

**PIOGLITAZONE AND METFORMIN- pioglitazone and metformin tablet, film coated**  
**Cambridge Therapeutics Technologies, LLC**

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**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, cause or exacerbate congestive heart failure in some patients. (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. (5.1)
- Pioglitazone and metformin hydrochloride is not recommended in patients with symptomatic heart failure.
- Initiation of pioglitazone and metformin hydrochloride in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated. (4, 5.1)

**Lactic Acidosis**

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

----- **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 of pioglitazone and metformin hydrochloride tablets based on the patient's current regimen. (2)
- May adjust the dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of pioglitazone 45 mg and metformin 2550 mg. (2)
- Pioglitazone and metformin hydrochloride tablets should be given in divided daily doses with meals to reduce the gastrointestinal (GI) side effects due to metformin. (2)
- Dose increases should be accompanied by careful monitoring for adverse events related to fluid retention. (2)
- Obtain liver tests before starting pioglitazone and metformin hydrochloride tablets. If abnormal, use caution when treating with pioglitazone and metformin hydrochloride tablets, investigate the probable cause, treat (if possible), and follow appropriately. Monitoring liver tests while on pioglitazone and metformin hydrochloride tablets is not recommended in patients without liver disease. (5.5)

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

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

## ----- CONTRAINDICATIONS -----

- Initiation in patients with established New York Heart Association (NYHA) Class III or IV heart failure [see Boxed Warning]. (4)
- Renal impairment. (4)
- Use in patients with known hypersensitivity to pioglitazone, metformin or any other component of pioglitazone and metformin hydrochloride. (4)
- Metabolic acidosis, including diabetic ketoacidosis. (4, 5.2)

## ----- WARNINGS AND PRECAUTIONS -----

- Congestive heart failure: Fluid retention may occur and can exacerbate or lead to congestive heart failure. Combination use with insulin and use in congestive heart failure NYHA Class I and II may increase risk. Monitor patients for signs and symptoms. (5.1)
- Lactic acidosis: Warn against excessive alcohol intake. Pioglitazone and metformin hydrochloride is not recommended in hepatic impairment and is contraindicated in renal impairment. Ensure normal renal function before initiating and at least annually thereafter. (5.2, 5.10)
- Edema: Dose-related edema may occur. (5.3)
- Hypoglycemia: When used with insulin or an insulin secretagogue, a lower dose of the insulin or insulin secretagogue may be needed to reduce the risk of hypoglycemia. (5.4)
- Hepatic effects: Postmarketing reports of hepatic failure, sometimes fatal. Causality cannot be excluded. If liver injury is detected, promptly interrupt 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: Preclinical and clinical trial data, and results from an observational study suggest an increased risk of bladder cancer in pioglitazone users. The observational data further suggest that the risk increases with duration of use. Do not use in patients with active bladder cancer. Use caution when using in patients with a prior history of bladder cancer. (5.6)
- Fractures: Increased incidence in female patients. Apply current standards of care for assessing and maintaining bone health. (5.7)
- Macular edema: Postmarketing reports. Recommend regular eye exams in all patients with diabetes according to current standards of care with prompt evaluation for acute visual changes. (5.8)
- Temporarily discontinue in patients undergoing radiologic studies with intravascular iodinated contrast materials or any surgical procedures necessitating restricted intake of food and fluids. (5.12)
- Vitamin B<sub>12</sub> deficiency: Metformin may lower vitamin B<sub>12</sub> levels. Monitor hematologic parameters annually. (5.14)
- Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with pioglitazone and metformin hydrochloride or any other antidiabetic drug. (5.15)

## ----- ADVERSE REACTIONS -----

Most common adverse reactions (>5%) are upper respiratory tract infection, edema, diarrhea, headache and weight gain. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Cambridge Therapeutic Technologies, LLC at 1-844-810-0004 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://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)
- Cationic drugs: May reduce metformin elimination. Use with caution in patients who are taking cationic medications eliminated by renal tubular secretion. (7.4)

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

- Nursing mothers: Discontinue drug or nursing, taking into consideration the importance of the drug to the mother. (8.3)
- Pediatrics: Not recommended for use in pediatric patients. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2016

## **WARNING: CONGESTIVE HEART FAILURE AND LACTIC ACIDOSIS**

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## FULL PRESCRIBING INFORMATION

### WARNING: CONGESTIVE HEART FAILURE AND LACTIC ACIDOSIS

#### Congestive Heart Failure

- **Thiazolidinediones, including pioglitazone, which is a component of 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 hydrochloride and metformin hydrochloride is not recommended in patients with symptomatic heart failure.**
- **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

- **Lactic acidosis is a rare but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure [see WARNINGS AND PRECAUTIONS (5.2)].**
- **The onset is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate [see WARNINGS AND PRECAUTIONS (5.2)].**
- **If acidosis is suspected, pioglitazone and metformin hydrochloride should be discontinued and the patient hospitalized immediately [see WARNINGS AND PRECAUTIONS (5.2)].**

## 1 INDICATIONS AND 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 AND 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 3 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 tablets are not recommended in patients without liver disease. Patients who have liver test abnormalities prior to initiation of pioglitazone and metformin hydrochloride tablets 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 Concomitant Use with an Insulin Secretagogue 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 co-administered 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.

## 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 tablets are 15 mg/850 mg daily when used in combination with gemfibrozil or other strong CYP2C8 inhibitors [see **DRUG INTERACTIONS (7.1)** and **CLINICAL PHARMACOLOGY (12.3)**].

### 3 DOSAGE FORMS AND STRENGTHS

- 15 mg/500 mg tablets are white, oval, biconvex, film-coated tablets with “SZ441” on one side

### 4 CONTRAINDICATIONS

- Initiation in patients with established NYHA Class III or IV heart failure [see Boxed Warning].
- Renal impairment (e.g., serum creatinine levels  $\geq 1.5$  mg/dL [males],  $\geq 1.4$  mg/dL [females], or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia [see **WARNINGS AND PRECAUTIONS (5.2, 5.10)**].
- Use in patients with known hypersensitivity to pioglitazone, metformin, or any other component of pioglitazone and metformin hydrochloride.
- 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 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 must be considered [see **BOXED WARNING, CONTRAINDICATIONS (4)**, and **ADVERSE REACTIONS (6.1)**].

