.

5.8 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 others were diagnosed on routine ophthalmologic examination.

Most patients had peripheral edema at the time macular edema was diagnosed. Some patients had improvement in their macular edema after discontinuation of the thiazolidinedione.

Patients with diabetes should have regular eye exams by an ophthalmologist according to current standards of care. Patients with diabetes who report any visual symptoms should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings *[see Adverse Reactions (6.1)]*.

5.9 Ovulation

Therapy with pioglitazone, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking ACTOPLUS MET *[see Use in Specific Populations (8.1)]*. This effect has not been investigated in clinical trials, so the frequency of this occurrence is not known. Adequate contraception in all premenopausal women treated with ACTOPLUS MET is recommended.

5.10 Monitoring of Renal Function

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Therefore, ACTOPLUS MET is contraindicated in patients with renal impairment.

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

Use of Concomitant Medications That May Affect Renal Function or Metformin Disposition

Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion, should be used with caution *[see Clinical Pharmacology (12.3)]*.

Radiological Studies and Surgical Procedures

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) can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin *[see Contraindications (4)]*. Therefore, in patients in whom any such study is planned, ACTOPLUS MET should be 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.

5.11 Hypoxic States

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

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

5.13 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.

5.14 Vitamin B_{12} Levels
In controlled clinical trials of metformin of 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 and any apparent abnormalities should be appropriately investigated and managed. 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.

5.15 Macrovascular Outcomes
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ACTOPLUS MET or any other oral antidiabetic drug.

6 ADVERSE REACTIONS
The following serious adverse reactions are discussed elsewhere in the labeling:

- Congestive heart failure *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Lactic acidosis *[see Boxed Warning and Warnings and Precautions (5.2)]*
- Edema *[see Warnings and Precautions (5.3)]*
- Fractures *[see Warnings and Precautions (5.5)]*

6.1 Clinical Studies Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Pioglitazone
Over 8500 patients with type 2 diabetes have been treated with pioglitazone in randomized, double-blind, controlled clinical trials, including 2605 patients with type 2 diabetes and macrovascular disease treated with pioglitazone from the PROactive clinical trial. In these trials, over 6000 patients have been treated with pioglitazone for six months or longer, over 4500 patients have been treated with pioglitazone for one year or longer, and over 3000 patients have been treated with pioglitazone for at least two years.

In six pooled 16- to 26-week placebo-controlled monotherapy and 16- to 24-week add-on combination therapy trials, the incidence of withdrawals due to adverse events was 4.5% for patients treated with pioglitazone and 5.8% for comparator-treated patients.

The most common adverse events leading to withdrawal were related to inadequate glycemic control, although the incidence of these events was lower (1.5%) with pioglitazone than with placebo (3.0%).

In the PROactive trial, the incidence of withdrawals due to adverse events was 9.0% for patients treated with pioglitazone and 7.7% for placebo-treated patients. Congestive heart failure was the most common serious adverse event leading to withdrawal occurring in 1.3% of patients treated with pioglitazone and 0.6% of patients treated with placebo.

Common Adverse Events: 16- to 26-Week Monotherapy Trials
A summary of the incidence and type of common adverse events reported in three pooled 16- to 26-week placebo-controlled monotherapy trials of pioglitazone is provided in Table 1. Terms that are reported represent those that occurred at an incidence of >5% and more commonly in patients treated with pioglitazone than in patients who received placebo. None of these adverse events were related to the pioglitazone dose.

Table 1. Three Pooled 16- to 26-Week Placebo-Controlled Clinical Trials of Pioglitazone Monotherapy: Adverse Events Reported at an Incidence >5% and More Commonly in Patients Treated with Pioglitazone than in Patients Treated with Placebo

	% of Patients	
	Placebo N=259	**Pioglitazone** N=606
Upper Respiratory Tract Infection	8.5	13.2
Headache	6.9	9.1
Sinusitis	4.6	6.3
Myalgia	2.7	5.4
Pharyngitis	0.8	5.1

Common Adverse Events: 16- to 24-Week Add-on Combination Therapy Trials
A summary of the overall incidence and types of common adverse events reported in trials of pioglitazone add-on to metformin is provided in Table 2. Terms that are reported represent those that occurred at an incidence of >5% and more commonly with the highest tested dose of pioglitazone.

Table 2. 16- to 24-Week Clinical Trials of Pioglitazone Add-on to Metformin		
	16-Week Placebo-Controlled Trial Adverse Events Reported in >5% of Patients and More Commonly in Patients Treated with Pioglitazone + Metformin than in Patients Treated with Placebo + Metformin	
	% of Patients	
	Placebo + Metformin N=160	**Pioglitazone 30 mg + Metformin** N=168
Edema	2.5	6.0
Headache	1.9	6.0
	24-Week Non-Controlled Double-Blind Trial Adverse Events Reported in >5% of Patients and More Commonly in Patients Treated with Pioglitazone 45 mg + Metformin than in Patients Treated with Pioglitazone 30 mg + Metformin	
	% of Patients	
	Pioglitazone 30 mg + Metformin N=411	**Pioglitazone 45 mg + Metformin** N=416
Upper Respiratory Tract Infection	12.4	13.5
Edema	5.8	13.9
Headache	5.4	5.8
Weight Increased	2.9	6.7

Note: The preferred terms of edema peripheral, generalized edema, pitting edema, and fluid retention were combined to form the aggregate term of “edema.”

Common Adverse Events: 24-Week ACTOPLUS MET Clinical Trial

Table 3 summarizes the incidence and types of adverse reactions reported in a controlled, 24-week double-blind clinical trial of ACTOPLUS MET dosed twice daily in patients with inadequate glycemic control on diet and exercise (N=600).

Table 3. Adverse Events (≥5% for ACTOPLUS MET) Reported by Patients with Inadequate Glycemic Control on Diet and Exercise in a 24-Week Double-Blind Clinical Trial of ACTOPLUS MET Administered Twice Daily			
	% of Patients		
	ACTOPLUS MET 15/850 mg Twice Daily N=201	**Pioglitazone 15 mg Twice Daily** N=190	**Metformin 850 mg Twice Daily** N=209
Diarrhea	9.0	2.6	15.3
Headache	5.5	2.6	4.8

In this 24-week trial, abdominal pain was reported in 2.0% of patients in the ACTOPLUS MET group, 1.6% in the pioglitazone monotherapy group and 3.3% in the metformin monotherapy group.

Common Adverse Events: PROactive Trial

A summary of the overall incidence and types of common adverse events reported in the PROactive trial is provided in Table 4. Terms that are reported represent those that occurred at an incidence of >5% and more commonly in patients treated with pioglitazone than in patients who received placebo.

Table 4. PROactive Trial: Incidence and Types of Adverse Events Reported in >5% of Patients Treated with Pioglitazone and More Commonly than Placebo		
	% of Patients	
	Placebo N=2633	**Pioglitazone** N=2605
Hypoglycemia	18.8	27.3
Edema	15.3	26.7
Cardiac Failure	6.1	8.1
Pain in Extremity	5.7	6.4
Back Pain	5.1	5.5
Chest Pain	5.0	5.1

Mean duration of patient follow-up was 34.5 months.

Congestive Heart Failure

A summary of the incidence of adverse events related to congestive heart failure is provided in Table 5 for the 16- to 24-week add-on to metformin trials. None of the events were fatal.

