PIOGLITAZOLE AND METFORMIN HYDROCHLORIDE - pioglitazole and metformin hydrochloride tablet
Macleods Pharmaceuticals Limited

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PIOGLITAZONE AND METFORMIN HYDROCHLORIDE tablets safely and effectively. See full prescribing information for PIOGLITAZONE AND METFORMIN HYDROCHLORIDE tablets.
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 pioglitazone and metformin hydrochloride tablets, cause or exacerbate congestive heart failure in some patients. (5.1)
• After initiation of pioglitazone and metformin hydrochloride tablets, 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 pioglitazone and metformin hydrochloride tablets must be considered. (5.1)
• Pioglitazone and metformin hydrochloride tablets are not recommended in patients with symptomatic heart failure. (5.1)
• Initiation of pioglitazone and metformin hydrochloride tablets 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 pioglitazone and metformin hydrochloride and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.2)

RECENT MAJOR CHANGES

Warning and Precautions
Urinary Bladder Tumors (5.6) 12/2016

INDICATIONS AND USAGE

Pioglitazone and metformin hydrochloride tablets are 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 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 metformin 2550 mg. (2.1)
• Give in divided daily doses with meals to reduce the gastrointestinal effects due to metformin. (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 pioglitazone and metformin hydrochloride tablets, investigate the probable cause, treat (if possible), and follow appropriately. (2.1, 5.5)
• Prior to initiation, assess renal function with estimated glomerular filtration rate (eGFR) (2.2)
  o Do not use in patients with eGFR below 30 mL/min/1.73 m^2
  o Initiation is not recommended in patients with eGFR between 30 – 45 mL/min/1.73 m^2
  o Assess risk/benefit of continuing Pioglitazone and metformin hydrochloride tablets if eGFR falls below 45 mL/min/1.73 m^2
  o Discontinue if eGFR falls below 30 mL/min/1.73 m^2
Pioglitazone and metformin hydrochloride tablets 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/500 mg metformin HCl and 15 mg pioglitazone/850 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 30mL/min/1.73 m^2). (4)
• Use in patients with known hypersensitivity to pioglitazone, metformin or any other component of pioglitazone and metformin hydrochloride tablets. (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 pioglitazone and metformin hydrochloride and assess patient for probable cause, then treat cause if possible, to resolution or stabilization. Do not restart pioglitazone and metformin hydrochloride 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)
• Vitamin B_{12} deficiency: Metformin may lower vitamin B_{12} levels. Monitor hematologic parameters annually. (5.9)
• Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with pioglitazone and metformin hydrochloride. (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 Macleods Pharma USA, Inc. at 1-888-943-3210 or 1-855-926-3384 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

• Strong CYP2C8 inhibitors (e.g., gemfibrozil) increase pioglitazone concentrations. Limit pioglitazone and metformin hydrochloride dose to 15 mg/850 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 reduce metformin clearance (such as ranolazine, vandetanib, dolutegravir, and cimetidine), may increase the accumulation of metformin. Consider the benefits and risks of concomitant use. (7.4)
• 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)
•Topiramate may decrease pioglitazone concentrations. (7.8)

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: 2/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

BOXED WARNING
1 INDICATIONS & USAGE

2 DOSAGE & ADMINISTRATION
2.1 Recommendations for All Patients
2.2 Recommendations for Use in Renal Impairment
2.3 Concomitant Use with Strong CYP2C8 Inhibitors
2.4 Discontinuation for Iodinated Contrast Imaging Procedures
3 DOSAGE FORMS & STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Congestive Heart Failure
5.2 Lactic Acidosis
5.3 Edema
5.4 Hypoglycemia
5.5 Hepatic Effects
5.6 Urinary Bladder Tumors
5.7 Fractures
5.8 Macular Edema
5.9 Vitamin B12 Levels
5.10 Macrovascular Outcomes
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Strong CYP2C8 Inhibitors
7.2 CYP2C8 Inducers
7.3 Carbonic Anhydrase Inhibitors
7.4 Drugs that Reduce Metformin Clearance
7.5 Alcohol
7.6 Insulin Secretagogues or Insulin
7.7 Drugs Affecting Glycemic Control
7.8 Topiramate
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis & Mutagenesis & Impairment Of Fertility
13.2 Animal Pharmacology & OR Toxicology
14 CLINICAL STUDIES
14.1 Patients Who Have Inadequate Glycemic Control with Diet and Exercise Alone
14.2 Patients Previously Treated with Metformin
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

BOXED WARNING

FULL PRESCRIBING INFORMATION

WARNING: CONGESTIVE HEART FAILURE AND LACTIC ACIDOSIS
Congestive Heart Failure
• Thiazolidinediones, including pioglitazone, which is a component of pioglitazone and metformin hydrochloride, cause or exacerbate congestive heart failure in some patients *[see Warnings and Precautions (5.1)].*
• After initiation of pioglitazone and metformin hydrochloride, 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 pioglitazone and metformin hydrochloride must be considered *[see Warnings and Precautions (5.1)].*
• Pioglitazone and metformin hydrochloride is not recommended in patients with symptomatic heart failure [*see Warnings and Precautions (5.1)*].
• Initiation of pioglitazone and metformin hydrochloride 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 pioglitazone and metformin hydrochloride tablets and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended *[see Warnings and Precautions (5.2)].*

1 INDICATIONS & USAGE

Pioglitazone and metformin hydrochloride tablets are 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. Pioglitazone and metformin hydrochloride tablets 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 & ADMINISTRATION

2.1 Recommendations for All Patients

Pioglitazone and metformin hydrochloride tablets 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: Pioglitazone and metformin hydrochloride tablets should be taken at doses that are as close as possible to the dose of pioglitazone and metformin already being taken.

Pioglitazone and metformin hydrochloride tablets 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 pioglitazone and metformin hydrochloride tablets 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 pioglitazone and metformin hydrochloride tablets. Routine periodic monitoring of liver tests during treatment with pioglitazone and metformin hydrochloride tablet is not recommended in patients without liver disease. Patients who have liver test abnormalities prior to initiation of pioglitazone and metformin hydrochloride tablet or who are found to have abnormal liver tests while taking pioglitazone and metformin hydrochloride tablets 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 pioglitazone and metformin hydrochloride tablets and periodically thereafter.

Pioglitazone and metformin hydrochloride tablets are contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2.

Initiation of pioglitazone and metformin hydrochloride tablets in patients with an eGFR between 30 – 45 mL/min/1.73 m^2 is not recommended.
In patients taking pioglitazone and metformin hydrochloride tablets whose eGFR later falls below 45 mL/min/1.73 m^2, assess the benefit risk of continuing therapy.

Discontinue pioglitazone and metformin hydrochloride tablets if the patient's eGFR later falls below 30 mL/min/1.73 m^2 *[see Contraindications (4) and Warnings and Precautions (5.2)]*.