#### 5.2 Lactic Acidosis

##### **Metformin hydrochloride**

##### *Lactic Acidosis*

Lactic acidosis is a serious, metabolic complication that can occur due to metformin accumulation during treatment with pioglitazone and metformin hydrochloride and it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate concentrations ( $>5$  mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels  $>5$  mcg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years. In more than 20,000 patient-years, exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, particularly when accompanied by hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal

function. Pioglitazone and metformin hydrochloride treatment should not be initiated in any patient unless measurement of creatinine clearance demonstrates that renal function is not reduced. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic impairment. Patients should be cautioned against excessive alcohol intake when taking metformin, because alcohol potentiates the effects of metformin on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure necessitating restricted intake of food or fluids [see **WARNINGS AND PRECAUTIONS (5.10, 5.11, 5.12, 5.13)**]. Use of topiramate, a carbonic anhydrase inhibitor, in epilepsy and migraine prophylaxis may frequently cause dose-dependent metabolic acidosis and may exacerbate the risk of metformin-induced lactic acidosis [see **DRUG INTERACTIONS (7.1)** and **CLINICAL PHARMACOLOGY (12.3)**].

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. Patients should be educated to promptly report these symptoms should they occur. If present, pioglitazone and metformin hydrochloride should be withdrawn until lactic acidosis is ruled out. Serum electrolytes, ketones, blood glucose, blood pH, lactate levels, and blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to recur. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling [see **WARNINGS AND PRECAUTIONS (5.10)**].

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery [see **CONTRAINDICATIONS (4)** and **WARNINGS AND PRECAUTIONS (5.10)**].

### 5.3 Edema

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

Pioglitazone and metformin hydrochloride 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 should be used with caution in patients at risk for congestive heart failure. Patients treated with pioglitazone and metformin hydrochloride 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 in combination with insulin or other

antidiabetic medications (particularly insulin secretagogues such as sulfonylureas) may be at risk for hypoglycemia. A reduction in the dose of the concomitant antidiabetic medication may be necessary to reduce the risk of hypoglycemia [see **DOSAGE AND ADMINISTRATION (2.2)**].

Hypoglycemia can also occur when caloric intake is deficient or when strenuous exercise is not compensated by caloric supplement. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

### 5.5 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 therapy.

In patients with abnormal liver tests, pioglitazone and metformin hydrochloride 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 treatment should be interrupted and investigation done to establish the probable cause. Pioglitazone and metformin hydrochloride 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 can be used with caution.

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

### 5.6 Urinary Bladder Tumors

Tumors were observed in the urinary bladder of male rats in the two-year carcinogenicity study [see **NONCLINICAL TOXICOLOGY (13.1)**]. In two 3-year trials in which pioglitazone was compared to placebo or glyburide, there were 16/3,656 (0.44%) reports of bladder cancer in patients taking pioglitazone compared to 5/3,679 (0.14%) in patients not taking pioglitazone. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were six (0.16%) cases on pioglitazone and two (0.05%) cases on placebo.

A five-year interim report of an ongoing 10-year observational cohort study found a nonsignificant increase in the risk for bladder cancer in subjects ever exposed to pioglitazone, compared to subjects never exposed to pioglitazone (HR 1.2 [95% CI 0.9 to 1.5]). Compared to never exposure, a duration of pioglitazone therapy longer than 12 months was associated with an increase in risk (HR 1.4 [95% CI 0.9 to 2.1]), which reached statistical significance after more than 24 months of pioglitazone use (HR 1.4

[95% CI 1.03 to 2]). Interim results from this study suggested that taking pioglitazone longer than 12 months increased the relative risk of developing bladder cancer in any given year by 40%, which equates to an absolute increase of 3 cases in 10,000 (from approximately 7 in 10,000 [without pioglitazone] to approximately 10 in 10,000 [with pioglitazone]).

There are insufficient data to determine whether pioglitazone is a tumor promoter for urinary bladder tumors. Consequently, pioglitazone and metformin hydrochloride 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 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), 5,238 patients with type 2 diabetes and a history of macrovascular disease were randomized to pioglitazone (N=2,605), force-titrated up to 45 mg daily or placebo (N=2,633) 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 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 Ovulation

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

## 5.10 Monitoring of Renal Function

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

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

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

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

### ***Radiological Studies and Surgical Procedures***

Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials) can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin [see **CONTRAINDICATIONS (4)**]. Therefore, in patients in whom any such study is planned, pioglitazone and metformin hydrochloride should be discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstated only after renal function has been re-evaluated and found to be normal.

### **5.11 Hypoxic States**

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

### **5.12 Surgical Procedures**

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

### **5.13 Alcohol Intake**

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving pioglitazone and metformin hydrochloride.

### **5.14 Vitamin B<sub>12</sub> Levels**

In controlled clinical trials of metformin of 29 weeks' duration, a decrease to subnormal levels of previously normal serum vitamin B<sub>12</sub> levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B<sub>12</sub> absorption from the B<sub>12</sub>-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B<sub>12</sub> supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on pioglitazone and metformin hydrochloride and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate vitamin B<sub>12</sub> or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B<sub>12</sub> levels. In these patients, routine serum vitamin B<sub>12</sub> measurements at two- to three-year intervals may be useful.

### **5.15 Macrovascular Outcomes**

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with pioglitazone and metformin hydrochloride or any other oral antidiabetic drug.

## **6 ADVERSE REACTIONS**

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

- Congestive heart failure [see **BOXED WARNING** and **WARNINGS AND PRECAUTIONS**

**(5.1)]**

- •Lactic acidosis [see **BOXED WARNING** and **WARNINGS AND PRECAUTIONS (5.2)**]
- •Edema [see **WARNINGS AND PRECAUTIONS (5.3)**]
- •Fractures [see **WARNINGS AND PRECAUTIONS (5.7)**]

**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 8,500 patients with type 2 diabetes have been treated with pioglitazone in randomized, double-blind, controlled clinical trials, including 2,605 patients with type 2 diabetes and macrovascular disease treated with pioglitazone from the PROactive clinical trial. In these trials, over 6,000 patients have been treated with pioglitazone for 6 months or longer, over 4,500 patients have been treated with pioglitazone for one year or longer, and over 3,000 patients have been treated with pioglitazone for at least 2 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%).