Table 5. Treatment-Emergent Adverse Events of Congestive Heart Failure (CHF) Patients Treated with Pioglitazone or Placebo Added on to Metformin

	Number (%) of Patients			
	Placebo-Controlled Trial (16 weeks)		Non-Controlled Double-Blind Trial (24 weeks)	
	Placebo + Metformin N=160	Pioglitazone 30 mg + Metformin N=168	Pioglitazone 30 mg + Metformin N=411	Pioglitazone 45 mg + Metformin N=416
At least one congestive heart failure event	0	1 (0.6%)	0	1 (0.2%)
Hospitalized	0	1 (0.6%)	0	1 (0.2%)

Table 6. Treatment-Emergent Adverse Events of Congestive Heart Failure (CHF)

Patients Treated with Pioglitazone or Placebo Added on to a Sulfonylurea

	Number (%) of Patients				
	Placebo-Controlled Trial (16 weeks)			Non-Controlled Double-Blind Trial (24 weeks)	
	Placebo + Sulfonylurea N=187	**Pioglitazone 15 mg + Sulfonylurea** N=184	**Pioglitazone 30 mg + Sulfonylurea** N=189	**Pioglitazone 30 mg + Sulfonylurea** N=351	**Pioglitazone 45 mg + Sulfonylurea** N=351
At least one congestive heart failure event	2 (1.1%)	0	0	1 (0.3%)	6 (1.7%)
Hospitalized	2 (1.1%)	0	0	0	2 (0.6%)

Patients Treated with Pioglitazone or Placebo Added on to Insulin

	Number (%) of Patients				
	Placebo-Controlled Trial (16 weeks)			Non-Controlled Double-Blind Trial (24 weeks)	
	Placebo + Insulin N=187	**Pioglitazone 15 mg + Insulin** N=191	**Pioglitazone 30 mg + Insulin** N=188	**Pioglitazone 30 mg + Insulin** N=345	**Pioglitazone 45 mg + Insulin** N=345
At least one congestive heart failure event	0	2 (1.0%)	2 (1.1%)	3 (0.9%)	5 (1.4%)
Hospitalized	0	2 (1.0%)	1 (0.5%)	1 (0.3%)	3 (0.9%)

Patients Treated with Pioglitazone or Placebo Added on to Metformin

	Number (%) of Patients			
	Placebo-Controlled Trial (16 weeks)		Non-Controlled Double-Blind Trial (24 weeks)	
	Placebo + Metformin N=160	**Pioglitazone 30 mg + Metformin** N=168	**Pioglitazone 30 mg + Metformin** N=411	**Pioglitazone 45 mg + Metformin** N=416
At least one congestive heart failure event	0	1 (0.6%)	0	1 (0.2%)
Hospitalized	0	1 (0.6%)	0	1 (0.2%)

Table 7. Treatment-Emergent Adverse Events of Congestive Heart Failure (CHF) in Patients with NYHA Class II or III Congestive Heart Failure Treated with Pioglitazone or Glyburide		
	Number (%) of Subjects	
	Pioglitazone N=262	**Glyburide** N=256
Death due to cardiovascular causes (adjudicated)	5 (1.9%)	6 (2.3%)
Overnight hospitalization for worsening CHF (adjudicated)	26 (9.9%)	12 (4.7%)
Emergency room visit for CHF (adjudicated)	4 (1.5%)	3 (1.2%)
Patients experiencing CHF progression during study	35 (13.4%)	21 (8.2%)

Congestive heart failure events leading to hospitalization that occurred during the PROactive trial are summarized in Table 8.

Table 8. Treatment-Emergent Adverse Events of Congestive Heart Failure (CHF) in PROactive Trial		
	Number (%) of Patients	
	Placebo N=2633	**Pioglitazone** N=2605
At least one hospitalized congestive heart failure event	108 (4.1%)	149 (5.7%)
Fatal	22 (0.8%)	25 (1.0%)
Hospitalized, nonfatal	86 (3.3%)	124 (4.7%)

Cardiovascular Safety

In the PROactive trial, 5238 patients with type 2 diabetes and a history of macrovascular disease were randomized to pioglitazone (N=2605), force-titrated up to 45 mg daily or placebo (N=2633) in addition to standard of care. Almost all patients (95%) were receiving cardiovascular medications (beta blockers, ACE inhibitors, angiotensin II receptor blockers, calcium channel blockers, nitrates, diuretics, aspirin, statins, and fibrates). At baseline, patients had a mean age of 62 years, mean duration of diabetes of 9.5 years, and mean HbA1c of 8.1%. Mean duration of follow-up was 34.5 months.

The primary objective of this trial was to examine the effect of pioglitazone 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 a cardiovascular composite endpoint that included all-cause mortality, nonfatal myocardial infarction (MI) including silent MI, stroke, acute coronary syndrome, cardiac intervention including coronary artery bypass grafting or

percutaneous intervention, major leg amputation above the ankle, and bypass surgery or revascularization in the leg. A total of 514 (19.7%) patients treated with pioglitazone and 572 (21.7%) placebo-treated patients experienced at least one event from the primary composite endpoint (HR 0.90; 95% CI: 0.80, 1.02; p=0.10).

Although there was no statistically significant difference between pioglitazone and placebo for the three-year incidence of a first event within this composite, there was no increase in mortality or in total macrovascular events with pioglitazone. The number of first occurrences and total individual events contributing to the primary composite endpoint is shown in Table 9.

Table 9. PROactive: Number of First and Total Events for Each Component Within the Cardiovascular Composite Endpoint

Cardiovascular Events	Placebo N=2633		Pioglitazone N=2605	
	First Events n (%)	Total events n	First Events n (%)	Total events n
Any event	572 (21.7)	900	514 (19.7)	803
All-cause mortality	122 (4.6)	186	110 (4.2)	177
Nonfatal myocardial infarction (MI)	118 (4.5)	157	105 (4.0)	131
Stroke	96 (3.6)	119	76 (2.9)	92
Acute coronary syndrome	63 (2.4)	78	42 (1.6)	65
Cardiac intervention (CABG/PCI)	101 (3.8)	240	101 (3.9)	195
Major leg amputation	15 (0.6)	28	9 (0.3)	28
Leg revascularization	57 (2.2)	92	71 (2.7)	115

CABG = coronary artery bypass grafting; PCI = percutaneous intervention

Weight Gain

Dose-related weight gain occurs when pioglitazone is used alone or in combination with other antidiabetic medications. The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Tables 10, 11, and 12 summarize the changes in body weight with pioglitazone and placebo in the 16- to 26-week randomized, double-blind monotherapy and 16- to 24-week combination add-on therapy trials, the PROactive trial, and the 24-week ACTOPLUS MET trial.

Table 10. Weight Changes (kg) from Baseline During Randomized, Double-Blind Clinical Trials					
		Control Group (Placebo)	**Pioglitazone 15 mg**	**Pioglitazone 30 mg**	**Pioglitazone 45 mg**
		Median (25th, 75th percentile)	Median (25th, 75th percentile)	Median (25th, 75th percentile)	Median (25th, 75th percentile)
Monotherapy (16 to 26 weeks)		-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 (16 to 24 weeks)	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 (-1.3, 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

Table 11. Median Change in Body Weight in Patients Treated with Pioglitazone Versus Patients Treated with Placebo During the Double-Blind Treatment Period in the PROactive Trial		
	Placebo	**Pioglitazone**
	Median (25th, 75th percentile)	Median (25th, 75th percentile)
Change from baseline to final visit (kg)	-0.5 (-3.3, 2.0) N=2581	+3.6 (0.0, 7.5) N=2560

Note: Median exposure for both pioglitazone and placebo was 2.7 years.