2.3 Concomitant Use with Strong CYP2C8 Inhibitors

Coadministration of pioglitazone (one of the ingredients in pioglitazone and metformin hydrochloride tablets) and gemfibrozil, a strong CYP2C8 inhibitor, increases pioglitazone exposure approximately 3-fold. Therefore, the maximum recommended dose of pioglitazone and metformin hydrochloride tablet is 15 mg/850 mg daily when used in combination with gemfibrozil or other strong CYP2C8 inhibitors *[see*

Drug Interactions (7.1) and ClinicalPharmacology (12.3)].

2.4 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue pioglitazone and metformin hydrochloride tablets 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 pioglitazone and metformin hydrochloride tablets if renal function is stable *[see Warnings and Precautions (5.2)].*

3 DOSAGE FORMS & STRENGTHS

• Pioglitazone and Metformin hydrochloride tablets USP 15 mg/500 mg: White to off-white coloured, capsule shaped, film-coated tablets debossed with 'C27' on one side and plain on the other side.

• Pioglitazone and Metformin hydrochloride tablets USP 15 mg/850 mg: White to off-white coloured, capsule shaped, film-coated tablets debossed with 'C28' on one side and plain on the other side.

4 CONTRAINDICATIONS

• Initiation in patients with established NYHA Class III or IV heart failure [see Boxed Warning].
• Severe renal impairment (eGFR below 30 mL/min/1.73 m^2) *[see Warnings and Precautions (5.2)].*
• Use in patients with known hypersensitivity to pioglitazone, metformin, or any other component of pioglitazone and metformin hydrochloride tablets.
• 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 pioglitazone and metformin hydrochloride tablets 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 pioglitazone and metformin hydrochloride tablets must be considered *[see Boxed Warning, Contraindications (4), and Adverse Reactions (6.1)].*

5.2 Lactic Acidosis

Metformin hydrochloride
Lactic Acidosis
There have been post-marketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (greater than 5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate: pyruvate ratio;metformin plasma levels generally greater than 5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of pioglitazone and metformin hydrochloride tablets. In pioglitazone and metformin hydrochloride-treated patients with a diagnosis or

strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable, with a clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue pioglitazone and metformin hydrochloride and report these symptoms to their healthcare provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

Renal Impairment
The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include *[see Dosage and Administration (2.2), Clinical Pharmacology (12.3)]*.
• Before initiating pioglitazone and metformin hydrochloride, obtain an eGFR.
• Pioglitazone and metformin hydrochloride is contraindicated in patients with an eGFR less than 30mL/min /1.73 m^2. Initiation of pioglitazone and metformin hydrochloride is not recommended in patients with eGFR between 30 – 45 mL/min/1.73 m^2 *[see Contraindications (4)]*.
• Obtain an eGFR at least annually in all patients taking pioglitazone and metformin hydrochloride. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.
• In patients taking pioglitazone and metformin hydrochloride whose eGFR later falls below 45 mL/min/1.73 m^2, assess the benefit and risk of continuing therapy.

Drug Interactions
The concomitant use of pioglitazone and metformin hydrochloride tablets with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation (e.g. cationic drugs) *[see Drug Interactions (7)]*. Therefore, consider more frequent monitoring of patients.

Age65 or Greater
The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients *[see Use in Specific Populations (8.5)]*.

Radiological Studies with Contrast
Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop pioglitazone and metformin hydrochloride tablets 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 hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart pioglitazone and metformin hydrochloride tablets if renal function is stable.

Surgery and Other Procedures
Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. Pioglitazone and metformin hydrochloride tablets should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States
Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue pioglitazone and metformin hydrochloride tablets.

Excessive Alcohol Intake
Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving pioglitazone and metformin hydrochloride tablets.

Hepatic Impairment
Patients with hepatic impairment have developed with cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of pioglitazone and metformin hydrochloride tablets in patients with clinical or laboratory evidence of hepatic disease.

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.

Pioglitazone and metformin hydrochloride tablets 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, pioglitazone and metformin hydrochloride tablets should be used with caution in patients at risk for congestive heart failure. Patients treated with pioglitazone and metformin hydrochloride tablets 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 Hypoglycemia

Patients receiving pioglitazone and metformin hydrochloride tablets 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 Drug Interactions (7.7)]*. 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.

5.5 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 pioglitazone and metformin hydrochloride tablets therapy.

In patients with abnormal liver tests, pioglitazone and metformin hydrochloride tablets 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), pioglitazone and metformin hydrochloride tablets treatment should be interrupted and investigation done to establish the probable cause. Pioglitazone and metformin hydrochloride tablets 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 pioglitazone and metformin hydrochloride. For patients with lesser elevations of serum ALT or bilirubin and with an alternate probable cause, treatment with pioglitazone and metformin hydrochloride tablets can be used with caution.

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 addition, during the three year PROactive clinical trial, 14 patients out of 2605 (0.54%) randomized to pioglitazone and 5 out of 2633 (0.19%) randomized to placebo were diagnosed with bladder cancer. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 6 (0.23%) cases on pioglitazone and two (0.08%) cases on placebo. After completion of the trial, a large subset of patients was observed for up to 10 additional years, with little additional exposure to pioglitazone. During the 13 years of both PROactive and observational follow-up, the occurrence of bladder cancer did not differ between patients randomized to pioglitazone or placebo (HR =1.00; [95% CI: 0.59–1.72]).

Findings regarding the risk of bladder cancer in patients exposed to pioglitazone vary among observational studies; some did not find an increased risk of bladder cancer associated with pioglitazone, while others did.

A large prospective10-year observational cohort study conducted in the United States found no statistically significant increase in the risk of bladder cancer in diabetic patients ever exposed to pioglitazone, compared to those never exposed to pioglitazone (HR =1.06 [95% CI 0.89–1.26]).

A retrospective cohort study conducted with data from the United Kingdom found a statistically significant association between ever exposure to pioglitazone and bladder cancer (HR: 1.63; [95% CI: 1.22–2.19]).

Associations between cumulative dose or cumulative duration of exposure to pioglitazone and bladder cancer were not detected in some studies including the 10-year observational study in the U.S., but were in others. Inconsistent findings and limitations inherent in these and other studies preclude conclusive interpretations of the observational data.

Pioglitazone may be associated with an increase in the risk of urinary bladder tumors. There are insufficient data to determine whether pioglitazone is a tumor promoter for urinary bladder tumors.

Consequently, pioglitazone and metformin hydrochloride tablets should not be used in patients with active bladder cancer and the benefits of glycemic control versus unknown risks for cancer recurrence with pioglitazone and metformin hydrochloride tablets should be considered in patients with a prior history of bladder cancer.

5.7 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 pioglitazone and metformin hydrochloride tablets and attention should be given to assessing and maintaining bone health according to current standards of care.

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 Vitamin B12 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 pioglitazone and metformin hydrochloride tablets and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate vitamin B12 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.

5.10 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with pioglitazone and metformin hydrochloride tablets.

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 (5.7)]*

6.1 Clinical Trials 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 pioglitazone and metformin hydrochloride Clinical Trial
Table 3 summarizes the incidence and types of adverse reactions reported in a controlled, 24-week double-blind clinical trial of pioglitazone and metformin hydrochloride dosed twice daily in patients

with inadequate glycemic control on diet and exercise (N=600).