In the PROactive trial, the incidence of withdrawals due to adverse events was 9% 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.

| <b>Table 1. Three Pooled 16- to 26-Week Placebo-Controlled Clinical Trials of Pioglitazone Monotherapy: Adverse Events Reported at an Incidence &gt;5% and More Commonly in Patients Treated with Pioglitazone than in Patients Treated with Placebo</b> |                          |                               |
|--|--------------------------|-------------------------------|
|  | <b>% of Patients</b>     |                               |
|  | <b>Placebo<br/>N=259</b> | <b>Pioglitazone<br/>N=606</b> |
| 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.

| <b>Table 2. 16- to 24-Week Clinical Trials of Pioglitazone Add-on to Metformin</b> |   |   |
|--|---|---|
|  | <b>16-Week Placebo-Controlled Trial<br/>Adverse Events Reported in &gt;5% of Patients and More Commonly in Patients Treated with Pioglitazone + Metformin than in Patients Treated with Placebo + Metformin</b>                           |   |
|  | <b>% of Patients</b>  |   |
|  | <b>Placebo + Metformin<br/>N=160</b>  | <b>Pioglitazone 30 mg + Metformin<br/>N=168</b> |
| Edema  | 2.5   | 6   |
| Headache   | 1.9   | 6   |
|  | <b>24-Week Non-Controlled Double-Blind Trial<br/>Adverse Events Reported in &gt;5% of Patients and More Commonly in Patients Treated with Pioglitazone 45 mg + Metformin than in Patients Treated with Pioglitazone 30 mg + Metformin</b> |   |
|  | <b>% of Patients</b>  |   |
|  | <b>Pioglitazone 30 mg + Metformin<br/>N=411</b>   | <b>Pioglitazone 45 mg + Metformin<br/>N=416</b> |
| 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 Exercise in a 24-Week Double-Blind Clinical Trial of Pioglitazone and Metformin Hydrochloride Administered Twice Daily**

|          | % of Patients   |   |   |
|----------|---|---|---|
|          | <b>Pioglitazone and Metformin Hydrochloride 15/850 mg Twice Daily N=201</b> | <b>Pioglitazone 15 mg Twice Daily N=190</b> | <b>Metformin 850 mg Twice Daily N=209</b> |
| Diarrhea | 9   | 2.6   | 15.3                                      |
| Headache | 5.5   | 2.6   | 4.8                                       |

In this 24-week trial, abdominal pain was reported in 2% 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.

| <b>Table 4. PROactive Trial: Incidence and Types of Adverse Events Reported in &gt;5% of Patients Treated with Pioglitazone and More Commonly than Placebo</b> |                       |                            |
|--|-----------------------|----------------------------|
|  | % of Patients         |                            |
|  | <b>Placebo N=2633</b> | <b>Pioglitazone N=2605</b> |
| 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   | 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.

| <b>Table 5. Treatment-Emergent Adverse Events of Congestive Heart Failure (CHF) Patients Treated with Pioglitazone or Placebo Added on to Metformin</b> |  |   |   |   |
|---|--|---|---|---|
|   | <b>Number (%) of Patients</b>              |   |   |   |
|   | <b>Placebo-Controlled Trial (16 weeks)</b> |   | <b>Non-Controlled Double-Blind Trial (24 weeks)</b> |   |
|   | <b>Placebo + Metformin<br/>N=160</b>       | <b>Pioglitazone 30 mg + Metformin<br/>N=168</b> | <b>Pioglitazone 30 mg + Metformin<br/>N=411</b>     | <b>Pioglitazone 45 mg + Metformin<br/>N=416</b> |
| At least one congestive heart failure event   | 0  | 1 (0.6%)  | 0   | 1 (0.2%)  |
| Hospitalized  | 0  | 1 (0.6%)  | 0   | 1 (0.2%)  |

| <b>Table 6. Treatment-Emergent Adverse Events of Congestive Heart Failure (CHF) Patients Treated with Pioglitazone or Placebo Added on to a Sulfonylurea</b> |  |  |  |   |  |
|--|--|--|--|---|--|
|  | <b>Number (%) of Patients</b>              |  |  |   |  |
|  | <b>Placebo-Controlled Trial (16 weeks)</b> |  |  | <b>Non-Controlled Double-Blind Trial (24 weeks)</b> |  |
|  | <b>Placebo + Sulfonylurea<br/>N=187</b>    | <b>Pioglitazone 15 mg + Sulfonylurea<br/>N=184</b> | <b>Pioglitazone 30 mg + Sulfonylurea<br/>N=189</b> | <b>Pioglitazone 30 mg + Sulfonylurea<br/>N=351</b>  | <b>Pioglitazone 45 mg + Sulfonylurea<br/>N=351</b> |
|  |  |  |  |   |  |

|   |          |   |   |          |          |
|---|----------|---|---|----------|----------|
| 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<br>N=187          | Pioglitazone 15 mg + Insulin<br>N=191 | Pioglitazone 30 mg + Insulin<br>N=188 | Pioglitazone 30 mg + Insulin<br>N=345        | Pioglitazone 45 mg + Insulin<br>N=345 |
| At least one congestive heart failure event | 0                                   | 2 (1%)                                | 2 (1.1%)                              | 3 (0.9%)                                     | 5 (1.4%)                              |
| Hospitalized                                | 0                                   | 2 (1%)                                | 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<br>N=160        | Pioglitazone 30 mg + Metformin<br>N=168 | Pioglitazone 30 mg + Metformin<br>N=411      | Pioglitazone 45 mg + Metformin<br>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           | Glyburide |
|  |                        |           |

|   | N=262      | 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<br>N=2633      | Pioglitazone<br>N=2605 |
| At least one hospitalized congestive heart failure event | 108 (4.1%)             | 149 (5.7%)             |
| Fatal  | 22 (0.8%)              | 25 (1%)                |
| Hospitalized, nonfatal                                   | 86 (3.3%)              | 124 (4.7%)             |

### *Cardiovascular Safety*

In the PROactive trial, 5,238 patients with type 2 diabetes and a history of macrovascular disease were randomized to pioglitazone (N=2,605), force-titrated up to 45 mg daily or placebo (N=2,633) 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 3-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**.

| Cardiovascular Events               | Placebo<br>n=2633     |                   | Pioglitazone<br>N=2605 |                   |
|-------------------------------------|-----------------------|-------------------|------------------------|-------------------|
|                                     | First Events<br>n (%) | Total Events<br>n | First Events<br>n (%)  | Total Events<br>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)                | 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.

|  | Control Group (Placebo) | Pioglitazone 15 mg | Pioglitazone 30 mg | Pioglitazone 45 mg |
|--|-------------------------|--------------------|--------------------|--------------------|
|  | Median                  | Median             | Median             | Median             |