Table 12. Weight Changes (kg) from Baseline During Double-Blind Clinical Trial with ACTOPLUS MET in Patients with Inadequate Glycemic Control on Diet and Exercise			
	ACTOPLUS MET 15/850 mg Twice Daily	**Pioglitazone 15 mg Twice Daily**	**Metformin 850 mg Twice Daily**
	Median (25th , 75th percentile)	Median (25th , 75th percentile)	Median (25th , 75th percentile)
Change from baseline to final visit (kg)	1.00 (-1.0, 3.0) N=198	1.35 (-0.7, 4.1) N=178	-1.00 (-2.6, 0.4) N=203

Note: Trial duration of 24 weeks.

Edema

Edema induced from taking pioglitazone is reversible when pioglitazone is discontinued. The edema usually does not require hospitalization unless there is coexisting congestive heart failure.

In the 24-week ACTOPLUS MET trial, edema was reported in 3.0% of patients in the ACTOPLUS MET group, 4.2% in the pioglitazone monotherapy group, and 1.4% in the metformin monotherapy group.

A summary of the frequency and types of edema adverse events occurring in clinical investigations of pioglitazone is provided in Table 13.

Table 13. Adverse Events of Edema in Patients Treated with Pioglitazone

		Number (%) of Patients			
		Placebo	**Pioglitazone 15 mg**	**Pioglitazone 30 mg**	**Pioglitazone 45 mg**
Monotherapy (16 to 26 weeks)		3 (1.2%) N=259	2 (2.5%) N= 81	13 (4.7%) N= 275	11 (6.5%) N=169
Combined Therapy (16 to 24 weeks)	Sulfonylurea	4 (2.1%) N=187	3 (1.6%) N=184	61 (11.3%) N=540	81 (23.1%) N=351
	Metformin	4 (2.5%) N=160	N/A	34 (5.9%) N=579	58 (13.9%) N=416
	Insulin	13 (7.0%) N=187	24 (12.6%) N=191	109 (20.5%) N=533	90 (26.1%) N=345

Note: The preferred terms of edema peripheral, generalized edema, pitting edema, and fluid retention were combined to form the aggregate term of “edema.”

Table 14. Adverse Events of Edema in Patients in the PROactive Trial

Number (%) of Patients	
Placebo N=2633	**Pioglitazone** N=2605
419 (15.9%)	712 (27.3%)

Note: The preferred terms of edema peripheral, generalized edema, pitting edema, and fluid retention were combined to form the aggregate term of “edema.”

Hepatic Effects

There has been no evidence of pioglitazone-induced hepatotoxicity in the pioglitazone controlled clinical trial database to date. One randomized, double-blind, three-year trial comparing pioglitazone to glyburide as add-on to metformin and insulin therapy was specifically designed to evaluate the incidence of serum ALT elevation to greater than three times the upper limit of the reference range, measured every eight weeks for the first 48 weeks of the trial then every 12 weeks thereafter. A total of 3/1051 (0.3%) patients treated with pioglitazone and 9/1046 (0.9%) patients treated with glyburide

developed ALT values greater than three times the upper limit of the reference range. None of the patients treated with pioglitazone in the pioglitazone controlled clinical trial database to date have had a serum ALT greater than three times the upper limit of the reference range and a corresponding total bilirubin greater than two times the upper limit of the reference range, a combination predictive of the potential for severe drug-induced liver injury.

Hypoglycemia

In the pioglitazone clinical trials, adverse events of hypoglycemia were reported based on clinical judgment of the investigators and did not require confirmation with fingerstick glucose testing.

In the 16-week add-on to sulfonylurea trial, the incidence of reported hypoglycemia was 3.7% with pioglitazone 30 mg and 0.5% with placebo. In the 16-week add-on to insulin trial, the incidence of reported hypoglycemia was 7.9% with pioglitazone 15 mg, 15.4% with pioglitazone 30 mg, and 4.8% with placebo.

The incidence of reported hypoglycemia was higher with pioglitazone 45 mg compared to pioglitazone 30 mg in both the 24-week add-on to sulfonylurea trial (15.7% versus 13.4%) and in the 24-week add-on to insulin trial (47.8% versus 43.5%).

Three patients in these four trials were hospitalized due to hypoglycemia. All three patients were receiving pioglitazone 30 mg (0.9%) in the 24-week add-on to insulin trial. An additional 14 patients reported severe hypoglycemia (defined as causing considerable interference with patient's usual activities) that did not require hospitalization. These patients were receiving pioglitazone 45 mg in combination with sulfonylurea (n=2) or pioglitazone 30 mg or 45 mg in combination with insulin (n=12).

Urinary Bladder Tumors

Tumors were observed in the urinary bladder of male rats in the two-year carcinogenicity study *[see Nonclinical Toxicology (13.1)]*. In two 3-year trials 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%) cases on placebo. There are too few events of bladder cancer to establish causality.

Metformin Hydrochloride

In a double-blind clinical study of metformin in patients with type 2 diabetes, a total of 141 patients received metformin therapy (up to 2550 mg per day) and 145 patients received placebo. Adverse reactions reported in greater than 5% of the metformin patients, and that were more common in metformin than placebo-treated patients, are listed in Table 15. In this trial, diarrhea led to discontinuation of study medication in 6% of patients treated with metformin.

Table 15. Most Common Adverse Reactions (>5.0%) in a Placebo-Controlled Clinical Study of Metformin Monotherapy*		
Adverse Reaction	**Metformin Monotherapy** (n=141)	**Placebo** (n=145)
	% of Patients	
Diarrhea	53.2	11.7
Nausea/Vomiting	25.5	8.3
Flatulence	12.1	5.5
Asthenia	9.2	5.5
Indigestion	7.1	4.1
Abdominal Discomfort	6.4	4.8
Headache	5.7	4.8

*Reactions that were more common in metformin than placebo-treated patients.

6.2 Laboratory Abnormalities

Hematologic Effects

Pioglitazone may cause decreases in hemoglobin and hematocrit. In placebo-controlled monotherapy trials, mean hemoglobin values declined by 2% to 4% in patients treated with pioglitazone compared with a mean change in hemoglobin of -1% to +1% in placebo-treated patients. 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 associated with pioglitazone therapy and are not likely to be associated with any clinically significant hematologic effects.

Vitamin B_{12} Concentrations

Metformin may lower serum vitamin B_{12} concentrations. Measurement of hematologic parameters on an annual basis is advised in patients on ACTOPLUS MET and any apparent abnormalities should be appropriately investigated and managed *[see Warnings and Precautions (5.14)]*.

Creatine Phosphokinase

During protocol-specified measurement of serum creatine phosphokinase (CPK) in pioglitazone clinical trials, an isolated elevation in CPK to greater than 10 times the upper limit of the reference range was noted in nine (0.2%) patients treated with pioglitazone (values of 2150 to 11400 IU/L) and in no comparator-treated patients. Six of these nine patients continued to receive pioglitazone, two patients were noted to have the CPK elevation on the last day of dosing, and one patient discontinued pioglitazone due to the elevation. These elevations resolved without any apparent clinical sequelae. The relationship of these events to pioglitazone therapy is unknown.

6.3 Postmarketing Experience

Pioglitazone

The following adverse reactions have been identified during postapproval use of pioglitazone. Because these reactions are reported voluntarily from a population of

uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- New onset or worsening diabetic macular edema with decreased visual acuity *[see Warnings and Precautions (5.8)]*.
- Fatal and nonfatal hepatic failure *[see Warnings and Precautions (5.4)]*.

Postmarketing reports of congestive heart failure have been reported in patients treated with pioglitazone, both with and without previously known heart disease and both with and without concomitant insulin administration.

In postmarketing experience, there have been reports of unusually rapid increases in weight and increases in excess of that generally observed in clinical trials. Patients who experience such increases should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure *[see Boxed Warning and Warnings and Precautions (5.1)]*.

