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

- **Post-marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally greater than 5 mcg/mL. (5.2)**
- **Risk factors include renal impairment, concomitant use of certain drugs, age ≥65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the Full Prescribing Information. (5.2)**
- **If lactic acidosis is suspected, discontinue ACTOPLUS MET XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.2)**

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

Boxed Warning	5/2016
Dosage and Administration	
Recommendations for Use in Renal Impairment (2.2)	5/2016
Discontinuation for Iodinated Contrast Imaging Procedures (2.4)	5/2016
Contraindications (4)	5/2016
Warnings and Precautions	
Lactic Acidosis (5.2)	5/2016
Hepatic Effects (5.5)	5/2016
Urinary Bladder Tumors (5.6)	12/2016

----------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 based on the patient's current regimen and 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. (2.1)
- Give in divided daily doses with meals to reduce gastrointestinal effects. (2.1)
- Monitor patients for adverse events related to fluid retention after initiation and dose increases. (2.1)
- Obtain liver tests before initiation. If abnormal, use caution when treating with ACTOPLUS MET XR, investigate the probable cause, treat (if possible) and follow appropriately. (2.1, 5.4)
- Prior to initiation, assess renal function with estimated glomerular
  - o Initiation is not recommended in patients with eGFR between 30 - 45 mL/min/1.73 m^2
  - o Assess risk/benefit of continuing if eGFR falls below 45 mL/min/1.73 m^2
  - o discontinue if eGFR falls below 30 mL/min/1.73 m^2
- ACTOPLUS MET XR may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures (2.4)

----------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)
- Severe renal impairment (eGFR below 30 mL/min/1.73 m^2). (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: See boxed warning. (5.2)
- 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: May increase the risk of bladder cancer. 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)
- Vitamin B12 deficiency: Metformin may lower vitamin B12 levels. Monitor hematologic parameters annually. (5.9)
- Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ACTOPLUS MET XR or any other antidiabetic drug. (5.10)

----------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)
- Carbonic anhydrase inhibitors may increase risk of lactic acidosis. Consider more frequent monitoring. (7.3)
- Drugs that are eliminated by renal tubular secretion (e.g., cationic drugs such as cimetidine), may increase the accumulation of metformin. Consider more frequent monitoring. (7.4)
- Alcohol can potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake. (7.5)
- Use of insulin secretagogues or insulin use may increase the risk for hypoglycemia and may require dose reduction. (7.6)

----------USE IN SPECIFIC POPULATIONS----------

- Females and Males of Reproductive Potential: Advise premenopausal females of the potential for an unintended pregnancy. (8.3)
- Pediatrics: Not recommended for use in pediatric patients.(8.4)
- Geriatric Use: Assess renal function more frequently. (8.5)
- Hepatic impairment: Avoid use in patients with hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 12/2016

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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 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 *[see Warnings and Precautions (5.1)]*.**
- **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

- **Post-marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (greater than 5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate:pyruvate ratio; and metformin plasma levels generally greater than 5 mcg/mL *[see Warnings and Precautions (5.2)].***
- **Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.**
- **Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the Full Prescribing Information *[see Dosage and Administration (2.2), Contraindications (4), Warnings and Precautions (5.2), Drug Interactions (7), and Use in Specific Populations (8.6, 8.7)]*.**
- **If metformin-associated lactic acidosis is suspected, immediately discontinue ACTOPLUS MET XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended *[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)].*

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)].*

2.2 Recommendations for Use in Renal Impairment

Assess renal function prior to initiation of ACTOPLUS MET XR and periodically thereafter.

ACTOPLUS MET XR is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2.

Initiation of ACTOPLUS MET XR in patients with an eGFR between 30 – 45 mL/min/1.73 m^2 is not recommended.

In patients taking ACTOPLUS MET XR whose eGFR later falls below 45 mL/min/1.73 m^2, assess the benefit risk of continuing therapy.

Discontinue ACTOPLUS MET XR if the patient's eGFR later falls below 30 mL/min/1.73 m^2 *[see Contraindications (4) and Warnings and Precautions (5.12)]*.

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)].*

2.4 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue ACTOPLUS MET XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m^2; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart ACTOPLUS MET XR if renal function is stable *[see Warnings and Precautions (5.2)]*.

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

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