Table 3. Adverse Events (≥5% for pioglitazone and metformin hydrochloride) Reported by Patients with Inadequate Glycemic Control on Diet and Exercisein a 24-Week Double-Blind Clinical Trial of Pioglitazone and Metformin hydrochloride Administered Twice Daily			
% of Patients			
	Pioglitazone and Metformin hydrochloride 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 pioglitazone and metformin hydrochloride 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, non-fatal 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 Trial: 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 pioglitazone and metformin hydrochloride 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 Pioglitazone and Metformin hydrochloridein Patients with Inadequate Glycemic Control on Diet and Exercise

	Pioglitazone and Metformin hydrochloride 15/850 mg Twice Daily	**Pioglitazone 15 mg Twice Daily**	**Metformin 850 mg Twice Daily**
	Median	Median	Median

	(25th , 75th percentile)	(25th , 75th percentile)	(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 pioglitazone and metformin hydrochloride trial, edema was reported in 3.0% of patients in the pioglitazone and metformin hydrochloride 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)*]. During the three year PROactive clinical trial, 14 patients out of 2605 (0.54%) randomized to pioglitazone and 5 out of 2633 (0.19%) randomized to placebo were diagnosed with bladder cancer. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 6 (0.23%) cases on pioglitazone and two (0.08%) cases on placebo. After completion of the trial, a large subset of patients was observed for up to 10 additional years, with little additional exposure to pioglitazone. During the 13 years of both PROactive and observational follow-up, the occurrence of bladder cancer did not differ between patients randomized to pioglitazone or placebo (HR =1.00; 95% CI: 0.59-1.72) [*see Warnings and Precautions (5.6)*].

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.

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 four 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 B12 concentrations. Measurement of hematologic parameters on an annual basis is advised in patients on pioglitazone and metformin hydrochloride tablets and any apparent abnormalities should be appropriately investigated and managed [*see Warnings and Precautions (5.9)*].

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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval 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.

Pioglitazone

• 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 (5.5)]*.

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)]*.

Metformin
Cholestatic, hepatocellular, and mixed hepatocellular liver injury.

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 ($t_{½}$) 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 causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with pioglitazone and metformin

hydrochloride tablets may increase the risk for lactic acidosis. Consider more frequent monitoring of these patients.

7.4 Drugs that Reduce Metformin Clearance

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2]/multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis *[see Clinical Pharmacology (12.3)]*. Consider the benefits and risks of concomitant use.

7.5 Alcohol

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving pioglitazone and metformin hydrochloride tablets.

7.6 Insulin Secretagogues or Insulin

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

If hypoglycemia occurs in a patient coadministered pioglitazone and metformin hydrochloride tablets 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.

7.7 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 pioglitazone and metformin hydrochloride tablets, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving pioglitazone and metformin hydrochloride tablets, the patient should be observed closely for hypoglycemia

7.8 Topiramate

A decrease in the exposure of pioglitazone and its active metabolites were noted with concomitant administration of pioglitazone and topiramate *[see Clinical Pharmacology (12.3)]*. The clinical relevance of this decrease is unknown; however, when pioglitazone and metformin hydrochloride and topiramate are used concomitantly, monitor patients for adequate glycemic control.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited data with pioglitazone and metformin hydrochloride or pioglitazone in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk [*see Data*]. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy [*see Clinical Considerations*].

In animal reproduction studies, no adverse developmental effects were observed when pioglitazone was administered to pregnant rats and rabbits during organogenesis at exposures up to 5- and 35-times the 45 mg clinical dose, respectively, based on body surface area. No adverse developmental effects were observed when metformin was administered to pregnant Sprague Dawley rats and rabbits during the

period of organogenesis at doses up to 2- to 6-times, respectively, a 2000 mg clinical dose, based on body surface area [*see Data*].

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with a HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, still birth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Data

Human Data

Published data from post-marketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during pregnancy. However, these studies cannot definitely establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Animal Data

Pioglitazone and Metformin hydrochloride

Animal reproduction studies were not conducted with the combined products in pioglitazone and metformin hydrochloride tablets. The following data are based on studies conducted with the individual components of pioglitazone and metformin hydrochloride tablets.

Pioglitazone

Pioglitazone administered to pregnant rats during organogenesis did not cause adverse developmental effects at a dose of 20 mg/kg (~5-times the 45 mg clinical dose), but delayed parturition and reduced embryofetal viability at 40 and 80 mg/kg, or ≥9-times the 45 mg clinical dose, by body surface area. In pregnant rabbits administered pioglitazone during organogenesis, no adverse developmental effects were observed at 80 mg/kg (~35-times the 45 mg clinical dose), but reduced embryofetal viability at 160 mg/kg, or ~69-times the 45 mg clinical dose, by body surface area. When pregnant rats received pioglitazone during late gestation and lactation, delayed postnatal development, attributed to decreased body weight, occurred in offspring at maternal doses of 10 mg/kg and above or ≥2-times the 45 mg clinical dose, by body surface area.

Metformin hydrochloride

Metformin hydrochloride did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of about 2- to 6-times a 2000 mg clinical dose based on body surface area (mg/m^2) for rats and rabbits, respectively.

8.2 Lactation

Risk Summary
There is no information regarding the presence of pioglitazone and metformin hydrochloride or pioglitazone in human milk, the effects on the breastfed infant, or the effects on milk production. Pioglitazone is present in rat milk; however, due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk. Limited published studies report that metformin is present in human milk [*see Data*]. However, there is insufficient information on the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for pioglitazone and metformin hydrochloride and any potential adverse effects on the breastfed infant from pioglitazone and metformin hydrochloride or from the underlying maternal condition.

Data

Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

8.3 Females and Males of Reproductive Potential

Discuss the potential for unintended pregnancy with premenopausal women as therapy with pioglitazone and metformin hydrochloride tablets, may result in ovulation in some anovulatory women.

8.4 Pediatric Use

Safety and effectiveness of pioglitazone and metformin hydrochloride tablets in pediatric patients have not been established.
Pioglitazone and metformin hydrochloride tablets are not recommended for use in pediatric patients based on adverse effects observed in adults, including fluid retention and congestive heart failure, fractures, and urinary bladder tumors *[see Warnings and Precautions (5.1, 5.3, 5.6, 5.7)]*.

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 Trial, 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 *[see Clinical Pharmacology (12.3)]*. Although clinical experiences have not identified differences in effectiveness and safety between the elderly (≥65 years) and younger patients, these conclusions are limited by small sample sizes for patients ≥75 years old.

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.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of

concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients [*see Warnings and Precautions(5.2)and Dosage and Administration (2.2)*].

8.6 Renal Impairment

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. pioglitazone and metformin hydrochloride tablets are contraindicated in severe renal impairment, patients with an eGFR below 30 mL/min/1.73 m^2[*see Dosage and Administration (2.2), Contraindications (4), Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. pioglitazone and metformin hydrochloride tablets are not recommended in patients with hepatic impairment [*see Warnings and Precautions (5.2)*].