7 DRUG INTERACTIONS

7.1 Strong CYP2C8 Inhibitors

An inhibitor of CYP2C8 (e.g., gemfibrozil) significantly increases the exposure (area under the serum concentration-time curve or AUC) and half-life of pioglitazone. Therefore, the maximum recommended dose of pioglitazone is 15 mg daily if used in combination with gemfibrozil or other strong CYP2C8 inhibitors *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

7.2 CYP2C8 Inducers

An inducer of CYP2C8 (e.g., rifampin) may significantly decrease the exposure (AUC) of pioglitazone. Therefore, if an inducer of CYP2C8 is started or stopped during treatment with pioglitazone, changes in diabetes treatment may be needed based on clinical response without exceeding the maximum recommended daily dose of 45 mg for pioglitazone *[see Clinical Pharmacology (12.3)]*.

7.3 Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis. Use these drugs with caution in patients treated with metformin, as the risk of lactic acidosis may increase.

7.4 Cationic Drugs

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of ACTOPLUS MET and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system *[see Clinical Pharmacology (12.3)]*.

7.5 Drugs Affecting Glycemic Control

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid. When such drugs are

administered to a patient receiving ACTOPLUS MET, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving ACTOPLUS MET, the patient should be observed closely for hypoglycemia.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies of ACTOPLUS MET or its individual components in pregnant women. Animal studies using pioglitazone show increased rates of post-implantation loss, delayed development, reduced fetal weights, and delayed parturition at doses 10 to 40 times the maximum recommended human dose. ACTOPLUS MET should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pioglitazone

Clinical Considerations

Abnormal blood glucose concentrations during pregnancy are associated with a higher incidence of congenital anomalies, as well as increased neonatal morbidity and mortality. Most experts recommend the use of insulin during pregnancy to maintain blood glucose concentrations as close to normal as possible for patients with diabetes.

Animal Data

In animal reproductive studies, pregnant rats and rabbits received pioglitazone at doses up to approximately 17 (rat) and 40 (rabbit) times the maximum recommended human oral dose (MRHD) based on body surface area (mg/m^2); no teratogenicity was observed *[see Nonclinical Toxicology (13.3)]*. Increases in embryotoxicity (increased postimplantation losses, delayed development, reduced fetal weights, and delayed parturition) occurred in rats that received oral doses approximately 10 or more times the MRHD (mg/m^2 basis). No functional or behavioral toxicity was observed in rat offspring. When pregnant rats received pioglitazone during late gestation and lactation, delayed postnatal development, attributed to decreased body weight, occurred in rat offspring at oral maternal doses approximately 2 or more times the MRHD (mg/m^2 basis). In rabbits, embryotoxicity occurred at oral doses approximately 40 times the MRHD (mg/m^2 basis).

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. However, because animal reproduction studies are not always predictive of human response, metformin should not be used during pregnancy unless clearly needed.

8.2 Labor and Delivery

The effect of ACTOPLUS MET on labor and delivery in humans is not known.

8.3 Nursing Mothers

No studies have been conducted with the combined components of ACTOPLUS MET. In studies performed with the individual components, both pioglitazone and metformin are secreted in the milk of lactating rats. It is not known whether pioglitazone and/or metformin are secreted in human milk. Because many drugs are excreted in human milk, and because of the potential for ACTOPLUS MET to cause serious adverse reactions in nursing infants, a decision should be made to discontinue nursing or

discontinue ACTOPLUS MET, taking into account the importance of ACTOPLUS MET to the mother.

8.4 Pediatric Use

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

ACTOPLUS MET is not recommended for the treatment of diabetes in pediatric patients based on adverse effects observed with pioglitazone in adults, including fluid retention and congestive heart failure, fractures, and urinary bladder tumors *[see Warnings and Precautions (5.1, 5.2, 5.5, 5.6)].*

8.5 Geriatric Use

Pioglitazone

A total of 92 patients (15.2%) treated with pioglitazone in the three pooled 16- to 26-week double-blind, placebo-controlled, monotherapy trials were ≥65 years old and two patients (0.3%) were ≥75 years old. In the two pooled 16- to 24-week add-on to sulfonylurea trials, 201 patients (18.7%) treated with pioglitazone were ≥65 years old and 19 (1.8%) were ≥75 years old. In the two pooled 16- to 24-week add-on to metformin trials, 155 patients (15.5%) treated with pioglitazone were ≥65 years old and 19 (1.9%) were ≥75 years old. In the two pooled 16- to 24- week add-on to insulin trials, 272 patients (25.4%) treated with pioglitazone were ≥65 years old and 22 (2.1%) were ≥75 years old.

In PROactive, 1068 patients (41.0%) treated with pioglitazone were ≥65 years old and 42 (1.6%) were ≥75 years old.

In pharmacokinetic studies with pioglitazone, no significant differences were observed in pharmacokinetic parameters between elderly and younger patients. These clinical experiences have not identified differences in effectiveness and safety between the elderly (≥65 years) and younger patients although small sample sizes for patients ≥75 years old limit conclusions *[see Clinical Pharmacology (12.3)]*.

Metformin Hydrochloride

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. Metformin is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, ACTOPLUS MET should only be used in patients with normal renal function *[see Contraindications (4)*, *Warnings and Precautions (5.2),* and *Clinical Pharmacology (12.3)]*. Because aging is associated with reduced renal function, ACTOPLUS MET should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of ACTOPLUS MET *[see Warnings and Precautions (5.2) and Dosage and Administration (2)]*.

10 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.

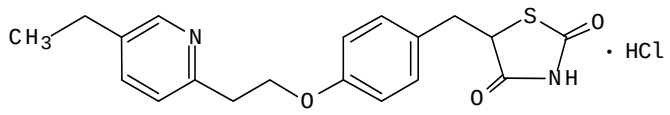
In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

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 and Precautions (5.2)]*. 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.

11 DESCRIPTION

ACTOPLUS MET (pioglitazone and metformin hydrochloride) tablets contain two oral antidiabetic medications used in the management of type 2 diabetes: pioglitazone hydrochloride and metformin hydrochloride.

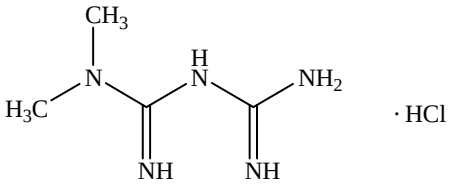
Pioglitazone [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl) ethoxy]phenyl]methyl]-2,4-] thiazolidinedione monohydrochloride contains one asymmetric carbon, and the compound is synthesized and used as the racemic mixture. The two enantiomers of pioglitazone interconvert *in vivo*. No differences were found in the pharmacologic activity between the two enantiomers. The structural formula is as shown:



pioglitazone hydrochloride

Pioglitazone hydrochloride is an odorless white crystalline powder that has a molecular formula of $C_{19}H_{20}N_2O_3S$•HCl and a molecular weight of 392.90 daltons. It is soluble in *N,N*-dimethylformamide, slightly soluble in anhydrous ethanol, very slightly soluble in acetone and acetonitrile, practically insoluble in water, and insoluble in ether.

Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide 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 15 mg pioglitazone (as the base) with 500 mg metformin hydrochloride (15 mg/500 mg) or 15 mg pioglitazone (as the base) with 850 mg metformin hydrochloride (15 mg/850 mg)

formulated with the following excipients: povidone USP, microcrystalline cellulose NF, croscarmellose sodium NF, magnesium stearate NF, hypromellose 2910 USP, polyethylene glycol 8000 NF, titanium dioxide USP, and talc USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ACTOPLUS MET combines two antidiabetic medications with different mechanisms of action to improve glycemic control in adults with type 2 diabetes: pioglitazone, a thiazolidinedione, and metformin hydrochloride, a biguanide. 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 is a thiazolidinedione that 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. Pioglitazone is not an insulin secretagogue. Pioglitazone is an 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.