|   |              | (25 <sup>th</sup> , 75 <sup>th</sup> percentile) |
|---|--------------|--|--|--|--|
| <b>Monotherapy<br/>(16 to 26 weeks)</b>             |              | -1.4 (-2.7, 0)<br>N=256                          | 0.9 (-0.5, 3.4)<br>N=79                          | 1 (-0.9, 3.4)<br>N=188                           | 2.6 (0.2, 5.4)<br>N=79                           |
| <b>Combination<br/>Therapy<br/>(16 to 24 weeks)</b> | Sulfonylurea | -0.5 (-1.8, 0.7)<br>N=187                        | 2 (0.2, 3.2)<br>N=183                            | 3.1 (1.1, 5.4)<br>N=528                          | 4.1 (1.8, 7.3)<br>N=333                          |
|   | Metformin    | -1.4 (-3.2, 0.3)<br>N=160                        | N/A  | 0.9 (-1.3, 3.2)<br>N=567                         | 1.8 (-0.9, 5)<br>N=407                           |
|   | Insulin      | 0.2 (-1.4, 1.4)<br>N=182                         | 2.3 (0.5, 4.3)<br>N=190                          | 3.3 (0.9, 6.3)<br>N=522                          | 4.1 (1.4, 6.8)<br>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<br>(25 <sup>th</sup> , 75 <sup>th</sup> percentile) | Median<br>(25 <sup>th</sup> , 75 <sup>th</sup> percentile) |
| Change from baseline to final visit (kg) | -0.5 (-3.3, 2)<br>N=2581                                   | +3.6 (0, 7.5)<br>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 Hydrochloride in Patients with Inadequate Glycemic Control on Diet and Exercise**

|  | <b>Pioglitazone and Metformin<br/>Hydrochloride<br/>15/850 mg<br/>Twice Daily</b> | <b>Pioglitazone<br/>15 mg<br/>Twice Daily</b>              | <b>Metformin<br/>850 mg<br/>Twice Daily</b>                |
|--|---|--|--|
|  | Median<br>(25 <sup>th</sup> , 75 <sup>th</sup> percentile)                        | Median<br>(25 <sup>th</sup> , 75 <sup>th</sup> percentile) | Median<br>(25 <sup>th</sup> , 75 <sup>th</sup> percentile) |
| Change from baseline to final visit (kg) | 1 (-1, 3)<br>N=198  | 1.35 (-0.7, 4.1)<br>N=178                                  | -1 (-2.6, 0.4)<br>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**.

| <b>Table 13. Adverse Events of Edema in Patients Treated with Pioglitazone</b> |              |                               |                               |                               |                               |
|--|--------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
|  |              | <b>Number (%) of Patients</b> |                               |                               |                               |
|  |              | <b>Placebo</b>                | <b>Pioglitazone<br/>15 mg</b> | <b>Pioglitazone<br/>30 mg</b> | <b>Pioglitazone<br/>45 mg</b> |
| <b>Monotherapy<br/>(16 to 26 weeks)</b>  |              | 3 (1.2%)<br>N=259             | 2 (2.5%)<br>N= 81             | 13 (4.7%)<br>N= 275           | 11 (6.5%)<br>N=169            |
| <b>Combined<br/>Therapy<br/>(16 to 24<br/>weeks)</b>                           | Sulfonylurea | 4<br>(2.1%)<br>N=187          | 3 (1.6%)<br>N=184             | 61 (11.3%)<br>N=540           | 81 (23.1%)<br>N=351           |
|  | Metformin    | 4<br>(2.5%)<br>N=160          | N/A                           | 34 (5.9%)<br>N=579            | 58 (13.9%)<br>N=416           |
|  | Insulin      | 13 (7%)<br>N=187              | 24 (12.6%)<br>N=191           | 109 (20.5%)<br>N=533          | 90 (26.1%)<br>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."

| <b>Table 14. Adverse Events of Edema in Patients in the PROactive Trial</b> |                               |
|---|-------------------------------|
| <b>Number (%) of Patients</b>   |                               |
| <b>Placebo</b><br>N=2633  | <b>Pioglitazone</b><br>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, 3-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 8 weeks for the first 48 weeks of the trial then every 12 weeks thereafter. A total of 3/1,051 (0.3%) patients treated with pioglitazone and 9/1,046 (0.9%) patients treated with glyburide developed ALT values greater than three times the upper limit of the reference range. None of the patients treated with pioglitazone in the pioglitazone controlled clinical trial database to date have had a serum ALT greater than three times the upper limit of the reference range and a corresponding total bilirubin greater than two times the upper limit of the reference range, a combination predictive of the potential for severe drug-induced liver injury.

### *Hypoglycemia*

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

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

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

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

### *Urinary Bladder Tumors*

Tumors were observed in the urinary bladder of male rats in the two-year carcinogenicity study [see **NONCLINICAL TOXICOLOGY (13.1)**]. In two 3-year trials in which pioglitazone was compared to placebo or glyburide, there were 16/3,656 (0.44%) reports of bladder cancer in patients taking pioglitazone compared to 5/3,679 (0.14%) in patients not taking pioglitazone. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were six (0.16%) cases on pioglitazone and two (0.05%) cases on placebo. There are too few events of bladder cancer to establish causality.

### **Metformin hydrochloride**

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

| <b>Table 15. Most Common Adverse Reactions (&gt;5%) in a Placebo-Controlled Clinical Study of Metformin Monotherapy*</b> |                                      |                        |
|--|--------------------------------------|------------------------|
| <b>Adverse Reaction</b>  | <b>Metformin Monotherapy (n=141)</b> | <b>Placebo (n=145)</b> |
|  | <b>% of Patients</b>                 |                        |
|  |                                      |                        |

|                      |      |      |
|----------------------|------|------|
| 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 4 to 12 weeks of therapy and remained relatively constant thereafter. These changes may be related to increased plasma volume associated with pioglitazone therapy and are not likely to be associated with any clinically significant hematologic effects.

### *Vitamin B<sub>12</sub> Concentrations*

Metformin may lower serum vitamin B<sub>12</sub> concentrations. Measurement of hematologic parameters on an annual basis is advised in patients on pioglitazone and metformin hydrochloride and any apparent abnormalities should be appropriately investigated and managed [see **WARNINGS AND PRECAUTIONS (5.14)**].

### *Creatine Phosphokinase*

During protocol-specified measurement of serum creatine phosphokinase (CPK) in pioglitazone clinical trials, an isolated elevation in CPK to greater than 10 times the upper limit of the reference range was noted in 9 (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

### **Pioglitazone**

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.

- 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)**].

## **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 ( $t_{1/2}$ ) of pioglitazone. Therefore, the maximum recommended dose of pioglitazone is 15 mg daily if used in combination with gemfibrozil or other strong CYP2C8 inhibitors [see **DOSAGE AND ADMINISTRATION (2.3)** and **CLINICAL PHARMACOLOGY (12.3)**].

### **7.2 CYP2C8 Inducers**

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

### **7.3 Carbonic Anhydrase Inhibitors**

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

### **7.4 Cationic Drugs**

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

### **7.5 Drugs Affecting Glycemic Control**

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid. When such drugs are administered to a patient receiving pioglitazone and metformin hydrochloride, 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, the patient should be observed closely for hypoglycemia.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

**Pregnancy Category C**

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

## **Pioglitazone**

### ***Clinical Considerations***

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

### ***Animal Data***

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

## **Metformin hydrochloride**

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about two and six times a human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. However, because animal reproduction studies are not always predictive of human response, metformin should not be used during pregnancy unless clearly needed.