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.

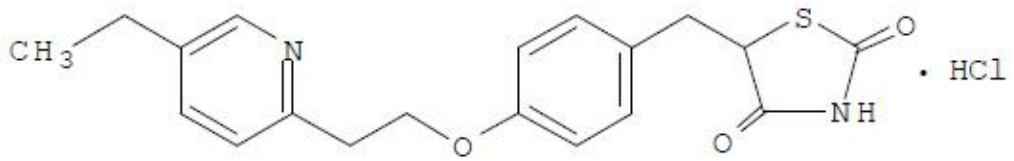
In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

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

Pioglitazone and metformin hydrochloride tablets USP are a thiazolidinediones and biguanide combination product that contains two oral antidiabetic medications: pioglitazone hydrochloride USP and metformin hydrochloride USP.

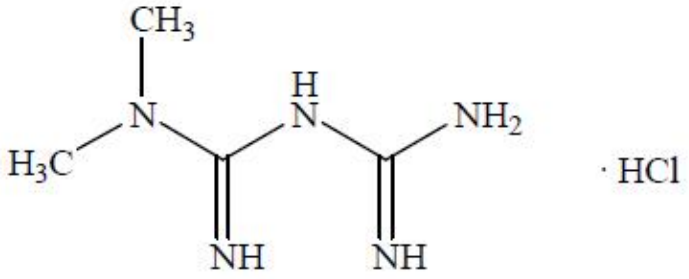
Pioglitazone [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl) ethoxy]phenyl]methyl]-2,4-] thiazolidinedione monohydrochloride contains one asymmetric carbon, and the compound is synthesized and used as the racemic mixture. The two enantiomers of pioglitazone interconvert in vivo. No differences were found in the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



pioglitazone hydrochloride

Pioglitazone hydrochloride USP 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 USP (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 USP 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 USP is 6.68. The structural formula is as shown:



metformin hydrochloride

Pioglitazone and metformin hydrochloride tablets USP are available as a tablet for oral administration containing 15 mg pioglitazone (as the base) with 500 mg metformin hydrochloride USP (15 mg/500 mg) or 15 mg pioglitazone (as the base) with 850 mg metformin hydrochloride USP (15 mg/850 mg) formulated with the following excipients: microcrystalline cellulose, croscarmellose sodium, povidone, magnesium stearate, hypromellose, polyethylene glycol, talc and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pioglitazone and metformin hydrochloride tablets 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 (5.4)]* 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 *[see Warnings and Precautions (5.10) 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

Pioglitazone and Metformin hydrochloride
In bioequivalence studies of pioglitazone and metformin hydrochloride 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 pioglitazone and metformin hydrochloride 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.

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, T_{max} of pioglitazone was within two hours. Food delays the 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% -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. 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.
Food decreases the rate and extent of metformin absorption, as shown by a 40% lower mean C_{max}, a 25% lower AUC, and a 35-minute prolongation of T_{max} 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 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.

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 which include 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 ($t_{1/2}$) of pioglitazone and its metabolites (M-III and M-IV) range from three to seven hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be five to seven L/hr.

Metformin hydrochloride
Renal clearance is approximately 3.5 times greater than creatinine clearance (CLcr), 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 t1/2 of approximately 6.2 hours. In blood, the elimination t1/2 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 (CLcr 30 to 50 mL/min) and severe (CLcr <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 , the plasma and blood $t_{1/2}$ of metformin is prolonged and the renal clearance is decreased [*see Dosage and Administration (2.2), Contraindications (4) and Warnings and Precautions (5.2)*].

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 C_{max} 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 pioglitazone and metformin hydrochloride tablets with caution in patients with liver disease *[see Warnings and Precautions (5.5)]*.

Metformin hydrochloride
No pharmacokinetic studies of metformin have been conducted in subjects with hepatic impairment *[see Warnings and Precautions (5.5)]*.

Geriatric Patients
Pioglitazone
In healthy elderly subjects, C_{max} of pioglitazone was not significantly different, but AUC values were approximately 21% higher than those achieved in younger subjects. The mean t1/2 of pioglitazone was also prolonged in elderly subjects (about ten 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 CL/F is decreased, the t1/2 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.

Pediatrics
Pioglitazone
Safety and efficacy of pioglitazone in pediatric patients have not been established. Pioglitazone and metformin hydrochloride tablets are 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 pioglitazone and metformin hydrochloride tablets 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

Pioglitazone Dosage Regimen (mg)*	Coadministered Drug: 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)	15-mg single dose	↑ 3.2-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%
Topiramate 96 mg twice daily for	30 mg§	↓15%¶	0%

7 days§ (N = 26)	30 mg§	↓15%¶	0%

*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 8.3 hours to 22.7 hours in the presence of gemfibrozil *[see Dosage and Administration (2.3) and Drug Interactions (7.1)]*
§Indicates duration of concomitant administration with highest twice-daily dose of topiramate from Day 14 onwards over the 22 days of study
¶Additional decrease in active metabolites; 60% for M-III and 16% for M-IV

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‡
Drugs that are eliminated by renal tubular secretion may increase the accumulation of metformin *[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*[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 = $AUC_{0\text{-}12h}$

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 = AUC0–∞
‡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

Pioglitazone and Metformin hydrochloride tablets
No animal studies have been conducted with pioglitazone and metformin hydrochloride tablets. 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 of male rats. 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). Urinary calculi with subsequent irritation and hyperplasia were postulated as the mechanism for bladder tumors observed in male rats. A two-year mechanistic study in male rats utilizing dietary acidification to reduce calculi formation was completed in 2009. Dietary acidification decreased but did not abolish the hyperplastic changes in the bladder. The presence of calculi exacerbated the hyperplastic response to pioglitazone but was not considered the primary cause of the hyperplastic changes.
The relevance to humans of the bladder findings in the male rat cannot be excluded.
A two-year carcinogenicity study was also 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 pioglitazone and metformin hydrochloride tablets 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 pioglitazone and metformin hydrochloride tablets based on body surface area comparisons.

13.2 Animal Pharmacology & OR Toxicology

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).

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 pioglitazone hydrochloride and metformin hydrochloride tablets 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 pioglitazone and metformin hydrochloride tablets compared to either pioglitazone or metformin alone (see Table 21).

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

	Treatment Group		
Parameter	**Pioglitazone and Metformin hydrochloridetablets 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 Pioglitazone and Metformin hydrochloride tablets (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 Pioglitazone and Metformin hydrochloridetablets (adjusted mean*) 95% Confidence Interval		18† (8, 28)	15† (6, 25)

* Adjusted for baseline
† $p \leq 0.05$ versus pioglitazone and metformin hydrochloride tablets

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 pioglitazone and metformin hydrochloride with coadministered pioglitazone and metformin tablets was demonstrated for both pioglitazone and metformin hydrochloride 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 ≤ 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

Pioglitazone and metformin hydrochloride tablets USP are 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:

Pioglitazone and metformin hydrochloride tablets USP 15 mg / 500 mg: White to off-white colored, capsule shaped, film-coated tablets debossed with 'C27' on one side and plain on the other side and are available as follows:

Bottles of 60 tablets (NDC 33342-176-09)
Bottles of 100 tablets (NDC 33342-176-11)
Bottles of 180 tablets (NDC 33342-176-57)
Bottles of 1000 tablets (NDC 33342-176-44)
Cartons of 100 unit dose tablets (10×10) (NDC 33342-176-12)

Pioglitazone and Metformin hydrochloride tablets USP 15 mg / 850 mg: White to off-white colored, capsule shaped, film-coated tablets debossed with 'C28' on one side and plain on the other side.