Because 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. Metformin does not produce hypoglycemia in either patients with type 2 diabetes or healthy subjects [except in specific circumstances, *see Warnings and Precautions (5.7)*] 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.

12.2 Pharmacodynamics

Pioglitazone

Clinical studies demonstrate that pioglitazone improves insulin sensitivity in insulin-resistant patients. Pioglitazone enhances cellular responsiveness to insulin, increases insulin-dependent glucose disposal and improves hepatic sensitivity to insulin. In patients with type 2 diabetes, the decreased insulin resistance produced by pioglitazone results in lower plasma glucose concentrations, lower plasma insulin concentrations, and lower HbA1c values. In controlled clinical trials, pioglitazone had an additive effect

on glycemic control when used in combination with a sulfonylurea, metformin, or insulin *[see Clinical Studies (14)]*.

Patients with lipid abnormalities were included in clinical trials with pioglitazone. Overall, patients treated with pioglitazone had mean decreases in serum triglycerides, mean increases in HDL cholesterol, and no consistent mean changes in LDL and total cholesterol. There is no conclusive evidence of macrovascular benefit with pioglitazone or any other antidiabetic medication *[see Warnings and Precautions (5.15) and Adverse Reactions (6.1)]*.

In a 26-week, placebo-controlled, dose-ranging monotherapy study, mean serum triglycerides decreased in the 15-mg, 30-mg, and 45-mg pioglitazone dose groups compared to a mean increase in the placebo group. Mean HDL cholesterol increased to a greater extent in patients treated with pioglitazone than in the placebo-treated patients. There were no consistent differences for LDL and total cholesterol in patients treated with pioglitazone compared to placebo *(see Table 16).*

Table 16. Lipids in a 26-Week Placebo-Controlled Monotherapy Dose-Ranging Study

	Placebo	**Pioglitazone 15 mg Once Daily**	**Pioglitazone 30 mg Once Daily**	**Pioglitazone 45 mg Once Daily**
Triglycerides (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	263	284	261	260
Percent change from baseline (adjusted mean*)	4.8%	-9.0%†	-9.6%†	-9.3%†
HDL Cholesterol (mg/dL)	N=79	N=79	N=83	N=77
Baseline (mean)	42	40	41	41
Percent change from baseline (adjusted mean*)	8.1%	14.1%†	12.2%	19.1%†
LDL Cholesterol (mg/dL)	N=65	N=63	N=74	N=62
Baseline (mean)	139	132	136	127
Percent change from baseline (adjusted mean*)	4.8%	7.2%	5.2%	6.0%
Total Cholesterol (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	225	220	223	214
Percent change from baseline (adjusted mean*)	4.4%	4.6%	3.3%	6.4%

*Adjusted for baseline, pooled center, and pooled center by treatment interaction
† $p < 0.05$ versus placebo

In the two other monotherapy studies (16 weeks and 24 weeks) and in combination therapy studies with metformin (16 weeks and 24 weeks), the results were generally consistent with the data above.

12.3 Pharmacokinetics

Absorption

ACTOPLUS MET

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

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

Pioglitazone

Following once-daily administration of pioglitazone, steady-state serum concentrations of both pioglitazone and its major active metabolites, M-III (keto derivative of pioglitazone) and M-IV (hydroxyl derivative of pioglitazone), are achieved within seven days. At steady-state, M-III and M-IV reach serum concentrations equal to or greater than that of pioglitazone. At steady-state, in both healthy volunteers and patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the peak total pioglitazone serum concentrations (pioglitazone plus active metabolites) and 20% to 25% of the total AUC.

Maximum serum concentration (C_{max}), AUC, and trough serum concentrations (C_{min}) for pioglitazone and M-III and M-IV, increased proportionally with administered doses of 15 mg and 30 mg per day.

Following oral administration of pioglitazone, peak concentrations of pioglitazone were observed within two hours. Food slightly delays the time to peak serum concentration (T_{max}) to three to four hours but does not alter the extent of absorption (AUC).

Metformin Hydrochloride

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

Distribution

Pioglitazone

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

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

Metabolism
Pioglitazone
Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-III and M-IV are the major circulating active metabolites in humans.

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* study of pioglitazone in combination with gemfibrozil, a strong CYP2C8 inhibitor, showed that pioglitazone is a CYP2C8 substrate *[see Dosage and Administration (2.3) and Drug Interactions (7.1)]*. Urinary 6ß-hydroxycortisol/cortisol ratios measured in patients treated with pioglitazone showed that pioglitazone is not a strong CYP3A4 enzyme inducer.

Metformin Hydrochloride
Intravenous single-dose studies in healthy 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.

Excretion and Elimination
Pioglitazone
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 its metabolites (M-III and M-IV) range 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
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.

Specific Populations
Renal Impairment
Pioglitazone
The serum elimination half-life of pioglitazone, M-III and M-IV remains unchanged in patients with moderate (creatinine clearance 30 to 50 mL/min) and severe (creatinine

clearance <30 mL/min) renal impairment when compared to subjects with normal renal function. Therefore, no dose adjustment in patients with renal impairment is required.

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 (4) and Warnings and Precautions (5.2)]*. Because metformin is contraindicated in patients with renal impairment, ACTOPLUS MET is also contraindicated in these patients.

Hepatic Impairment
Pioglitazone
Compared with healthy controls, subjects with impaired hepatic function (Child-Turcotte-Pugh Grade B/C) have an approximate 45% reduction in pioglitazone and total pioglitazone (pioglitazone, M-III, and M-IV) mean peak concentrations but no change in the mean AUC values. Therefore, no dose adjustment in patients with hepatic impairment is required.

There are postmarketing reports of liver failure with pioglitazone and clinical trials have generally excluded patients with serum ALT >2.5 times the upper limit of the reference range. Use ACTOPLUS MET with caution in patients with liver disease *[see Warnings and Precautions (5.4)]*.

Metformin Hydrochloride
No pharmacokinetic studies of metformin have been conducted in subjects with hepatic impairment. Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. ACTOPLUS MET is not recommended in patients with hepatic impairment *[see Warnings and Precautions (5.4)]*.

Geriatric Patients
Pioglitazone
In healthy elderly subjects, peak serum concentrations of pioglitazone are not significantly different, but AUC values are approximately 21% higher than those achieved in younger subjects. The mean terminal half-life values of pioglitazone were also longer in elderly subjects (about 10 hours) as compared to younger subjects (about seven hours). These changes were not of a magnitude that would be considered clinically relevant.

Metformin Hydrochloride
Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

As is true for all patients, ACTOPLUS MET treatment should not be initiated in geriatric patients unless measurement of creatinine clearance demonstrates that renal function is not reduced *[see Warnings and Precautions (5.2)]*.

Pediatrics
Pioglitazone
Safety and efficacy of pioglitazone in pediatric patients have not been established. ACTOPLUS MET is not recommended for use in pediatric patients *[see Use in Specific Populations (8.4)]*.

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

Gender
Pioglitazone
The mean C_{max} and AUC values of pioglitazone were increased 20% to 60% in women compared to men. In controlled clinical trials, HbA1c decreases from baseline were generally greater for females than for males (average mean difference in HbA1c 0.5%). Because therapy should be individualized for each patient to achieve glycemic control, no dose adjustment is recommended based on gender alone.

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

Ethnicity
Pioglitazone
Pharmacokinetic data among various ethnic groups are not available.