## **8.2 Labor and Delivery**

The effect of pioglitazone and metformin hydrochloride on labor and delivery in humans is not known.

## **8.3 Nursing Mothers**

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

## **8.4 Pediatric Use**

Safety and effectiveness of pioglitazone and metformin hydrochloride in pediatric patients have not been established.

Pioglitazone and metformin hydrochloride is 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  $\geq 65$  years old and 2 patients (0.3%) were  $\geq 75$  years old. In the two pooled 16- to 24-week add-on to sulfonylurea trials, 201 patients (18.7%) treated with pioglitazone were  $\geq 65$  years old and 19 (1.8%) were  $\geq 75$  years old. In the two pooled 16- to 24-week add-on to metformin trials, 155 patients (15.5%) treated with pioglitazone were  $\geq 65$  years old and 19 (1.9%) were  $\geq 75$  years old. In the two pooled 16- to 24-week add-on to insulin trials, 272 patients (25.4%) treated with pioglitazone were  $\geq 65$  years old and 22 (2.1%) were  $\geq 75$  years old.

In PROactive Trial, 1,068 patients (41%) treated with pioglitazone were  $\geq 65$  years old and 42 (1.6%) were  $\geq 75$  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 ( $\geq 65$  years) and younger patients, these conclusions are limited by small sample sizes for patients  $\geq 75$  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. Metformin is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, pioglitazone and metformin hydrochloride should only be used in patients with normal renal function [see **CONTRAINDICATIONS (4), WARNINGS AND PRECAUTIONS (5.2), and CLINICAL PHARMACOLOGY (12.3)**]. Because aging is associated with reduced renal function, pioglitazone and metformin hydrochloride should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of pioglitazone and metformin hydrochloride [see **WARNINGS AND PRECAUTIONS (5.2)** and **DOSAGE AND ADMINISTRATION (2)**].

## 10 OVERDOSAGE

### Pioglitazone

During controlled clinical trials, one case of overdose with pioglitazone was reported. A male patient took 120 mg per day for four days, then 180 mg per day for seven days. The patient denied any clinical symptoms during this period.

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

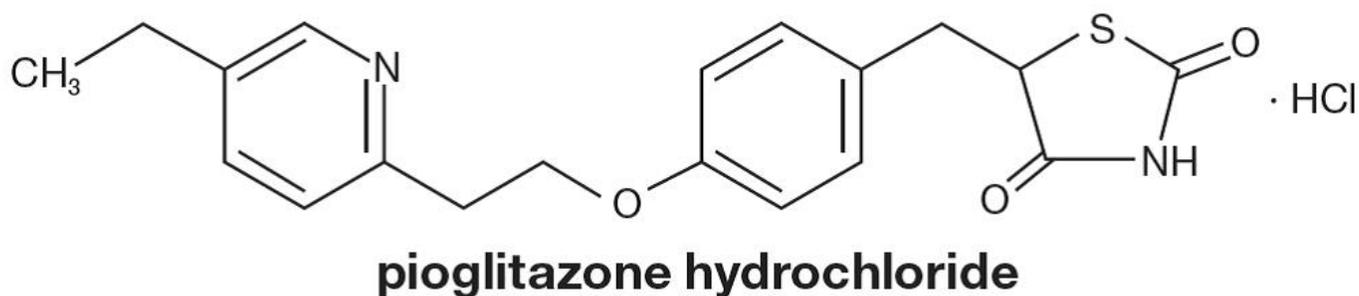
### Metformin hydrochloride

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases [see **WARNINGS AND PRECAUTIONS (5.2)**]. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated metformin from patients in whom metformin overdosage is suspected.

## 11 DESCRIPTION

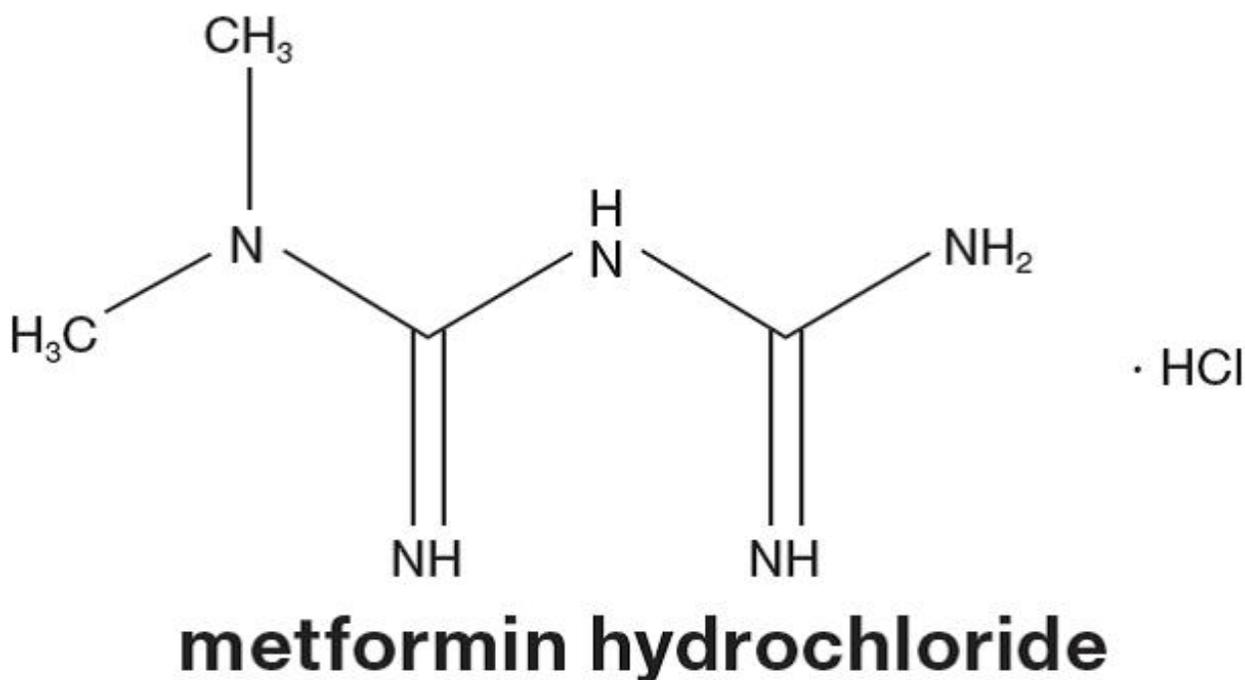
Pioglitazone and metformin hydrochloride tablets, USP are a thiazolidinediones and biguanide combination product that contains two oral antidiabetic medications: pioglitazone and metformin hydrochloride.