Bottles of 60 tablets (NDC 33342-177-09)
Bottles of 100 tablets (NDC 33342-177-11)
Bottles of 180 tablets (NDC 33342-177-57)

Bottles of 1000 tablets (NDC 33342-177-44)
Cartons of 100 unit dose tablets (10×10) (NDC 33342-177-12)

Storage: Store at 20º to 25º C (68º to 77º F); excursions permitted to 15º to 30º C (59º to 86º 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)
• 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 pioglitazone and metformin hydrochloride immediately and to promptly notify their healthcare professional if unexplained hyperventilation, myalgia, gastrointestinal symptoms, malaise, unusual somnolence or other nonspecific symptoms occur. Instruct patients to inform their doctor that they are taking pioglitazone and metformin hydrochloride prior to any surgical or radiological procedure, as temporary discontinuation of pioglitazone and metformin hydrochloride may be required until renal function has been confirmed to be normal.
• Counsel patients against excessive alcohol intake while receiving pioglitazone and metformin hydrochloride.
• 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 pioglitazone and metformin hydrochloride.
• Tell patients to promptly stop taking pioglitazone and metformin hydrochloride 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 pioglitazone and metformin hydrochloride.
• Inform female patients that treatment with pioglitazone and metformin hydrochloride may result in an unintended pregnancy in some premenopausal anovulatory females due to its effect on ovulation *[see Use in Specific Populations (8.3)*].

• Patients should be advised to notify their health practitioner or call the Poison Control Center immediately in case of pioglitazone and metformin hydrochloride overdose.
• Combination antihyperglycemic therapy may cause hypoglycemia. When initiating pioglitazone and metformin hydrochloride, 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 pioglitazone and metformin hydrochloride 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.

Manufactured for:
Macleods Pharma USA, INC,
Plainsboro, NJ 08536

Manufactured by:
Macleods Pharmaceutical Ltd.
Baddi, Himachal Pradesh, India.

Trademarks are the property of their respective owners.

SPL MEDGUIDE SECTION

Pioglitazone and Metformin Hydrochloride Tablets USP
(pye-oh-GLI-ta-zone / met-FOR-min HYE-droe-KLOR-ide)

Read this Medication Guide carefully before you start taking pioglitazone and metformin hydrochloride tablets 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 pioglitazone and metformin hydrochloride tablets, ask your doctor or pharmacist.

What is the most important information I should know about pioglitazone and metformin hydrochloride tablets? Pioglitazone and metformin hydrochloride tablets can cause serious side effects, including:

• **new or worse heart failure.** Pioglitazone, one of the medicines in pioglitazone and metformin hydrochloride tablets, 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.
o Do not take pioglitazone and metformin hydrochloride tablets if you have severe heart failure
o If you have heart failure with symptoms (such as shortness of breath or swelling), even if these symptoms are not severe, pioglitazone and metformin hydrochloride tablets may not be right for you.
Call your doctor right away if you have any of the following:
o swelling or fluid retention, especially in the ankles or legs
o shortness of breath or trouble breathing, especially when you lie down
o an unusually fast increase in weight
o unusual tiredness

• **lactic acidosis.Metformin, one of the medicines in pioglitazone and metformin hydrochloride tablets, 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 cold in your hands or feet
- you feel dizzy or lightheaded
- you have a slow or irregular heartbeat
- you feel very weak or tired
- you have unusual (not normal) muscle pain
- you have trouble breathing
- you feel sleepy or drowsy
- you have stomach pains, nausea, or vomiting

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 pioglitazone and metformin hydrochloride tablets if you:

• have severe kidney problems or your kidneys are affected by certain x-ray tests that use injectable dye.
• 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

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 pioglitazone and metformin hydrochloride tablets for a while if you have any of these things.

Pioglitazone and metformin hydrochloride tablets can have other serious side effects. See “What are the possible side effects of pioglitazone and metformin hydrochloride tablets?”

What are Pioglitazone and Metformin hydrochloride Tablets?

Pioglitazone and metformin hydrochloride tablet contains two prescription diabetes medicines called pioglitazone (ACTOS) and metformin hydrochloride (GLUCOPHAGE). Pioglitazone and metformin hydrochloride tablets can be used with diet and exercise to improve blood sugar (glucose) control in adults with type 2 diabetes.

Pioglitazone and metformin hydrochloride tablets are not for people with type 1 diabetes.
Pioglitazone and metformin hydrochloride tablets are not for people with diabetic ketoacidosis (increased ketones in your blood or urine).

It is not known if pioglitazone and metformin hydrochloride tablets are safe and effective in children under the age of 18. pioglitazone and metformin hydrochloride tablets are not recommended for use in children.

Who should not take pioglitazone and metformin hydrochloride tablets?

See “What is the most important information I should know about pioglitazone and metformin hydrochloride tablets?”

Do not take pioglitazone and metformin hydrochloride tablets if you:

• have severe heart failure
• are allergic to pioglitazone, metformin or any of the ingredients in pioglitazone and metformin hydrochloride tablets. See the end of this Medication Guide for a complete list of ingredients in pioglitazone and metformin hydrochloride tablets
• have severe kidney problems
• have a condition called metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin

Tell your doctor before taking pioglitazone and metformin hydrochloride tablets if you have any of these conditions.

What should I tell my doctor before taking pioglitazone and metformin hydrochloride tablets?

Before you take pioglitazone and metformin hydrochloride tablets, tell your doctor if you:
• **have heart failure**
• **have severe 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**
• **have or have had cancer of the bladder**
• **are pregnant or plan to become pregnant.** It is not known if pioglitazone and metformin hydrochloride tablets can 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.** Pioglitazone and metformin hydrochloride tablets may increase your chance of becoming pregnant. Talk to your doctor about birth control choices while taking pioglitazone and metformin hydrochloride tablets. Tell your doctor right away if you become pregnant while taking pioglitazone and metformin hydrochloride tablets

• **are breastfeeding or plan to breastfeed.** It is not known if pioglitazone and metformin hydrochloride tablets pass into your milk and if it can harm your baby. 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 over the counter medicine, vitamins, and herbal supplements.

Pioglitazone and metformin hydrochloride tablets and some of your other medicines can affect each other. You may need to have your dose of pioglitazone and metformin hydrochloride tablets 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 pioglitazone and metformin hydrochloride tablets with other medicines.

