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

ACTOPLUS MET XR (pioglitazone and metformin hydrochloride extended-release) tablets for oral use

Initial U.S. Approval: 2009

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 XR, cause or exacerbate congestive heart failure in some patients. (5.1)**
- **After initiation of ACTOPLUS MET XR, 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 XR must be considered. (5.1)**
- **ACTOPLUS MET XR is not recommended in patients with symptomatic heart failure. (5.1)**
- **Initiation of ACTOPLUS MET XR 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 XR and hospitalize the patient immediately. (5.2)**

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

ACTOPLUS MET XR 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)

Important Limitations of Use:

- Not for treatment of type 1 diabetes or diabetic ketoacidosis. (1)

----------DOSAGE AND ADMINISTRATION----------

- Individualize the starting dose of ACTOPLUS MET XR 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 extended-release metformin 2000 mg. (2)
- ACTOPLUS MET XR 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 XR. If abnormal, use caution when treating with ACTOPLUS MET XR, investigate the probable cause, treat (if possible) and follow appropriately. Monitoring liver tests while on ACTOPLUS MET XR is not recommended in patients without liver disease. (2, 5.4)

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

- Tablets: 15 mg pioglitazone/1000 mg metformin HCl. (3)
- Tablets: 30 mg pioglitazone/1000 mg metformin HCl. (3)

----------CONTRAINDICATIONS----------

- Initiation in patients with established New York Heart Association (NYHA) Class III or IV heart failure *[see Boxed Warning]*. (4)
- Renal impairment. (4)
- Use in patients with known hypersensitivity to pioglitazone, metformin or any other component of ACTOPLUS MET XR. (4)
- 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)
- Lactic acidosis: Warn against excessive alcohol intake. ACTOPLUS MET XR 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, 5.10)
- Edema: Dose-related edema may occur. (5.3)
- 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. (5.4)
- Hepatic effects: Postmarketing reports of hepatic failure, sometimes fatal. Causality cannot be excluded. If liver injury is detected, promptly interrupt ACTOPLUS MET XR and assess patient for probable cause, then treat cause if possible, to resolution or stabilization. Do not restart ACTOPLUS MET XR if liver injury is confirmed and no alternate etiology can be found. (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)
- Fractures: Increased incidence in female patients. Apply current standards of care for assessing and maintaining bone health. (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)
- 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)
- Vitamin B12 deficiency: Metformin may lower vitamin B12 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 XR or any other antidiabetic drug. (5.15)

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

Most common adverse reactions (>5%) are 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 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 XR dose to 15 mg/1000 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)
- Pediatrics: Not recommended for use in pediatric patients.(8.4)
- Geriatric Use: Caution should be used when prescribing ACTOPLUS MET XR to elderly patients because reduced renal functions are associated with increasing age. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 11/2013

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

DOCKET ALARM

Find authenticated court documents without watermarks at docketalarm.com.

FULL PRESCRIBING INFORMATION

WARNING: CONGESTIVE HEART FAILURE AND LACTIC ACIDOSIS

Congestive Heart Failure

- **Thiazolidinediones, including pioglitazone, which is a component of ACTOPLUS MET XR, cause or exacerbate congestive heart failure in some patients *[see Warnings and Precautions (5.1)]*.**
- **After initiation of ACTOPLUS MET XR, 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 XR must be considered *[see Warnings and Precautions (5.1)]*.**
- **ACTOPLUS MET XR is not recommended in patients with symptomatic heart failure.**
- **Initiation of ACTOPLUS MET XR 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 XR should be discontinued and the patient hospitalized immediately *[see Warnings and Precautions (5.2)]*.**

1 INDICATIONS AND USAGE

ACTOPLUS MET XR 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)]*.

Important Limitations of Use

Pioglitazone exerts its antihyperglycemic effect only in the presence of endogenous insulin. ACTOPLUS MET XR 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 (5.5)].*

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

2 DOSAGE AND ADMINISTRATION

2.1 Recommendations for All Patients

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

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

- 15 mg/1000 mg or 30 mg/1000 mg once daily and gradually titrated as needed, after assessing adequacy of therapeutic response and tolerability,
- for patients with NYHA Class I or Class II congestive heart failure: 15 mg/1000 mg or 30 mg/1000 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/1000 mg twice daily or 30 mg/1000 mg once 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/1000 mg twice daily or 30 mg/1000 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 XR should be taken at doses that are as close as possible to the dose of pioglitazone and metformin already being taken.

ACTOPLUS MET XR may be titrated up to a maximum daily dose of 45 mg/2000 mg of pioglitazone/extended-release metformin.

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

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

After initiation of ACTOPLUS MET XR 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 XR. Routine periodic monitoring of liver tests during treatment with ACTOPLUS MET XR is not recommended in patients without liver disease. Patients who have liver test abnormalities prior to initiation of ACTOPLUS MET XR or who are found to have abnormal liver tests while taking ACTOPLUS MET XR should be managed as described under Warnings and Precautions *[see Warnings and Precautions (5.5)* and *Clinical Pharmacology (12.3)].*

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

2.2 Concomitant Use with an Insulin Secretagogue or Insulin

If hypoglycemia occurs in a patient coadministered ACTOPLUS MET XR 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 XR 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 Concomitant Use with Strong CYP2C8 Inhibitors

Coadministration of pioglitazone (one of the ingredients in ACTOPLUS MET XR) and gemfibrozil, a strong CYP2C8 inhibitor, increases pioglitazone exposure by approximately 3-fold. Therefore, the maximum recommended dose of ACTOPLUS MET XR is 15 mg/1000 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/1000 mg tablets: White to off-white, round, film-coated tablets debossed with “4833X” on one side and “15/1000” on the other
- 30 mg/1000 mg tablets: White to off-white, oblong, film-coated tablets debossed with “4833X” on one side and “30/1000” on the other

4 CONTRAINDICATIONS

- Initiation in patients with established NYHA Class III or IV heart failure *[see Boxed Warning]*.
- 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)].*
- Use in patients with known hypersensitivity to pioglitazone, metformin or any other component of ACTOPLUS MET XR.
- 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 XR 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 XR must be considered *[see Boxed Warning*, *Contraindications (4),* and *Adverse Reactions (6.1)]*.

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.