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



Pioglitazone hydrochloride is an odorless white to off white crystalline powder that has a molecular formula of  $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_3\text{S}\cdot\text{HCl}$  and a molecular weight of 392.91. It is soluble in *N,N*-dimethylformamide, slightly soluble in anhydrous ethanol, very slightly soluble in acetone and acetonitrile, practically insoluble in water, and insoluble in ether.

Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) is a white to almost white crystalline powder with a molecular formula of  $\text{C}_4\text{H}_{11}\text{N}_5\cdot\text{HCl}$  and a molecular weight of 165.62. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula is as shown:



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

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Pioglitazone and metformin hydrochloride 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 (PPAR $\gamma$ ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPAR $\gamma$  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 or any other antidiabetic medication [see **WARNINGS AND PRECAUTIONS (5.15)** and **ADVERSE REACTIONS (6.1)**].

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

| <b>Table 16. Lipids in a 26-Week Placebo-Controlled Monotherapy Dose-Ranging Study</b> |                |  |  |  |
|--|----------------|--|--|--|
|  | <b>Placebo</b> | <b>Pioglitazone<br/>15 mg<br/>Once Daily</b> | <b>Pioglitazone<br/>30 mg<br/>Once Daily</b> | <b>Pioglitazone<br/>45 mg<br/>Once Daily</b> |
| <b>Triglycerides (mg/dL)</b>   | N=79           | N=79   | N=84   | N=77   |
| Baseline (mean)  | 263            | 284  | 261  | 260  |
| Percent change from baseline (adjusted mean <sup>*</sup> )                             | 4.8%           | -9% <sup>†</sup>                             | -9.6% <sup>†</sup>                           | -9.3% <sup>†</sup>                           |
| <b>HDL Cholesterol (mg/dL)</b>   | N=79           | N=79   | N=83   | N=77   |
| Baseline (mean)  | 42             | 40   | 41   | 41   |
| Percent change from baseline (adjusted mean <sup>*</sup> )                             | 8.1%           | 14.1% <sup>†</sup>                           | 12.2%  | 19.1% <sup>†</sup>                           |
| <b>LDL Cholesterol (mg/dL)</b>   | N=65           | N=63   | N=74   | N=62   |
| Baseline (mean)  | 139            | 132  | 136  | 127  |
| Percent change from baseline (adjusted mean <sup>*</sup> )                             | 4.8%           | 7.2%   | 5.2%   | 6%   |
| <b>Total Cholesterol (mg/dL)</b>   | N=79           | N=79   | N=84   | N=77   |
| Baseline (mean)  | 225            | 220  | 223  | 214  |
| Percent change from baseline (adjusted mean <sup>*</sup> )                             | 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 pioglitazone hydrochloride 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 7 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 2 hours. Food delays the  $T_{max}$  to 3 to 4 hours but does not alter the extent of absorption (AUC).

### ***Metformin hydrochloride***

The absolute bioavailability of a 500 mg metformin tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin tablets of 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. 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 ( $V_d/F$ ) of pioglitazone following single-dose administration is  $0.63 \pm 0.41$  (mean  $\pm$  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  $V_d/F$  of metformin following single oral doses of 850 mg immediate-release metformin averaged  $654 \pm 358$  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 6 $\beta$ -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 3 to 7 hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be 5 to 7 L/hr.

### ***Metformin hydrochloride***

Renal clearance is approximately 3.5 times greater than creatinine clearance (CL<sub>cr</sub>), 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  $t_{1/2}$  of approximately 6.2 hours. In blood, the elimination  $t_{1/2}$  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 (CL<sub>cr</sub> 30 to 50 mL/min) and severe (CL<sub>cr</sub> <30 mL/min) renal impairment when compared to subjects with normal renal function. Therefore, no dose adjustment in patients with renal impairment is required.

#### **Metformin hydrochloride**

In patients with decreased renal function (based on CL<sub>cr</sub>), the plasma and blood  $t_{1/2}$  of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in CL<sub>cr</sub> [see **CONTRAINDICATIONS (4)** and **WARNINGS AND PRECAUTIONS (5.2)**]. Because metformin is contraindicated in patients with renal impairment, pioglitazone and metformin hydrochloride is also contraindicated in these patients.

### ***Hepatic Impairment***

#### **Pioglitazone**

Compared with healthy controls, subjects with impaired hepatic function (Child-Turcotte-Pugh Grade B/C) have an approximate 45% reduction in pioglitazone and total pioglitazone (pioglitazone, M-III, and M-IV) mean  $C_{max}$  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 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. Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Pioglitazone and metformin hydrochloride is not recommended in patients 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  $t_{1/2}$  of pioglitazone was also prolonged in elderly subjects (about 10 hours) as compared to younger subjects (about 7 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  $t_{1/2}$  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.

As is true for all patients, pioglitazone and metformin hydrochloride treatment should not be initiated in geriatric patients unless measurement of CL<sub>cr</sub> demonstrates that renal function is not reduced [see **WARNINGS AND PRECAUTIONS (5.2)**].

### ***Pediatrics***

#### **Pioglitazone**

Safety and efficacy of pioglitazone in pediatric patients have not been established. Pioglitazone and metformin hydrochloride is not recommended for use in pediatric patients [see **USE IN SPECIFIC POPULATIONS (8.4)**].

#### **Metformin hydrochloride**

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

### ***Gender***

#### **Pioglitazone**

The mean  $C_{max}$  and AUC values of pioglitazone were increased 20% to 60% in women compared to men. In controlled clinical trials, HbA<sub>1c</sub> decreases from baseline were generally greater for females than for males (average mean difference in HbA<sub>1c</sub> 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 have not been performed, although such studies have been conducted with the individual pioglitazone and metformin components.