How should I take pioglitazone and metformin hydrochloride tablets?
• Take pioglitazone and metformin hydrochloride tablets exactly as your doctor tells you to take it

• Your doctor may need to change your dose of pioglitazone and metformin hydrochloride tablets. Do not change your pioglitazone and metformin hydrochloride tablets dose unless your doctor tells you to

• Pioglitazone and metformin hydrochloride tablets may be prescribed alone or with other diabetes medicines. This will depend on how well your blood sugar is controlled
• Take pioglitazone and metformin hydrochloride tablets with meals to lower your chance of an upset stomach

• If you miss a dose of pioglitazone and metformin hydrochloride tablets, 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 pioglitazone and metformin hydrochloride tablets, 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 pioglitazone and metformin hydrochloride tablets
• Your doctor should do certain blood tests before you start and while you take pioglitazone and metformin hydrochloride tablets
• Your doctor should also do hemoglobin A1C testing to check how well your blood sugar is controlled with pioglitazone and metformin hydrochloride tablets

• Your doctor should check your eyes regularly while you take pioglitazone and metformin hydrochloride tablets

What are the possible side effects of pioglitazone and metformin hydrochloride tablets?
Pioglitazone and metformin hydrochloride tablets may cause serious side effects, including:
• See "What is the most important information I should know about pioglitazone and metformin hydrochloride tablets?"
• 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
• liver problems. Call your doctor right away if you have:
o nausea or vomiting
o stomach pain
o unusual or unexplained tiredness
o loss of appetite
o dark urine
o yellowing of your skin or the whites of your eyes
• bladder cancer. There may be an increased chance of having bladder cancer when you take pioglitazone and metformin hydrochloride tablets. You should not take pioglitazone and metformin hydrochloride tablets if you are receiving treatment for bladder cancer. Tell your doctor right away if you have any of the following symptoms of bladder cancer:
o blood or a red color in your urine
o an increased need to urinate
o pain while you urinate
• 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
• 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 pioglitazone and metformin hydrochloride tablets. This can increase your chance of getting pregnant.

• low red blood cell count (anemia).

The most common side effects of pioglitazone and metformin hydrochloride tablets include:
o cold-like symptoms (upper respiratory tract infection)
o swelling (edema)
o diarrhea
o headache
o 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 pioglitazone and metformin hydrochloride tablets. 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 pioglitazone and metformin hydrochloride tablets?
Store pioglitazone and metformin hydrochloride tablets at 68°F to 77°F (20°C to 25°C).
Keep pioglitazone and metformin hydrochloride tablets in the original container and protect from light
Keep the pioglitazone and metformin hydrochloride tablets bottle tightly closed and keep tablets dry

Keep pioglitazone and metformin hydrochloride tablets and all medicines out of the reach of children.

General information about the safe and effective use of pioglitazone and metformin hydrochloride tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use pioglitazone and metformin hydrochloride tablets for a condition for which it was not prescribed. Do not give pioglitazone and metformin hydrochloride tablets 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 pioglitazone and metformin hydrochloride tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about pioglitazone and metformin hydrochloride tablets that is written for healthcare professionals.

For more information about pioglitazone and metformin hydrochloride tablets call 1-888-943-3210 or 1-855-926-3384.

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

Trademarks are the property of their respective owners.

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

Manufactured for:
Macleods Pharma USA, INC,
Plainsboro, NJ 08536

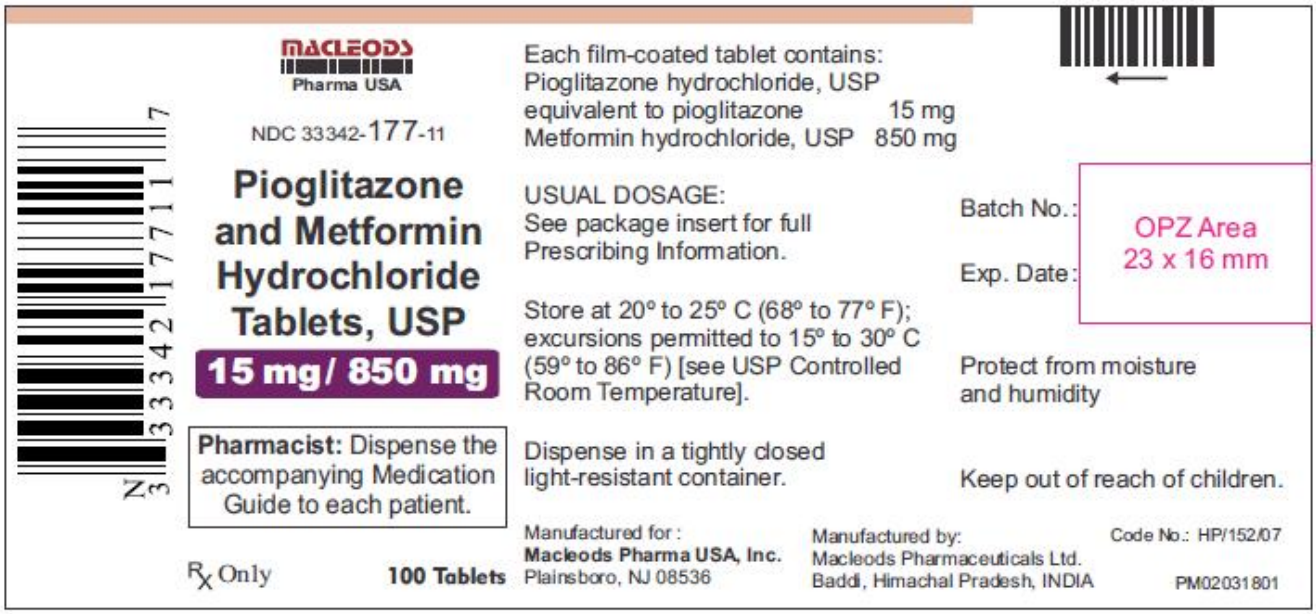
Manufactured by:
Macleods Pharmaceutical Ltd.
Baddi, Himachal Pradesh, India.
Revised: October 2019
PM02032004

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

Rx only
Pioglitazone and Metformin Hydrochloride Tablets, USP 15 mg/850 mg
60 Tablets
NDC: 33342-177-09

Rx only
Pioglitazone and Metformin Hydrochloride Tablets, USP 15 mg/850 mg
100 Tablets