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

Drug-Drug Interactions
Specific pharmacokinetic drug interaction studies with ACTOPLUS MET have not been performed, although such studies have been conducted with the individual pioglitazone and metformin components.

Pioglitazone

Table 17. Effect of Pioglitazone Coadministration on Systemic Exposure of Other Drugs					
	Coadministered Drug				
Pioglitazone Dosage Regimen (mg)*	Name and Dose Regimens	Change in AUC†		Change in C_{max}†	
45 mg (N = 12)	**Warfarin‡**				
	Daily loading then maintenance doses based PT and INR values Quick's Value = 35 ± 5%	R-Warfarin	↓3%	R-Warfarin	↓2%
		S-Warfarin	↓1%	S-Warfarin	↑1%
45 mg (N = 12)	**Digoxin**				
	0.200 mg twice daily (loading dose) then 0.250 mg daily (maintenance dose, 7 days)	↑15%		↑17%	
45 mg daily for 21 days (N = 35)	**Oral Contraceptive**				
	[Ethinyl Estradiol (EE) 0.035 mg plus Norethindrone (NE) 1 mg] for 21 days	EE	↓11%	EE	↓13%
		NE	↑3%	NE	↓7%
45 mg (N = 23)	**Fexofenadine**				
	60 mg twice daily for 7 days	↑30%		↑37%	
45 mg (N = 14)	**Glipizide**				
	5 mg daily for 7 days	↓3%		↓8%	
45 mg daily for 8 days (N = 16)	**Metformin**				
	1000 mg single dose on Day 8	↓3%		↓5%	
45 mg (N = 21)	**Midazolam**				
	7.5 mg single dose on Day 15	↓26%		↓26%	
45 mg (N = 24)	**Ranitidine**				
	150 mg twice daily for 7 days	↑1%		↓1%	
45 mg daily for 4 days (N = 24)	**Nifedipine ER**				
	30 mg daily for 4 days	↓13%		↓17%	
45 mg (N = 25)	**Atorvastatin Ca**				
	80 mg daily for 7 days	↓14%		↓ 23%	
45 mg (N = 22)	**Theophylline**				
	400 mg twice daily for 7 days	↑2%		↑5%	

*Daily for 7 days unless otherwise noted
†% change (with/without coadministered drug and no change = 0%); symbols of ↑ and ↓ indicate the exposure increase and decrease, respectively
‡Pioglitazone had no clinically significant effect on prothrombin time

Table 18. Effect of Coadministered Drugs on Pioglitazone Systemic Exposure

Coadministered Drug and Dosage Regimen	Pioglitazone		
	Dose Regimen (mg)*	Change in AUC†	Change in C_{max}†
Gemfibrozil 600 mg twice daily for 2 days (N = 12)	30-mg single dose	↑3.4-fold‡	↑6%
Ketoconazole 200 mg twice daily for 7 days (N = 28)	45 mg	↑34%	↑14%
Rifampin 600 mg daily for 5 days (N = 10)	30-mg single dose	↓54%	↓5%
Fexofenadine 60 mg twice daily for 7 days (N = 23)	45 mg	↑1%	0%
Ranitidine 150 mg twice daily for 4 days (N = 23)	45 mg	↓13%	↓16%
Nifedipine ER 30 mg daily for 7 days (N = 23)	45 mg	↑5%	↑4%
Atorvastatin Ca 80 mg daily for 7 days (N = 24)	45 mg	↓24%	↓31%
Theophylline 400 mg twice daily for 7 days (N = 22)	45 mg	↓4%	↓2%

*Daily for 7 days unless otherwise noted

†Mean ratio (with/without coadministered drug and no change = 1-fold) % change (with/without coadministered drug and no change = 0%); symbols of ↑ and ↓ indicate the exposure increase and decrease, respectively

‡The half-life of pioglitazone increased from 6.5 hours to 15.1 hours in the presence of gemfibrozil *[see Dosage and Administration (2.3) and Drug Interactions (7.1)]*

Metformin Hydrochloride

Table 19. Effect of Coadministered Drug on Plasma Metformin Systemic Exposure				
Coadministered Drug	**Dose of Coadministered Drug***	**Dose of Metformin***	**Geometric Mean Ratio (ratio with/without coadministered drug)** No effect = 1.00	
			AUC†	**C_{max}**
No dosing adjustments required for the following:				
Glyburide	5 mg	500 mg§	0.98‡	0.99‡
Furosemide	40 mg	850 mg	1.09‡	1.22‡
Nifedipine	10 mg	850 mg	1.16	1.21
Propranolol	40 mg	850 mg	0.90	0.94
Ibuprofen	400 mg	850 mg	1.05‡	1.07‡
Cationic drugs eliminated by renal tubular secretion may reduce metformin elimination: use with caution *[see Warnings and Precautions (5) and Drug Interactions (7)]*.				
Cimetidine	400 mg	850 mg	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis: use with caution *[see Warnings and Precautions (5) and Drug Interactions (7)]*.				
Topiramate	100 mg¶	500 mg¶	1.25¶	1.17

*All metformin and coadministered drugs were given as single doses
†AUC = $AUC_{0-\infty}$
‡Ratio of arithmetic means
§Metformin hydrochloride extended-release tablets, 500 mg
¶At steady-state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours; AUC = AUC_{0-12h}

Table 20. Effect of Metformin on Coadministered Drug Systemic Exposure				
Coadministered Drug	**Dose of Coadministered Drug***	**Dose of Metformin***	**Geometric Mean Ratio (ratio with/without coadministered drug) No effect = 1.00**	
			AUC†	**C_{max}**
No dosing adjustments required for the following:				
Glyburide	5 mg	500 mg§	0.78‡	0.63‡
Furosemide	40 mg	850 mg	0.87‡	0.69‡
Nifedipine	10 mg	850 mg	1.10§	1.08
Propranolol	40 mg	850 mg	1.01§	0.94
Ibuprofen	400 mg	850 mg	0.97¶	1.01¶
Cimetidine	400 mg	850 mg	0.95§	1.01

*All metformin and coadministered drugs were given as single doses
†AUC = $AUC_{0-\infty}$
‡Ratio of arithmetic means, p-value of difference <0.05
§AUC_{0-24hr} reported
¶Ratio of arithmetic means

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ACTOPLUS MET

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

Pioglitazone

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.

Pioglitazone hydrochloride 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 hydrochloride daily prior to and throughout mating and gestation (approximately nine times the maximum recommended human oral dose based on mg/m^2).

Metformin Hydrochloride

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

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

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

13.2 Animal Toxicology and/or Pharmacology

Heart enlargement has been observed in mice (100 mg/kg), rats (4 mg/kg and above) and dogs (3 mg/kg) treated orally with pioglitazone hydrochloride (approximately 11, one, and two 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 four 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).

13.3 Reproductive and Developmental Toxicology

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 two times the maximum recommended human oral dose based on mg/m^2).

14 CLINICAL STUDIES

14.1 Patients Who Have Inadequate Glycemic Control with Diet and Exercise Alone

In a 24-week, randomized, double-blind clinical trial, 600 patients with type 2 diabetes mellitus inadequately controlled with diet and exercise alone (mean baseline HbA1c 8.7%) were randomized to ACTOPLUS MET 15/850 mg, pioglitazone 15 mg, or metformin 850 mg twice daily. Statistically significant improvements in HbA1c and fasting plasma glucose (FPG) were observed in patients treated with ACTOPLUS MET compared to either pioglitazone or metformin alone *(see Table 21)*.