### ***Pioglitazone***

| <b>Table 17. Effect of Pioglitazone Coadministration on Systemic Exposure of Other Drugs</b> |   |                                  |      |  |      |
|--|---|----------------------------------|------|--|------|
| <b>Coadministered Drug</b>   |   |                                  |      |  |      |
| <b>Pioglitazone Dosage Regimen (mg)*</b>   | <b>Name and Dose Regimens</b>   | <b>Change in AUC<sup>†</sup></b> |      | <b>Change in C<sub>max</sub><sup>†</sup></b> |      |
| 45 mg<br>(N = 12)  | <b>Warfarin<sup>‡</sup></b>   |                                  |      |  |      |
|  | Daily loading then maintenance doses based PT and INR values<br>Quick's Value = 35 ± 5% | R-Warfarin                       | ↓3%  | R-Warfarin                                   | ↓2%  |
|  |   | S-Warfarin                       | ↓1%  | S-Warfarin                                   | ↑1%  |
| 45 mg<br>(N = 12)  | <b>Digoxin</b>  |                                  |      |  |      |
|  | 0.200 mg twice daily (loading dose) then 0.250 mg daily (maintenance dose, 7 days)      | ↑15%                             |      | ↑17%   |      |
| 45 mg daily for 21 days<br>(N = 35)  | <b>Oral Contraceptive</b>   |                                  |      |  |      |
|  | [Ethinyl Estradiol (EE) 0.035 mg plus Norethindrone (NE) 1 mg] for 21 days              | EE                               | ↓11% | EE   | ↓13% |
|  |   | NE                               | ↑3%  | NE   | ↓7%  |
| 45 mg<br>(N = 23)  | <b>Fexofenadine</b>   |                                  |      |  |      |
|  | 60 mg twice daily for 7 days  | ↑30%                             |      | ↑37%   |      |

|                                       |                        |                               |      |      |
|---------------------------------------|------------------------|-------------------------------|------|------|
| 45 mg<br>(N = 14)                     | <b>Glipizide</b>       | 5 mg daily for 7 days         | ↓3%  | ↓8%  |
|                                       |                        |                               |      |      |
| 45 mg daily for<br>8 days<br>(N = 16) | <b>Metformin</b>       | 1000 mg single dose on Day 8  | ↓3%  | ↓5%  |
|                                       |                        |                               |      |      |
| 45 mg<br>(N = 21)                     | <b>Midazolam</b>       | 7.5 mg single dose on Day 15  | ↓26% | ↓26% |
|                                       |                        |                               |      |      |
| 45 mg<br>(N = 24)                     | <b>Ranitidine</b>      | 150 mg twice daily for 7 days | ↑1%  | ↓1%  |
|                                       |                        |                               |      |      |
| 45 mg daily for<br>4 days<br>(N = 24) | <b>Nifedipine ER</b>   | 30 mg daily for 4 days        | ↓13% | ↓17% |
|                                       |                        |                               |      |      |
| 45 mg<br>(N = 25)                     | <b>Atorvastatin Ca</b> | 80 mg daily for 7 days        | ↓14% | ↓23% |
|                                       |                        |                               |      |      |
| 45 mg<br>(N = 22)                     | <b>Theophylline</b>    | 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

| <b>Table 18. Effect of Coadministered Drugs on Pioglitazone Systemic Exposure</b> |                           |                                  |  |
|---|---------------------------|----------------------------------|--|
| <b>Coadministered Drug and Dosage Regimen</b>                                     | <b>Pioglitazone</b>       |                                  |  |
|   | <b>Dose Regimen (mg)*</b> | <b>Change in AUC<sup>†</sup></b> | <b>Change in C<sub>max</sub><sup>†</sup></b> |
| 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   | 30-mg                     | ↓54%                             | ↓5%  |

|   |             |      |      |
|---|-------------|------|------|
| daily for 5 days<br>(N = 10)                              | single dose |      |      |
| Fexofenadine 60 mg<br>twice daily for 7 days<br>(N = 23)  | 45 mg       | ↑1%  | 0%   |
| Ranitidine 150 mg<br>twice daily for 4 days<br>(N = 23)   | 45 mg       | ↓13% | ↓16% |
| Nifedipine ER 30 mg<br>daily for 7 days<br>(N = 23)       | 45 mg       | ↑5%  | ↑4%  |
| Atorvastatin Ca 80 mg<br>daily for 7 days<br>(N = 24)     | 45 mg       | ↓24% | ↓31% |
| Theophylline 400 mg<br>twice daily for 7 days<br>(N = 22) | 45 mg       | ↓4%  | ↓2%  |

\* Daily for 7 days unless otherwise noted

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

‡ The half-life of pioglitazone increased from 8.3 hours to 22.7 hours in the presence of gemfibrozil [see **DOSAGE AND ADMINISTRATION (2.3) and DRUG INTERACTIONS (7.1)**]

### Metformin hydrochloride

| <b>Table 19. Effect of Coadministered Drug on Plasma Metformin Systemic Exposure</b> |                              |                     |   |                   |
|--|------------------------------|---------------------|---|-------------------|
| Coadministered Drug  | Dose of Coadministered Drug* | Dose of Metformin*  | Geometric Mean Ratio (ratio with/without coadministered drug)<br>No effect = 1.00 |                   |
|  |                              |                     | AUC <sup>†</sup>  | C <sub>max</sub>  |
| No dosing adjustments required for the following:                                    |                              |                     |   |                   |
| Glyburide  | 5 mg                         | 500 mg <sup>§</sup> | 0.98 <sup>‡</sup>   | 0.99 <sup>‡</sup> |
| Furosemide   | 40 mg                        | 850 mg              | 1.09 <sup>‡</sup>   | 1.22 <sup>‡</sup> |
| 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 <sup>‡</sup>   | 1.07 <sup>‡</sup> |

Cationic drugs eliminated by renal tubular secretion may reduce metformin elimination: use with caution [see **WARNINGS AND PRECAUTIONS (5)** and **DRUG INTERACTIONS (7)**].

|            |        |        |      |      |
|------------|--------|--------|------|------|
| Cimetidine | 400 mg | 850 mg | 1.40 | 1.61 |
|------------|--------|--------|------|------|

Carbonic anhydrase inhibitors may cause metabolic acidosis: use with caution [SEE **WARNINGS AND PRECAUTIONS (5)** and **DRUG INTERACTIONS (7)**].

|            |                     |                     |                   |      |
|------------|---------------------|---------------------|-------------------|------|
| Topiramate | 100 mg <sup>¶</sup> | 500 mg <sup>¶</sup> | 1.25 <sup>¶</sup> | 1.17 |
|------------|---------------------|---------------------|-------------------|------|

\*All metformin and coadministered drugs were given as single doses

†AUC = AUC<sub>0-∞</sub>

‡Metformin hydrochloride extended-release tablets, 500 mg

§Ratio of arithmetic means

¶At steady-state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours; AUC = AUC<sub>0-12h</sub>

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

All metformin and coadministered drugs were given as single doses

\*AUC = AUC<sub>0-∞</sub>

†AUC<sub>0-24 hr</sub> reported

§Ratio of arithmetic means, p-value of difference <0.05

¶Ratio of arithmetic means

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### Pioglitazone and Metformin Hydrochloride

No animal studies have been conducted with pioglitazone and metformin hydrochloride. 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<sup>2</sup>). 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<sup>2</sup>). 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<sup>2</sup>). 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 9 times the maximum recommended human oral dose based on mg/m<sup>2</sup>).

#### 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 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 based on body surface area comparisons.