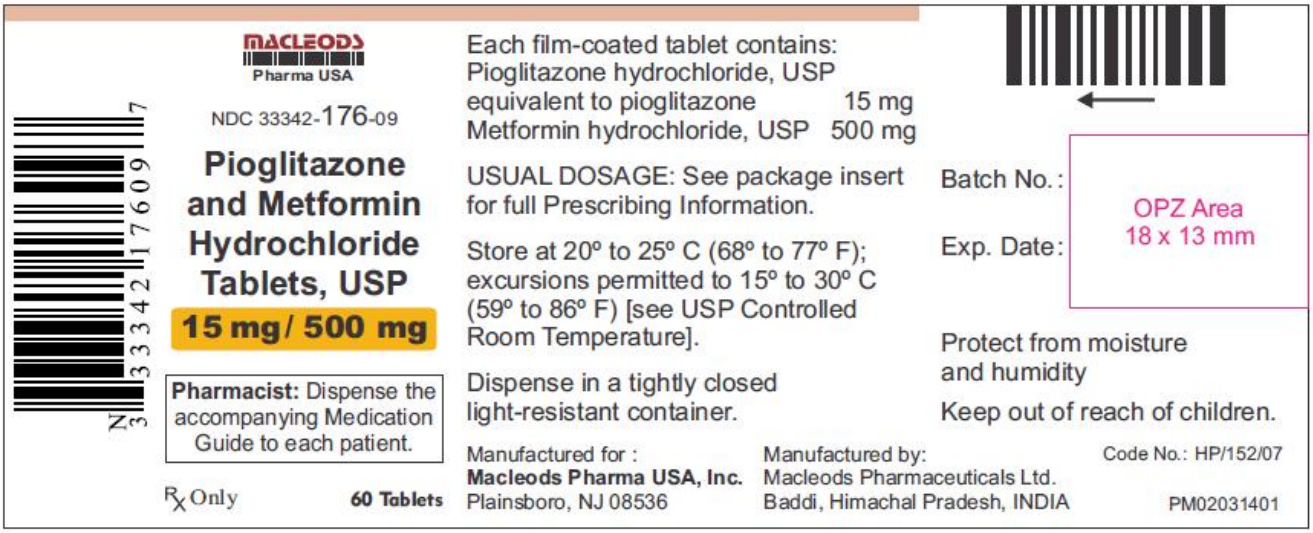
NDC: 33342-177-11



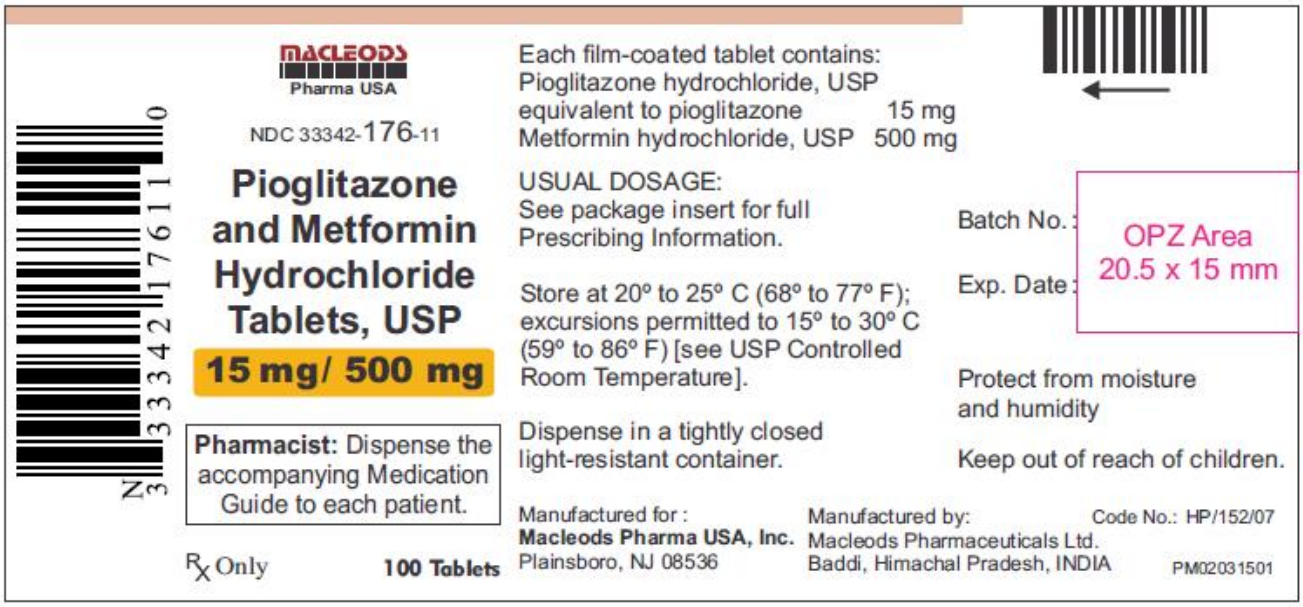
Rx only
Pioglitazone and Metformin Hydrochloride Tablets, USP 15 mg/850 mg
180 Tablets
NDC: 33342-177-57

Rx only
Pioglitazone and Metformin Hydrochloride Tablets, USP 15 mg/850 mg
1000 Tablets
NDC: 33342-177-44

Rx only
Pioglitazone and Metformin Hydrochloride Tablets, USP 15 mg/500 mg
60 Tablets
NDC: 33342-176-09



Rx only
Pioglitazone and Metformin Hydrochloride Tablets, USP 15 mg/500 mg
100 Tablets
NDC: 33342-176-11



Rx only
Pioglitazone and Metformin Hydrochloride Tablets, USP 15 mg/500 mg
180 Tablets
NDC: 33342-176-57

Rx only
Pioglitazone and Metformin Hydrochloride Tablets, USP 15 mg/500 mg
1000 Tablets
NDC: 33342-176-44

Rx only
Pioglitazone and Metformin Hydrochloride Tablets, USP 15 mg/ 500 mg
10 X 10s Tablets
NDC: 33342-176-12

MACLEODS
Pharma USA
NDC 33342-176-12

Pioglitazone and Metformin Hydrochloride Tablets, USP

15 mg/ 500 mg

Pharmacist: Dispense the accompanying Medication Guide to each patient.

℞ Only

100 Unit Dose Tablets (10 x 10)

Pioglitazone and Metformin Hydrochloride Tablets, USP 15 mg/ 500 mg

Manufactured for :
Macleods Pharma USA, Inc.
Plainsboro, NJ 08536

Manufactured by:
Macleods Pharmaceuticals Ltd.
Baddi, Himachal Pradesh, INDIA

Code No.: HP/152/07

Batch No.:

Exp. Date:

N 3 33342 17612 7

℞ Only

100 Unit Dose Tablets (10 x 10)

Pharmacist: Dispense the accompanying Medication Guide to each patient.

15 mg/ 500 mg

Pioglitazone and Metformin Hydrochloride Tablets, USP

NDC 33342-176-12

Pharma USA

MACLEODS

Pioglitazone and Metformin Hydrochloride Tablets, USP 15 mg/ 500 mg

Each film-coated tablet contains:
Pioglitazone hydrochloride, USP
equivalent to pioglitazone 15 mg
Metformin hydrochloride, USP 500 mg

USUAL DOSAGE: See package insert for full Prescribing Information.