Table 21. Glycemic Parameters in 24-Week Study of ACTOPLUS MET in Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Diet and Exercise

Parameter	Treatment Group		
	ACTOPLUS MET 15/850 mg Twice Daily	**Pioglitazone 15 mg Twice Daily**	**Metformin 850 mg Twice Daily**
HbA1c (%)	N=188	N=162	N=193
Baseline (mean)	8.9	8.7	8.7
Change from Baseline (adjusted mean*)	-1.8	-1.0	-1.0
Difference between ACTOPLUS MET (adjusted mean*) 95% Confidence Interval		0.9† (0.5, 1.2)	0.8† (0.5, 1.2)
% of patients with HbA1c ≤7%	64	47	39
Fasting Plasma Glucose (mg/dL)	N=196	N=176	N=202
Baseline (mean)	177	171	171
Change from Baseline (adjusted mean*)	-40	-22	-25
Difference between ACTOPLUS MET (adjusted mean*) 95% Confidence Interval		18† (8, 28)	15† (6, 25)

*Adjusted for baseline
†p ≤0.05 versus ACTOPLUS MET

14.2 Patients Previously Treated with Metformin

The efficacy and safety of pioglitazone as add-on to metformin therapy have been established in two clinical studies. Bioequivalence of ACTOPLUS MET with coadministered pioglitazone and metformin tablets was demonstrated for both ACTOPLUS MET strengths *[see Clinical Pharmacology (12.3)]*.

The two clinical trials testing pioglitazone as add-on to metformin therapy included patients with type 2 diabetes on any dose of metformin, either alone or in combination with another antidiabetic agent. All other antidiabetic agents were withdrawn at least three weeks prior to starting study treatment.

In the first trial, 328 patients were randomized to receive either 30 mg of pioglitazone or placebo once daily for 16 weeks in addition to their current metformin regimen. Treatment with pioglitazone as add-on to metformin produced statistically significant improvements in HbA1c and FPG at endpoint compared to placebo add-on to metformin *(see Table 22)*.

Table 22. Glycemic Parameters in a 16-Week Placebo-Controlled, Add-on to Metformin Trial		
	Placebo + Metformin	**Pioglitazone 30 mg + Metformin**
Total Population		
HbA1c (%)	N=153	N=161
Baseline (mean)	9.8	9.9
Change from baseline (adjusted mean*)	0.2	-0.6
Difference from placebo + metformin (adjusted mean*) 95% Confidence Interval		-0.8† (-1.2, -0.5)
Fasting Plasma Glucose (mg/dL)	N=157	N=165
Baseline (mean)	260	254
Change from baseline (adjusted mean*)	-5	-43
Difference from placebo + metformin (adjusted mean*) 95% Confidence Interval		-38† (-49, -26)

*Adjusted for baseline, pooled center, and pooled center by treatment interaction
†$p \leq 0.05$ vs. placebo + metformin

In the second trial, 827 patients were randomized to receive either 30 mg or 45 mg of pioglitazone once daily for 24 weeks in addition to their current metformin regimen. The mean reduction from baseline at Week 24 in HbA1c was 0.8% for the 30-mg dose and 1.0% for the 45-mg dose *(see Table 23)*. The mean reduction from baseline at Week 24 in FPG was 38 mg/dL for the 30-mg dose and 51 mg/dL for the 45-mg dose.

Table 23. Glycemic Parameters in a 24-Week Add-on to Metformin Study		
	Pioglitazone 30 mg + Metformin	**Pioglitazone 45 mg + Metformin**
Total Population		
HbA1c (%)	N=400	N=398
Baseline (mean)	9.9	9.8
Change from baseline (adjusted mean*)	-0.8	-1.0
Difference from 30 mg daily pioglitazone + metformin (adjusted mean*) (95% CI)		-0.2 (-0.5, 0.1)
Fasting Plasma Glucose (mg/dL)	N=398	N=399
Baseline (mean)	233	232
Change from baseline (adjusted mean*)	-38	-51
Difference from 30 mg daily pioglitazone + metformin (adjusted mean*) (95% CI)		-12† (-21, -4)

95% CI = 95% confidence interval
*Adjusted for baseline, pooled center, and pooled center by treatment interaction
†$p \leq 0.05$ vs. 30 mg daily pioglitazone + metformin

The therapeutic effect of pioglitazone in combination with metformin was observed in patients regardless of the metformin dose.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

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

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

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

17.1 Instructions

- It is important to instruct patients to adhere to dietary instructions and to have blood glucose and glycosylated hemoglobin tested regularly. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be reminded to seek medical advice promptly.
- Tell patients to promptly report any sign of macroscopic hematuria or other symptoms such as dysuria or urinary urgency that develop or increase during treatment as these may be due to bladder cancer.
- Explain to patients the risks of lactic acidosis, its symptoms and conditions that predispose to its development, as noted in the *Warnings and Precautions (5.2)* section. Advise patients to discontinue ACTOPLUS MET immediately and to promptly notify their healthcare professional if unexplained hyperventilation, myalgia, gastrointestinal symptoms, malaise, unusual somnolence, or other nonspecific symptoms occur.
- Counsel patients against excessive alcohol intake while receiving ACTOPLUS MET.
- Inform patients to immediately report symptoms of an unusually rapid increase in weight or edema, shortness of breath, or other symptoms of heart failure while receiving ACTOPLUS MET.
- Tell patients to promptly stop taking ACTOPLUS MET and seek immediate medical advice if there is unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine as these symptoms may be due to hepatotoxicity.
- Inform patients about the importance of regular testing of renal function and hematologic parameters when receiving treatment with ACTOPLUS MET.
- Therapy with a thiazolidinedione, which is the active pioglitazone component of the ACTOPLUS MET tablet, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking ACTOPLUS MET. Recommend adequate contraception for all premenopausal women who are prescribed ACTOPLUS MET.
- Patients should be advised to notify their health practitioner or call the Poison Control Center immediately in case of ACTOPLUS MET overdose.
- Combination antihyperglycemic therapy may cause hypoglycemia. When initiating ACTOPLUS MET, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.
- Patients should be told to take ACTOPLUS MET as prescribed and instructed that any change in dosing should only be done if directed by their physician. If a dose is missed on one day, the dose should not be doubled the following day.

17.2 FDA-Approved Medication Guide

See attached leaflet.

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Takeda Pharmaceuticals America, Inc.
Deerfield, IL 60015

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APM001 R11

MEDICATION GUIDE
ACTOPLUS MET (ak-TŌ-plus-met)
(pioglitazone and metformin hydrochloride) tablets

Read this Medication Guide carefully before you start taking ACTOPLUS MET and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about ACTOPLUS MET, ask your doctor or pharmacist.

What is the most important information I should know about ACTOPLUS MET?
ACTOPLUS MET can cause serious side effects, including:

- **New or worse heart failure.** Pioglitazone, one of the medicines in ACTOPLUS MET, can cause your body to keep extra fluid (fluid retention), which leads to swelling (edema) and weight gain. Extra body fluid can make some heart problems worse or lead to heart failure. Heart failure means your heart does not pump blood well enough.
  - Do not take ACTOPLUS MET if you have severe heart failure
  - If you have heart failure with symptoms (such as shortness of breath or swelling), even if these symptoms are not severe, ACTOPLUS MET may not be right for you.

  Call your doctor right away if you have any of the following:
  - swelling or fluid retention, especially in the ankles or legs
  - shortness of breath or trouble breathing, especially when you lie down
  - an unusually fast increase in weight
  - unusual tiredness

- **Lactic Acidosis.** Metformin, one of the medicines in ACTOPLUS MET, can cause a rare but serious condition called lactic acidosis (a buildup of an acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital.