### 13.2 Animal Toxicology and/or Pharmacology

Heart enlargement has been observed in mice (100 mg/kg), rats (4 mg/kg and above) and dogs (3 mg/kg) treated orally with pioglitazone hydrochloride (approximately 11, 1, and 2 times the maximum recommended human oral dose for mice, rats, and dogs, respectively, based on mg/m<sup>2</sup>). 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<sup>2</sup>). Heart enlargement was seen in a 13-week study in monkeys at oral doses of 8.9 mg/kg and above (approximately 4 times the maximum recommended human oral dose based on mg/m<sup>2</sup>), 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<sup>2</sup>).

## 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 and metformin hydrochloride 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 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**

| Parameter   | Treatment Group  |                                |                              |
|---|--|--------------------------------|------------------------------|
|   | Pioglitazone and Metformin Hydrochloride 15/850 mg Twice Daily | Pioglitazone 15 mg Twice Daily | Metformin 850 mg Twice Daily |
| <b>HbA1c (%)</b>  | N=188  | N=162                          | N=193                        |
| Baseline (mean)   | 8.9  | 8.7                            | 8.7                          |
| Change from Baseline (adjusted mean*)   | -1.8   | -1                             | -1                           |
| Difference between pioglitazone and metformin hydrochloride (adjusted mean*)<br>95% Confidence Interval |  | 0.9†<br>(0.5, 1.2)             | 0.8†<br>(0.5, 1.2)           |
| % of patients with HbA1c ≤7%  | 64   | 47                             | 39                           |
| <b>Fasting Plasma Glucose (mg/dL)</b>   | N=196  | N=176                          | N=202                        |
| Baseline (mean)   | 177  | 171                            | 171                          |

|   |     |                |                |
|---|-----|----------------|----------------|
| Change from Baseline (adjusted mean*)   | -40 | -22            | -25            |
| Difference between pioglitazone and metformin hydrochloride (adjusted mean*)<br>95% Confidence Interval |     | 18†<br>(8, 28) | 15†<br>(6, 25) |

\*Adjusted for baseline

†p ≤0.05 versus pioglitazone and metformin hydrochloride

#### 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 was demonstrated for both pioglitazone and metformin hydrochloride tablets 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 3 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**).

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

\* Adjusted for baseline, pooled center, and pooled center by treatment interaction

† p ≤ 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% 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.

| <b>Table 23. Glycemic Parameters in a 24-Week Add-on to Metformin Study</b>    |   |   |
|--|---|---|
|  | <b>Pioglitazone<br/>30 mg +<br/>Metformin</b> | <b>Pioglitazone<br/>45 mg +<br/>Metformin</b> |
| <b>Total Population</b>  |   |   |
| HbA1c (%)  | N=400   | N=398   |
| Baseline (mean)  | 9.9   | 9.8   |
| Change from baseline (adjusted mean*)  | -0.8  | -1  |
| Difference from 30 mg daily pioglitazone + metformin (adjusted mean*) (95% CI) |   | -0.2<br>(-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 <sup>†</sup><br>(-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 as follows:

Pioglitazone and metformin hydrochloride 15 mg/500 mg tablets are white, oval, biconvex, film-coated tablets with “SZ441” on one side and are supplied as follows:

NDC 70882-105-56, Package of 56 tablets (4 x 14 unit-of-dose blisters)

### **Storage**

Store at 20° to 25° C (68° to 77°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.
- 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 patients that therapy with a thiazolidinedione, which is the active pioglitazone component of the pioglitazone and metformin hydrochloride tablet, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking pioglitazone and metformin hydrochloride. Recommend adequate contraception for all premenopausal women who are prescribed pioglitazone and metformin hydrochloride.
- 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.

### **For FDA-Approved Medication Guide**

Refer to the medication guide provided separately in a pad.

Manufactured for Cambridge Therapeutic Technologies, Teaneck, NJ 07666  
by Lek Pharmaceuticals d.d., SI-1526 Ljubljana, Slovenia

Packaged by Legacy Pharmaceutical Packaging, LLC  
Earth City, MO 63045

Principal Display Panel

| PIOGLITAZONE AND METFORMIN                     |   |                           |                              |
|--|---|---------------------------|------------------------------|
| pioglitazone and metformin tablet, film coated |   |                           |                              |
| <b>Product Information</b>                     |   |                           |                              |
| <b>Product Type</b>                            | HUMAN PRESCRIPTION DRUG   | <b>Item Code (Source)</b> | NDC:70882-105(NDC:0781-5626) |
| <b>Route of Administration</b>                 | ORAL  |                           |                              |
| <b>Active Ingredient/Active Moiety</b>         |   |                           |                              |
|  | <b>Ingredient Name</b>  | <b>Basis of Strength</b>  | <b>Strength</b>              |
|  | <b>PIOGLITAZONE HYDROCHLORIDE</b> (UNII: JQT35NPK6C) (PIOGLITAZONE - UNII:X4OV71U42S) | PIOGLITAZONE              | 15 mg                        |
|  | <b>METFORMIN HYDROCHLORIDE</b> (UNII: 786Z46389E) (METFORMIN - UNII:9100L32L2N)       | METFORMIN HYDROCHLORIDE   | 500 mg                       |

**Inactive Ingredients**

| Ingredient Name                                     | Strength |
|---|----------|
| CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)            |          |
| HYDROXYPROPYL CELLULOSE (TYPE H) (UNII: RFW2ET671P) |          |
| HYPROMELLOSE 2910 (6 MPAS) (UNII: 0WZ8WG20P6)       |          |
| MAGNESIUM STEARATE (UNII: 70097M6I30)               |          |
| CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)      |          |
| POLYETHYLENE GLYCOL 6000 (UNII: 30IQX730WE)         |          |
| POVIDONE K25 (UNII: K0KQV10C35)                     |          |
| TALC (UNII: 7SEV7J4R1U)                             |          |
| TITANIUM DIOXIDE (UNII: 15FIX9V2JP)                 |          |

**Product Characteristics**

|          |       |              |          |
|----------|-------|--------------|----------|
| Color    | WHITE | Score        | no score |
| Shape    | OVAL  | Size         | 14mm     |
| Flavor   |       | Imprint Code | SZ441    |
| Contains |       |              |          |

**Packaging**

| # | Item Code        | Package Description                                     | Marketing Start Date | Marketing End Date |
|---|------------------|---|----------------------|--------------------|
| 1 | NDC:70882-105-56 | 56 in 1 BLISTER PACK; Type 0: Not a Combination Product | 05/02/2013           |                    |

**Marketing Information**

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|--------------------|--|----------------------|--------------------|
| ANDA               | ANDA091273                               | 05/02/2013           |                    |

**Labeler** - Cambridge Therapeutics Technologies, LLC (080072003)

Revised: 11/2016

Cambridge Therapeutics Technologies, LLC