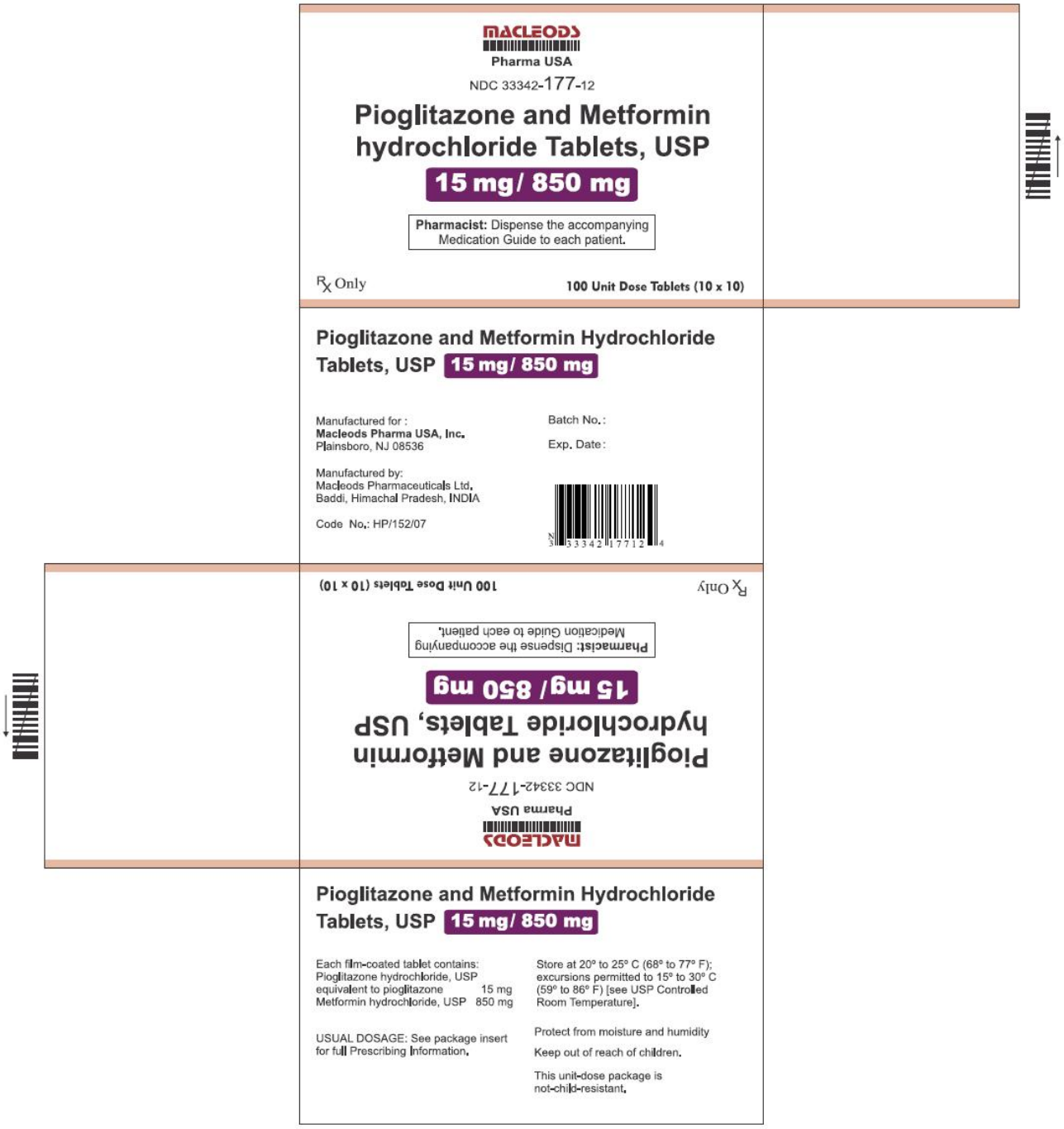
Store at 20° to 25° C (68° to 77° F); excursions permitted to 15° to 30° C (59° to 86° F) [see USP Controlled Room Temperature].

Protect from moisture and humidity

Keep out of reach of children.

This unit-dose package is not-child-resistant.

Rx only
Pioglitazone and Metformin Hydrochloride Tablets, USP 15 mg/ 850 mg
10 X10s Tablets
NDC: 33342-177-12



PIOGLITAZOLE AND METFORMIN HYDROCHLORIDE

pioglitazole and metformin hydrochloride tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:33342-176
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
PIOGLITAZONE HYDROCHLORIDE (UNII: JQT35NPK6C) (PIOGLITAZONE - UNII:X4OV71U42S)	PIOGLITAZONE	15 mg
METFORMIN HYDROCHLORIDE (UNII: 786Z46389E) (METFORMIN -	METFORMIN	500 mg

UNII:9100L32L2N)	HYDROCHLORIDE	500 mg

Inactive Ingredients

Ingredient Name	Strength
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
POVIDONE (UNII: FZ989GH94E)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	WHITE (White to off-white)	**Score**	no score
Shape	CAPSULE (capsule shaped)	**Size**	14mm
Flavor		**Imprint Code**	C;27
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:33342-176-09	60 in 1 BOTTLE; Type 0: Not a Combination Product	11/06/2015	
2	NDC:33342-176-11	100 in 1 BOTTLE; Type 0: Not a Combination Product	11/06/2015	
3	NDC:33342-176-57	180 in 1 BOTTLE; Type 0: Not a Combination Product	11/06/2015	
4	NDC:33342-176-44	1000 in 1 BOTTLE; Type 0: Not a Combination Product	11/06/2015	
5	NDC:33342-176-12	10 in 1 CARTON	11/06/2015	
5		10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA204802	11/06/2015	

PIOGLITAZOLE AND METFORMIN HYDROCHLORIDE

pioglitazole and metformin hydrochloride tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:33342-177
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
PIOGLITAZONE HYDROCHLORIDE (UNII: JQT35NPK6C) (PIOGLITAZONE - UNII:X4OV71U42S)	PIOGLITAZONE	15 mg
METFORMIN HYDROCHLORIDE (UNII: 786Z46389E) (METFORMIN - UNII:9100L32L2N)	METFORMIN HYDROCHLORIDE	850 mg

Inactive Ingredients

Ingredient Name	Strength
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
POVIDONE (UNII: FZ989GH94E)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	WHITE (White to off-white)	**Score**	no score
Shape	CAPSULE (capsule shaped)	**Size**	18mm
Flavor		**Imprint Code**	C;28
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:33342-177-09	60 in 1 BOTTLE; Type 0: Not a Combination Product	11/06/2015	
2	NDC:33342-177-11	100 in 1 BOTTLE; Type 0: Not a Combination Product	11/06/2015	
3	NDC:33342-177-57	180 in 1 BOTTLE; Type 0: Not a Combination Product	11/06/2015	
4	NDC:33342-177-44	1000 in 1 BOTTLE; Type 0: Not a Combination Product	11/06/2015	
5	NDC:33342-177-12	10 in 1 CARTON	11/06/2015	
5		10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA204802	11/06/2015	

Labeler - Macleods Pharmaceuticals Limited (862128535)

Establishment

Name	Address	ID/FEI	Business Operations
Macleods Pharmaceuticals Limited		676369519	ANALYSIS(33342-176, 33342-177) , LABEL(33342-176, 33342-177) , MANUFACTURE(33342-176, 33342-177) , PACK(33342-176, 33342-177)