  Call your doctor right away if you have any of the following symptoms, which could be signs of lactic acidosis:
  - you feel weak or tired
  - you have unusual (not normal) muscle pain
  - you have stomach pains, nausea, or vomiting
  - you have trouble breathing
  - you feel dizzy or lightheaded
  - you have a slow or irregular heartbeat

Most people who have had lactic acidosis with metformin have other things that, combined with the metformin, led to the lactic acidosis. Tell your doctor if you have any of the following, because you have a higher chance for getting lactic acidosis with ACTOPLUS MET if you:

- have kidney problems or your kidneys are affected by certain x-ray tests that use injectable dye. People whose kidneys are not working properly should not take ACTOPLUS MET
- have liver problems
- drink alcohol very often, or drink a lot of alcohol in short-term "binge" drinking
- get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids
- have surgery
- have a heart attack, severe infection, or stroke
- are 80 years of age or older and have not had your kidneys tested

The best way to keep from having a problem with lactic acidosis from metformin is to tell your doctor if you have any of the problems in the list above. Your doctor may decide to stop your ACTOPLUS MET for a while if you have any of these things.

ACTOPLUS MET can have other serious side effects. See “What are the possible side effects of ACTOPLUS MET?”

What is ACTOPLUS MET?
ACTOPLUS MET contains two prescription diabetes medicines called pioglitazone (ACTOS) and metformin hydrochloride (GLUCOPHAGE). ACTOPLUS MET can be used with diet and exercise to improve blood sugar (glucose) control in adults with type 2 diabetes.

ACTOPLUS MET is not for people with type 1 diabetes.

ACTOPLUS MET is not for people with diabetic ketoacidosis (increased ketones in your blood or urine).

It is not known if ACTOPLUS MET is safe and effective in children.

Who should not take ACTOPLUS MET?
See “What is the most important information I should know about ACTOPLUS MET?”

Do not take ACTOPLUS MET if you:
- have severe heart failure
- are allergic to pioglitazone, metformin, or any of the ingredients in ACTOPLUS MET. See the end of this Medication Guide for a complete list of ingredients in ACTOPLUS MET
- have kidneys which are not working properly
- have a condition called metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin

Tell your doctor before taking ACTOPLUS MET if you have any of these conditions.

What should I tell my doctor before taking ACTOPLUS MET?
Before you start taking ACTOPLUS MET, tell your doctor if you:
- **have heart failure**
- **have kidney problems**
- **are going to have dye injected into a vein for an x-ray, CAT scan, heart study, or other type of scanning**
- **will be undergoing a surgical procedure**
- **drink a lot of alcohol** (all the time or short binge drinking)
- **have type 1 (“juvenile”) diabetes or had diabetic ketoacidosis**
- **have a type of diabetic eye disease that causes swelling in the back of the eye (macular edema)**
- **have liver problems**
- **are pregnant or plan to become pregnant.** It is not known if ACTOPLUS MET will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant about the best way to control your blood glucose levels while pregnant
- **are a premenopausal woman (before the “change of life”) who does not have periods regularly or at all.** ACTOPLUS MET may increase your chance of becoming pregnant. Talk to your doctor about birth control choices while taking ACTOPLUS MET. Tell your doctor right away if you become pregnant while taking ACTOPLUS MET
- **are breastfeeding or plan to breastfeed.** It is not known if ACTOPLUS MET passes into your breast milk. You and your doctor should decide if you will take ACTOPLUS MET or breastfeed. You should not do both. Talk to your doctor about the best way to control your blood glucose levels while breastfeeding

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

ACTOPLUS MET and some of your other medicines can affect each other. You may need to have your dose of ACTOPLUS MET or certain other medicines changed.

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist before you start a new medicine. They will tell you if it is okay to take ACTOPLUS MET with other medicines.

How should I take ACTOPLUS MET?

- Take ACTOPLUS MET exactly as your doctor tells you to take it
- Your doctor may need to change your dose of ACTOPLUS MET. Do not change your ACTOPLUS MET dose unless your doctor tells you to
- ACTOPLUS MET may be prescribed alone or with other diabetes medicines. This will depend on how well your blood sugar is controlled
- Take ACTOPLUS MET with meals to lower your chance of an upset stomach
- If you miss a dose of ACTOPLUS MET, take your next dose as prescribed unless your doctor tells you differently. **Do not take** two doses at one time the next day
- If you take too much ACTOPLUS MET, call your doctor or go to the nearest hospital emergency room right away
- If your body is under stress such as from a fever, infection, accident, or surgery, the dose of your diabetes medicines may need to be changed. Call your doctor right away
- Stay on your diet and exercise programs and test your blood sugar regularly while taking ACTOPLUS MET
- Your doctor should do certain blood tests before you start and while you take ACTOPLUS MET
- Your doctor should also do hemoglobin A1C testing to check how well your blood sugar is controlled with ACTOPLUS MET
- Your doctor should check your eyes regularly while you take ACTOPLUS MET

What are the possible side effects of ACTOPLUS MET?
ACTOPLUS MET may cause serious side effects, including:

- **See "What is the most important information I should know about ACTOPLUS MET?"**
- **liver problems.** Call your doctor right away if you have:
  - nausea or vomiting
  - stomach pain
  - unusual or unexplained tiredness
  - loss of appetite
  - dark urine
  - yellowing of your skin or the whites of your eyes
- **broken bones (fractures).** Usually in the hand, upper arm, or foot in women. Talk to your doctor for advice on how to keep your bones healthy
- **bladder cancer.** There may be an increased chance of having bladder cancer when you take ACTOPLUS MET. You should not take ACTOPLUS MET if you are receiving treatment for bladder cancer. Tell your doctor right away if you have any of the following symptoms of bladder cancer:
  - blood or a red color in your urine
  - an increased need to urinate
  - pain while you urinate

- **low blood sugar (hypoglycemia).** This can happen if you skip meals, if you also use another medicine that lowers blood sugar, or if you have certain medical problems. Lightheadedness, dizziness, shakiness, or hunger may happen if your blood sugar is too low. Call your doctor if low blood sugar levels are a problem for you
- **diabetic eye disease with swelling in the back of the eye (macular edema).** Tell your doctor right away if you have any changes in your vision. Your doctor should check your eyes regularly
- **release of an egg from an ovary in a woman (ovulation) leading to pregnancy.** Ovulation may happen when premenopausal women who do not have regular monthly periods take ACTOPLUS MET. This can increase your chance of getting pregnant.
- **low red blood cell count (anemia).**

The most common side effects of ACTOPLUS MET include:

- coldlike symptoms (upper respiratory tract infection)
- swelling (edema)
- diarrhea
- headache
- increased weight

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the side effects of ACTOPLUS MET. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ACTOPLUS MET?

- Store ACTOPLUS MET at 59°F to 86°F (15°C to 30°C). Keep ACTOPLUS MET in the original container and protect from light
- Keep the ACTOPLUS MET bottle tightly closed and protect from getting wet (away from moisture and humidity)

Keep ACTOPLUS MET and all medicines out of the reach of children.

General information about the safe and effective use of ACTOPLUS MET
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ACTOPLUS MET for a condition for which it was not prescribed. Do not give ACTOPLUS MET to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about ACTOPLUS MET. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about ACTOPLUS MET that is written for healthcare professionals.

For more information, go to www.actoplusmet.com or call 1-877-825-3327.

What are the ingredients in ACTOPLUS MET?
Active Ingredients: pioglitazone hydrochloride and metformin hydrochloride
Inactive Ingredients: povidone, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, hypromellose 2910, polyethylene glycol 8000, titanium dioxide, and talc

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Distributed by:
Takeda Pharmaceuticals America, Inc.
Deerfield, IL 60015

Revised: September 2012

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